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Poster

639. Neuronal Differentiation

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 639.01/A1

Topic: A.01. Neurogenesis and Gliogenesis

Support: INPer Grant 3230-21202-01-2015
Conacyt Grant CB-2015-254847
Conacyt Grant CB-2013-220448
Conacyt Scholarship 255136

Title: The systemic administration of histamine H_1 receptor antagonist chlorpheniramine to pregnant rats impairs offspring nigrostriatal dopaminergic innervation and function

Authors: *B. M. VALADEZ[1], G. AQUINO-MIRANDA[2], M.-O. QUINTERO-ROMERO[3], H. PAPACOSTAS-QUINTANILLA[1], C. LOPEZ-RUBALCAVA[4], N.-F. DÍAZ-MARTÍNEZ[3], J.-A. ARIAS-MONTANO[5], A. MOLINA-HERNÁNDEZ[3];
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Abstract: The dopaminergic and histaminergic systems are the first to appear during central nervous system development. During embryo development histamine increases deep cortical layer neurogenesis through H_1 receptor (H_1R) activation, while reducing the dopaminergic phenotype in the ventral mesencephalon. Furthermore, the intrauterine or systemic injection of the H_1R antagonist/inverse agonist chlorpheniramine, decreases FoxP2 cortical phenotype neurons at embryo day (E) 14, and increases the dopaminergic markers tyrosine hydroxylase (TH) and Pitx3 in the ventral mesencephalon at E16. Although the short-term effect of histamine and H_1R pharmacological blocking has been reported, the postnatal functional implications have to be stablished. To do so, here the H_1R antagonist/inverse agonist chlorpheniramine was systemically administered (5 mg/kg, i.p.) to pregnant Wistar rats from gestational days 12 to 14 and, male and female offspring were evaluated at postnatal day 21 for changes in nigro-striatal innervation and function. The administration of chlorpheniramine to pregnant rats promotes a decrease in TH-immunoreactivity in the substantia nigra pars compacta (SNpc) and dorsal striatum in 21-day-old offspring compared to the controls. The reduction on TH correlates with 26 % lesser TH^+ cells in the SNpc, with a substantial increase of 77 % in ectopic TH^+ cells, compared to control animals. Furthermore, the striatal dopamine content and depolarization-evoked [^{3}H]-dopamine release in the striatum were reduced in pups of chlorpheniramine-treated rats. To explore if the changes observed in 21-day-old pups may have functional relevance, total motor activity was evaluated in an open field under basal and metha-amphetamine stimulated

dopamine release. Interestingly, the motor activity of stimulated pups of chlorpheniramine-treated rats was decreased. These results in addition to the increased dopamine neurogenesis reported by chlorpheniramine at embryo stages, suggests that the impaired nigro-striatal innervation and function may be due to migration defects of the dopamine neurons during embryo development to correctly form the SNpc. This information may have clinical relevance since first-generation antihistamine drugs are still used during pregnancy.

Disclosures: B.M. Valadez: None. **G. Aquino-Miranda:** None. **M. Quintero-Romero:** None. **H. Papacostas-Quintanilla:** None. **C. Lopez-Rubalcava:** None. **N. Díaz-Martínez:** None. **J. Arias-Montano:** None. **A. Molina-Hernández:** None.

Poster

639. Neuronal Differentiation

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 639.02/A2

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant 5F99NS108539-02

Title: Mismatched Sox: differential partner proteins & downstream targets of Sox11 in neural development

Authors: *K. S. SINGLETON[1], P. SILVA RODRIGUEZ[2], E. M. SILVA[2];
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Abstract: Neural development involves the progression of proliferating cells to mature neurons in order to form a complete and precisely functioning central nervous system. Transcription factors (TFs) maintain the balance of proliferating and differentiating cells, and Sox TFs, in particular, are key regulators of neural development. Along with partner proteins, Sox TFs control the production, differentiation and maturation of cells in the nervous system. Sox11, a member of the SoxC family, has been shown to play a critical role in every step of neural development including: establishment of neuronal identity, promotion of neural differentiation, and axon development. Deficits in Sox11 function have been linked to various neurodevelopmental disorders, focal temporal lobe epilepsy and malformations in the neural tube, cortex and spinal cord. However, little is known about the molecular mechanism underlying Sox11 function. Our previous work revealed that despite high evolutionary conservation and similar temporal and spatial expression, *Xenopus laevis* (frog) and *Mus musculus* (mouse) Sox11 cannot substitute for one another in neuronal differentiation. To further investigate the cause of this functional difference, we us co-immunoprecipitation to identify partner proteins that directly bind frog Sox11. In parallel, we performed RNA-seq to identify novel Sox11 targets during neurogenesis. Our results indicate that frog and mouse Sox11 partner

with different proteins and regulate different downstream targets in order to promote neuronal differentiation. Additionally, by using Sox11 deletion constructs, we were able to establish which domains are necessary and sufficient for Sox11 function during neural development. Collectively, this data demonstrates how Sox11 function, but not mechanisms, is evolutionarily conserved in the process of neural development.

Disclosures: K.S. Singleton: None. **P. Silva Rodriguez:** None. **E.M. Silva:** None.

Poster

639. Neuronal Differentiation

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 639.03/A3

Topic: A.01. Neurogenesis and Gliogenesis

Support: Proyecto INPer: 3230-21202-01-2015
Proyecto Conacyt: CB-2015-1-25484
Becario Conacyt No.339239

Title: Possible implication of histamine H1 receptor on impaired motor cortex cytoarchitecture and function in diabetic rat offspring's

Authors: *R. VALLE-BAUTISTA[1,2], G. HERRERA-LOPEZ[3], E. GRIEGO-MELO[3], E. GALVÁN[3], N. DÍAZ[1], J. ARIAS-MONTAÑO[2], A. MOLINA-HERNÁNDEZ[1];
[1]Inst. Nacional De Perinatologia, México D.F., Mexico; [2]Fisiología Biofisica y Neurociencias, Cinvestav Norte, México D.F., Mexico; [3]Cinvestav Sur, Mexico City, Mexico

Abstract: Gestational diabetes mellitus has been related to cognitive dysfunction in children, probably due to impaired neocortical embryo development. In rodents maternal diabetes decreases proliferation and increases differentiation during early corticogenesis. Interestingly, histamine H_1 receptor (H_1R) regulates the differentiation of FoxP2 projection neurons in the deep layers V and VI, and is overexpressed in the cortical neuroepithelium of embryos from diabetic rats at E12, its ligand is also increased at E14. The above suggests that changes in the transitory histaminergic embryo system under high glucose may be involved in the increased deep layers neurogenesis that will lead to postnatal changes in the cytoarchitectonic pattern. The aim of this study was to evaluate the effect of maternal hyperglycemia on postnatal motor cortex cytoarchitecture and function, and under this condition to evaluate the effect of embryos exposure to an H_1R antagonist. Hyperglycemia was induced by a single intraperitoneal injection of streptozotocin to pregnant rats at day 5 of gestation for the diabetic experimental group (Db), while buffered citrate solution was administrated to the control (Ctrl), the Db group was further divided in chlorpheniramine-treated and non-treated animals. Offsprings were sacrificed at postnatal days (P) 0, 5 and 21, and the frontal cerebral cortex was obtained to evaluate HA

content and H_1R density, by ELISA and binding assays respectively. The laminar localization of H_1R, reelin and Satb2 was evaluated by immunofluorescence, while the expression of *H_1R*, *FoxP2* and *Tbr1* was evaluated by qRT-PCR at P0. Furthermore, P21 cortical cytoarchitecture was assessed using Golgi-Cox stain and the functionality of pyramidal neurons was evaluated by electrophysiology. Results at P0 showed that the neonates from diabetic rats presented significant increases in *H_1R*, and in the deep cortical markers *FoxP2* and *Tbr1*, as well as, altered reelin and Satb2 laminar expression. Interestingly chlorpheniramine from E12 to E14, prevented the changes in *H_1R* and *FoxpP2*, observed at P0 in the diabetic group. Important changes were also observed in P21 pups from diabetic rats, such as: increased HA content, decreased dendritic complexity, alterations in cell polarity, and changes in passive and active electrophysiological properties of projection neurons. Overall, our results suggest that maternal hyperglycemia during corticogenesis affects postnatal motor cortex cytoarchitecture and function, and suggest a possible participation of that H_1R and HA in early neuronal differentiation and migration in cerebral cortex development in health and disease.

Disclosures: R. Valle-Bautista: None. **G. Herrera-Lopez:** None. **E. Griego-Melo:** None. **E. Galván:** None. **N. Díaz:** None. **J. Arias-Montaño:** None. **A. Molina-Hernández:** None.

Poster

639. Neuronal Differentiation

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 639.04/A4

Topic: A.01. Neurogenesis and Gliogenesis

Title: The transcription factor Sp9 represses the identity of the D1 MSN and promotes the identity of the D2 MSN in the striatum

Authors: *H. DU, Z. LI, Z. XU, Y. YOU, Z. ZHANG, Z. YANG;
State Key Lab. of Med. Neurobiology, Inst. of Brain Sci., Fudan Univ., Shanghai, China

Abstract: Striatal medium-sized spiny neurons (MSNs), composed of striatonigral dopamine receptor DRD1-expressing neurons (D1 MSNs) and striatopallidal dopamine receptor DRD2-expressing neurons (D2 MSNs), are derived from radial glial cells in the ventral lateral ganglionic eminence (LGE). Previously, *Sp9* constitutional and conditional loss-of-function analyses demonstrate that *Sp9* is required for the development of D2 MSNs in the striatum. Here, *Sp9* conditional gain-of-function analyses show that SP9 represses the identity of the D1 MSNs and promotes the identity of the D2 MSN. We generated a Sp9 conditional overexpression (*Rosa-Sp9-OE/+*) line, in which Sp9 expression is triggered by mating *Dlx5/6-Cre-ires-EGFP* (*Dlx5/6-CIE*) or *Sp9-Cre* driver lines. Upon Sp9 is overexpressed in the LGE, we observed that the expression of D1 MSN marker genes, such as Drd1 and Tac1, was greatly downregulated, whereas the expression of D2 MSN marker genes, such as Drd2 and Adora2a, was upregulated.

In *Dlx5/6-CIE; Rosa-Sp9-OE/+* or *Sp9-Cre; Rosa-Sp9-OE/+* mice at P20, we observed that most D1 MSNs have become D2 MSNs. RNA-Seq analysis confirmed this observation. Finally, using ChIP-Seq analysis, we show that SP9 directly binds to the promoter and/or enhancers of MSN-enriched genes, such as *Bcl11a, Bcl11b, Gad1, Gad2, Foxp1, Foxp2, Ebf1, Isl1, Drd1, Tac1, Drd2, Gpr88, Grik3, Ptprm, Nt5e,* etc. Thus, Sp9 is crucial for the development of both D1 and D2 MSNs.

Disclosures: H. Du: None. **Z. Li:** None. **Z. Xu:** None. **Y. You:** None. **Z. Zhang:** None. **Z. Yang:** None.

Poster

639. Neuronal Differentiation

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 639.05/A5

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant R01NS109358
NIH Medical Scientist Training Program Training Grant T32GM007205
Hydrocephalus Association
Rudi Schulte Research Institute
Simons Foundation

Title: Trim71 links an ancient microrna pathway to neural stem cell development and human congenital hydrocephalus

Authors: *D. Q. PHAN[1], S. WEISE[3], B. JUX[3], E. LAKE[1], L. T. FERNANDEZ[3], Y. YANG[1], D. FOSTER[4], F. SLACK[4], T. CONSTABLE[1], H. LIN[1], W. KOLANUS[3], K. KAHLE[2];
[2]Cell. and Mol. Physiol., [1]Yale Univ. Sch. of Med., New Haven, CT; [3]Univ. of Bonn, Bonn, Germany; [4]Harvard Med. Sch., Boston, MA

Abstract: Congenital hydrocephalus (CH), the most common brain malformation that affects 1:1000 live births, remains poorly treated owing to incomplete understanding of disease pathogenesis. Identification of novel CH disease genes is a powerful approach to understanding the molecular genetics of CH. Whole exome sequencing in humans has identified *TRIM71* as a *bona fide CH* disease gene. Trim71 is the major target of the ancient *let-7* pathway that famously regulates cell differentiation and organismal development via microRNA-mediated gene silencing in *C. elegans*. Previous works have implicated Trim71 in the regulation of embryonic neural stem cell (NSC) fate, yet its cellular and molecular function in NSCs remain poorly understood. To gain a better understanding of *Trim71* as a paradigm of neural stem cell involvement in CH, we have generated a mouse model that harbors the point mutation in *Trim71* that results in human CH (R595H) using CRISPR-Cas9. We found that a subset of mice

heterozygous for the *Trim71* R595H mutant allele developed severe communicating hydrocephalus with accompanying macrocephaly by four weeks of age. Mice homozygous for the mutant allele were embryonic lethal and exhibited profound neural tube by embryonic day 9.5. Investigation into the function of *Trim71* and its CH-causing mutations using our novel mouse models presents outstanding opportunities to increase understanding of human NSC regulation, brain development, and CH pathogenesis.

Disclosures: D.Q. Phan: None. **B. Jux:** None. **E. Lake:** None. **D. Foster:** None. **F. Slack:** None. **T. Constable:** None. **W. Kolanus:** None. **K. Kahle:** None.

Poster

639. Neuronal Differentiation

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 639.06/A6

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH

Title: R-loops as mechanisms governing neural differentiation and cell-type specific transcription

Authors: *E. A. LAMARCA[1], S. ESPESO-GIL[2], N. M. TSANKOVA[1], K. BRENNAND[2], S. AKBARIAN[2];
[1]Icahn Sch. of Med. At Mount Sinai, New York, NY; [2]Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Schizophrenia, bipolar disorder, and major depression together affect over 16% of the worldwide population, but their etiologies are poorly understood. Gene expression variation is a common attribute of these disorders, so research to identify and target aberrant mRNA regulation may provide novel therapeutic benefit. mRNA can anneal to template DNA during transcription, forming a DNA/RNA hybrid known as an R-loop. New genome-wide mapping strategies have identified a connection between R-loops and transcriptional regulation, suggesting a role for R-loops in gene expression variation. However, R-loops have never been characterized on a genome-wide scale in human brain cells, precluding research exploring their role in neuropsychiatric illnesses. Here, using DNA/RNA immunoprecipitation followed by deep sequencing (DRIP-seq), we show that R-loops are abundant in human neural cells and display a distinctive distribution relative to non-neural cells. We find evidence that R-loops may be poising genes for transcription, particularly those genes involved in neural differentiation and cell type-specific function. We predict that aberrant R-loop regulation may be involved in the pathophysiology of neuropsychiatric illness, and our future studies will test this hypothesis by

directly manipulating R-loop formation and examining the phenotypic consequences in neural cells both in vitro and in vivo.

Disclosures: E.A. LaMarca: None. **S. Espeso-Gil:** None. **N.M. Tsankova:** None. **K. Brennand:** None. **S. Akbarian:** None.

Poster

639. Neuronal Differentiation

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 639.07/A7

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant EY028625

Title: Classification, diversification and maturation of mouse retinal ganglion cells using single-cell transcriptomics

Authors: *K. SHEKHAR[1], I. E. WHITNEY[2], W. YAN[3], Y.-R. PENG[4], X. ADICONIS[1], J. Z. LEVIN[1], A. REGEV[1], J. R. SANES[5];
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Abstract: Retinal ganglion cells (RGCs) represent a diverse class of neurons, all of which project axons through the optic nerve and communicate distinct visual features to the rest of the brain. Using high-throughput single-cell RNA-seq (scRNA-seq), we profiled >35,000 RGCs from adult mice (post-natal day 56, or P56) and assembled a comprehensive atlas of this class, identifying 45 molecularly distinct types. We used histological approaches to match molecular identity to morphology for many types, and to validate new markers for known types. We next investigated the diversification RGCs by profiling them at 4 developmental timepoints, from embryonic day (E) 14, when they are newly postmitotic, through P5. Using the mathematical framework of Optimal Transport (OT) (Schiebinger et al., Cell, 2018), we identified lineage relationships between developing RGC and their mature counterparts. OT analysis predicted an asynchronous diversification across RGC subclasses and types, with certain subclasses (e.g. Opn4+ RGCs) specified as early as E14, while others (e.g. Neurod2+ RGCs) emerging as a distinct group only at P0. Altogether, >95% of types are fully diversified by P5, with type-specific transcriptional distinctions at this stage exhibiting a 1:1 correspondence with their adult counterparts. While we detected ~700 differentially expressed genes between P5 and adult RGCs, these were largely shared across types, and corresponded to transcriptional programs representing neuronal maturation (axon guidance, cell adhesion, and ion channel activity). Lastly, we asked if molecular maturation of RGCs was intrinsic or dependent on visual experience, by examining the transcriptomes of adult RGCs in mice that were either dark reared,

or possessed a mutation (Rd1) that leads to early and rapid photoreceptor degeneration. In both cases, all RGC types were present, and were transcriptomically far more similar to control adult RGCs than to P5 RGCs. Taken together, our results suggest that visual input plays a relatively minor role in the diversification and maturation of this neuronal class in the retina.

Disclosures: K. Shekhar: None. **I.E. Whitney:** None. **W. Yan:** None. **Y. Peng:** None. **X. Adiconis:** None. **J.Z. Levin:** None. **A. Regev:** None. **J.R. Sanes:** None.

Poster

639. Neuronal Differentiation

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 639.08/A8

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH 5T32GM008136-33
NIH 5T32GM007267-38
Owens Family Fund

Title: The neurodevelopmental consequences of genomic stress

Authors: *N. MICHEL[1], U. B. MAJUMDAR[3], J. LANNIGAN[2], M. MCCONNELL[1]; [1]Biochem. and Mol. Genet., [2]Univ. of Virginia, Charlottesville, VA; [3]Icahn Sch. of Med., Mount Sinai, New York, NY

Abstract: Somatic mosaicism is a common consequence of normal development. DNA repair is simply not perfect, and each cell's genome incurs continuous DNA damage as a consequence of transcription, replication, and other cell biological stressors. Brain somatic mosaicism is particularly noteworthy because the vast majority of an individual's neurons are with that individual for life and neural circuits give rise directly to behavioral phenotypes. Brain somatic mosaicism, now revealed and tractable due to advances in single cell 'omic approaches, has emerged as an intriguing and unexplored aspect of neuronal diversity. Furthermore, the study of DNA damage during early neurodevelopment, when the rate of mutagenesis is high, is the perfect starting point to understand the origins of brain mosaicism. Flow cytometry is a highly efficient technique to study cell cycle and intracellular proteins of interest; particularly those related to DNA damage, but lacks the high resolution of microscopy to examine the localization of these proteins. In this study we outline a novel single-cell approach to quantify DNA Double-Strand Break (DNA DSB) dynamics during early human neurodevelopment by applying imaging flow cytometry (IFC) to human-induced pluripotent stem cell derived neural progenitor cells (NPCs) undergoing neurogenesis. We establish an increase of DNA DSBs by quantifying γH2AX foci in mildly stressed NPCs using various single-cell approaches in addition to IFC including fluorescent microscopy, conventional flow cytometry, and measuring DNA DSBs with

the comet assay. We demonstrate the dose-dependent sensitive detection of γH2AX foci through IFC and reveal the dynamics of DNA DSBs in proliferating and differentiating neural cells in early neurogenesis.

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Poster

639. Neuronal Differentiation

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 639.09/A9

Topic: A.01. Neurogenesis and Gliogenesis

Title: Global effects of Parkinson's disease risk-SNP rs356182 at the SNCA locus

Authors: *J. D. PRAHL, T. TYSON, S. PIERCE, J. VANDERSCHANS, G. COETZEE; Van Andel Inst., Grand Rapids, MI

Abstract: Genome wide association studies (GWAS) have revealed 92 independent genetic risk signals associated with Parkinson's disease (PD). Most single-nucleotide polymorphisms (SNPs) identified by GWAS occur in non-exonic regions, making functional characterization difficult. Here we investigate the most significantly associated PD-risk SNP, rs356182. Its proximity to *SNCA* has led to the assumption that rs356182 confers risk through allele-dependent differences in alpha-synuclein expression. However, preliminary evidence suggests that the genetic enhancer encompassing rs356182 (referred to here as SNCA-ENH1) impinges on the expression of many genes across the genome, and mediates a phenotype not typically ascribed to SNCA. Together these data indicate that rs356182 may relate to PD in an unexpected way. To determine the biological mechanism(s) linking PD with rs356182 we employ LUHMES cells and induced pluripotent stem cells (iPSCs) as models of normal dopaminergic neurons (DANs) in a mature or still developing human brain. To examine possible roles of SNCA-ENH1 we are measuring its temporal activity by performing chromatin immunoprecipitation (ChIP) for histone H3 lysine 27 acetylation (H3K27ac; marker of active enhancers and promoters) at time points during DAN differentiation. We are also examining transcription factor (TF) binding at rs356182 by predicting candidate TFs based on expression and known binding motifs, and then verifying these TFs using ChIP. Finally, we are investigating the allele-specific differential gene expression due to the risk (G) or protective (A) alleles at rs356182. We speculate that the rs356182 risk allele could increase the likelihood of PD by changing TF occupancy during a key step in DAN differentiation (compared to the protective allele), resulting in repression of key differentiation genes and reduction in the mature DAN population. Subsequent stresses leading to neuronal death are then more likely to result in Parkinsonian symptoms compared to an individual with a larger neuronal cell population.

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Poster

639. Neuronal Differentiation

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 639.10/A10

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant AG058856
Vanderbilt Institute for Clinical and Translational Research
VA Tennessee Valley Geriatric Research, Education and Clinical Center (GRECC)
NIH Grant MH064913

Title: Accelerated expression of functional NMDA receptors on mature hiPSC-derived neurons

Authors: *J. B. RUDEN[1], M. DIXIT[2], L. L. DUGAN[3];
[1]Vanderbilt Univ., Nashville, TN; [2]Med., [3]Dept Medicine/Geriatrics & Vanderbilt Brain Inst., Vanderbilt Univ. Med. Ctr., Nashville, TN

Abstract: NMDA receptors are glutamatergic receptors that come late in development and are critical for neurotransmission of higher-order CNS function. They are necessary for LTP, memory entrainment, and many other neural processes. Many protocols to derive cortical neurons from human neural progenitor cells produce neurons that exhibit excitatory postsynaptic potentials and/or AMPA receptor activity. A limited number of protocols can produce glutamatergic neurons with functional NMDA receptors from human inducible pluripotent stem cells (hiPSCs), but the process is time-consuming. We wanted to develop an accelerated protocol to derive mature cortical neurons that have functional NMDA receptors in order to test several neuroinflammatory factors *in vitro*. Here, we derived neurons from commercially available hiPSC-derived neural progenitor cells that exhibit increased cytoplasmic calcium translocation in response to NMDA, demonstrating that they have functional NMDA receptors. We were able to derive these mature neurons with functional NMDA receptors in approximately six weeks. The presence of NMDA receptors was confirmed with RT-PCR and Western blot. These mature neurons can be used to address many scientific questions beyond our specific questions.

Disclosures: **J.B. Ruden:** None. **M. Dixit:** None. **L.L. Dugan:** None.

Poster

639. Neuronal Differentiation

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 639.11/A11

Topic: A.01. Neurogenesis and Gliogenesis

Title: The effects of metformin on early cortical development

Authors: *W. ALSANIE, H. HABEEBALLAH, O. BAHRI, M. ALHOMRANI, A. GABER, K. ALSWAT;
Taif Univ., Taif, Saudi Arabia

Abstract: Metformin is widely used as an antidiabetic drug to treat patients who have been diagnosed with type 2 diabetes mellitus. Although it is known to cross the placenta, it is one of only two oral medications that can be prescribed for pregnant diabetic women. To date, the effects of metformin on the development of human neurons, particularly cortical neurons in the fetus, have not been evaluated in any study. Human pluripotent stem cells (hPSCs) are considered an invaluable tool in studying of normal development and drug testing in vitro. Thus, the effects of metformin on cortical neurons derived from hPSCs were evaluated in the current study. Metformin has been added to cortical differentiation cultures established from hPSCs to examine whether metformin has an effect on this early developmental process. The expression of several genes and transcription factors were evaluated at different time points throughout the differentiation. Metformin was shown to increase the differentiation of PAX6-positive early cortical progenitors into TBR2-positive intermediate progenitors ($p = < 0.050$). In agreement, the expression of several cortical progenitor genes were increased significantly in metformin treated cultures in comparison with the control cultures ($p = < 0.050$). During maturation, an increase in the number of CTIP2-positive neurons, which normally reside in the deep layers of the cerebral cortex, was evident in the metformin-treated differentiation culture compared to the control differentiation culture ($p = < 0.050$). By contrast, there was no difference observed in the number of TBR1-positive neurons identified in the two differentiation cultures. The delay in differentiation in the metformin-treated culture was found to be due to the activation of the adenosine monophosphate-activated protein kinase (AMPK) signaling pathway on further analysis. By inhibiting the AMPK signaling pathway in the metformin-treated cultures, differentiation of the human cortical neurons therein was similar to that in the control group. To the best of our knowledge, this is the first study to have demonstrated the effect of metformin on human cortical development in vitro. Further studies are warranted to examine the effects of metformin on the morphogenesis and synaptogenesis of cortical neurons.

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Poster

639. Neuronal Differentiation

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 639.12/A12

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH grant # 1R01NS110760-01

Title: Premature birth results in dysmaturation of dentate granule neurons and cognitive deficits

Authors: *D. R. SHARMA[1], B. CHENG[1], D. SINGH[1], N. PARIKH[1], S. MAMTANI[1], S. YADAV[1], M. K. JAISWAL[2], P. BALLABH[1];
[1]Neurosci., Albert Einstein Col. of Med., Bronx, NY; [2]Psychaitry, Icahn Sch. of Med. At Mount Sinai, New York, NY

Abstract: Every year ½ million infants are born prematurely in the US and 15 million worldwide. Preterm-born children suffer deficits in memory and learning, which suggests disruption in hippocampal development. As dentate gyrus develops perinatally, premature-birth can impact its maturation. Preterm infants are deprived of safe intrauterine environment and reared in the stressful environment of Neonatal Units. However, the effect of premature-birth on dentate gyrus development is obscure. We hypothesized that premature-birth and non-maternal care would disrupt the structure and function of dentate gyrus and induce cognitive deficits. To test our hypotheses, we compared preterm (E28.5) and term (E32) rabbit kits at an equivalent post-conceptional age (P28). Preterm kits were reared in an infant incubator and were gavage fed, whereas term kits were reared by mother rabbit. Neurobehavioral tests included open field test, object placement test and Barnes Maze test, using ANY-maze video tracking system. Granule cells were immunostained with NeuN, and Calbindin, and interneurons with GABA, parvalbumin and somatostatin antibodies. Neurons in dentate gyrus were stereologically quantified. Granule cell were also assessed in Golgi-stained sections. Synapses were quantified in PSD95 and Vglut2 immunostained sections. Markers of stress, glucocorticoid receptor (GR) and p-GR were assessed by western blot analyses. Object placement test revealed that preterm kits spent less time exploring the moved object compared to term kits. Modified Barnes maze showed that preterm kits had longer-latency and made more errors in finding food relative to term kits. This suggests reduced spatial memory and learning in preterm kits. Stereological Quantification showed that both $NeuN^+$ granule cells and interneurons--$GABA^+$, $Parvalbumin^+$ and $somatostatin^+$ cells--were higher in number in the dentate gyrus of preterm kits compared to term controls. However, $calbindin^+$ neurons were reduced in preterm relative to term kits. Accordingly, Golgi stained sections showed more abundant granule cells in preterm compared to term kits. Despite granule cells were larger in number in preterm kits, VGlut2-$PSD95^+$ synaptic puncta in the molecular layer of dentate gyrus were reduced in preterm compared to term kits.

Moreover, phospho-glucocorticoid-receptor expression was higher in preterm relative to term kits. Hence, dysmaturation of dentate granule neurons in premature kits results in reduced synaptic connectivity, and contributes to poor memory and learning. Strategies to enhance maturation of granule cells might improve the cognitive outcome of premature infants.

Disclosures: D.R. Sharma: None. **B. Cheng:** None. **D. Singh:** None. **N. Parikh:** None. **S. Mamtani:** None. **S. Yadav:** None. **M.K. Jaiswal:** None. **P. Ballabh:** None.

Poster

639. Neuronal Differentiation

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 639.13/A13

Topic: A.01. Neurogenesis and Gliogenesis

Support: Taiwan International Graduate Program
Intramural funding of Institute of Cell and Oraganismic Biology, Academia Sinica

Title: Dual-specificity phosphatase 15 (DUSP15) modulates notch signaling through enhancing the stability of notch protein

Authors: *N. BHORE, B.-J. WANG, P.-F. WU, Y.-W. CHEN, Y.-F. LIAO;
Inst. of Cell. and Organismic Biol., Academia Sinica, Taipei, Taiwan

Abstract: Dual-specificity phosphatases (DUSPs) are a unique group of phosphatases which are involved in protein dephosphorylation at both phospho-serine/threonine and phospho-tyrosine residues. A preliminary RNAi screen led us to identify DUSP15, whose downregulation significantly affected the interaction between Notch and presenilin-1, thus hinting at potential modulation of Notch signaling. Accumulated evidence has suggested that Notch signaling is a conserved pathway essential for cell fate determination and development, and is also upregulated in cortical regions of patients with Alzheimer's disease (AD). Thus, we sought to determine the underlying molecular mechanism of this DUSP15-mediated alteration of Notch processing. Our data suggest that over-expression of DUSP15 increases the steady-state levels of recombinant Notch (extracellular domain-truncated Notch, NΔE) protein and concomitantly its cleaved product, Notch intracellular domain (NICD), in a dose-dependent manner. Consistently, the overexpression of DUSP15 effectively increased the levels of endogenous NICD in cultured cellular models. However, the overall ratio between Notch substrate and the cleaved product was unchanged in response to overexpression of DUSP15, suggesting that γ-secretase activity is not significantly affected by DUSP15. Previous studies have shown that ERK phosphorylation is positively correlated with the levels of Notch protein. Our results also confirmed that overexpression of DUSP15 increases the phosphorylation of ERK in a dose-dependent manner,

suggesting that DUSP15 could regulate the levels of Notch protein through an ERK-dependent pathway. We will determine whether this DUSP15-ERK-Notch pathway could play a role in neuronal differentiation, and provide proof-of-principle evidence validating that DUSP15 could be a novel therapeutic target for neurodevelopmental and neurodegenerative diseases.

Disclosures: **N. Bhore:** None. **B. Wang:** None. **P. Wu:** None. **Y. Chen:** None. **Y. Liao:** None.

Poster

639. Neuronal Differentiation

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 639.14/A14

Topic: A.01. Neurogenesis and Gliogenesis

Title: Automated neonatal and adult mouse brain dissociation and magnetic isolation of neurons increases efficiency and sensitivity for single-cell gene expression profiling

Authors: S. REISS[1], R. KLÄVER[1], S. TOMIUK[1], J. SOYKA[1], M. DELSO VALLEJO[1], C. JONES[2], *A. BOSIO[1], M. JUNGBLUT[1];
[1]Miltenyi Biotec, Bergisch Gladbach, Germany; [2]10x Genomics, Pleasanton, CA

Abstract: Single-cell RNA sequencing has emerged as a powerful technology for the analysis of cell types with high resolution during the last years. Especially in case of the huge heterogeneity of neural cells, the technology can help to better understand their phenotype and function by deciphering the transcriptome of different subtypes. A prerequisite for single-cell analysis of tissue derived cells is the preparation of single-cell suspensions with high cell viability and a minimum of cell debris, which is particularly challenging in case of highly sensitive neurons. To improve cellular analysis of neural cells, we established an elaborated technology for the automated dissociation of neonatal and adult mouse brain tissue, which is based on the combination of an ideal mechanical dissociation using the gentleMACS™ Octo Dissociator with Heaters (Miltenyi Biotec) and an optimized enzymatic treatment. After tissue dissociation, neurons were isolated using the Neuron Isolation Kit (Miltenyi Biotec) to increase the percentage of target cells for single cell genomics. Gene expression profiling of adult unsorted cells and isolated neurons was performed using the Chromium Single Cell 3′ Reagent Kits v3 (10x Genomics) for preparation of Single-cell RNA-seq libraries. In detail, 16000 cells per samples were loaded into the Chromium Chip B Single Cell and processed according to the manufacturer's instructions. Furthermore, we compared single cell sequencing data from manually and automatically dissociated neonatal mouse brain loading 8000 cells per sample. All Single-cell RNA-seq libraries were pooled and sequenced using two Next Seq 500 High Output Cartridges on the NextSeq 500 Instrument (Illumina). For processing and visualization of the single cell RNA sequencing data, the Seurat package (v3.0.0) was used. The analysis resulted in the identification of 5800-10800 cells per sample with an average of 15000 reads per cell.

Results showed that isolation of neurons led to substantial enrichment in the number of target cells and allowed for the identification of different neuronal subpopulations that could not be distinguished in the unsorted brain fraction. Comparison of automatically and manually dissociated neonatal mouse brain tissue led to the identification of the same neural cell clusters, proving that the automated gentleMACS based dissociation did not have any negative influence. In summary, we showed that an optimized automated dissociation protocol based on the gentleMACS octo Dissociator and magnetic isolation of neurons significantly improves sensitivity and resolution of single cell sequencing for characterization of neuronal subtype complexity.

Disclosures: S. Reiss: None. **A. Bosio:** None. **R. Kläver:** None. **S. Tomiuk:** None. **J. Soyka:** None. **M. Delso Vallejo:** None. **M. Jungblut:** None. **C. Jones:** None.

Poster

639. Neuronal Differentiation

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 639.15/A15

Topic: A.01. Neurogenesis and Gliogenesis

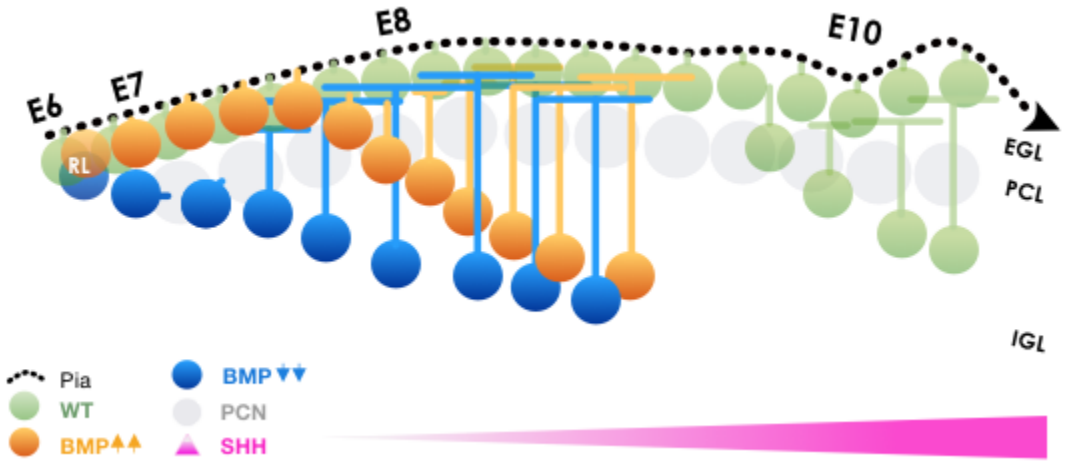
Support: Queen Mary University London

Title: Novel roles of BMP signalling in cerebellar granule cell neurogenesis

Authors: *V. ROOK[1,2], R. J. WINGATE[2], T. BUTTS[3,1];
[1]Sch. of Biol. and Chem. Sci., Queen Mary Univ. London, London, United Kingdom; [2]Ctr. for Neurodevelopmental Disorders, King's Col. London, London, United Kingdom; [3]Sch. of Life Sci., Univ. of Liverpool, Liverpool, United Kingdom

Abstract: Cerebellar granule cell precursors (GNP) are the most abundant neuronal progenitor population in the brain, making them a good model for studying principles of neurogenesis. GNPs are born at the rhombic lip and migrate tangentially to form a transiently proliferative layer that covers the cerebellar anlage; the external granule layer (EGL). GNPs undergo massive proliferation in the EGL influenced by Sonic Hedgehog (SHH) secreted by underlying Purkinje neurons. Mutations in SHH are implicated in medulloblastoma; the most common paediatric brain cancer. However, triggers for termination of GNP proliferation are poorly understood. Whilst BMP signalling has been implicated at various stages of cerebellar development, data from *in vitro* and transgenic mouse studies has been conflicting. In this study we show, by *in ovo* genetic manipulation of the embryonic chick hindbrain, the role of BMP signalling changes as the local signalling environment of the developing cerebellum changes. In the absence of BMP signalling the EGL fails to form at embryonic day 7 (E7), but GNPs are nevertheless specified and migrate away from the rhombic lip and immediately differentiate, sending axonal projections

into the molecular layer of the cerebellum. In contrast, with the misexpression of an activated form of the intracellular mediator of BMP signalling, Smad1, GNPs are recruited to the EGL or differentiate and migrate away from the pial surface. Following the onset of proliferation at E8, Smad1 misexpression only induces radial migration and premature differentiation. In conclusion, our data suggests that the correct level of BMP signalling is required to regulate the developmental chorography, but not the ultimate fate of granule cell neurons. These data unify previous conflicting observations surrounding the role of BMP signalling in the granule lineage and uncover an important function of BMP signalling in late cerebellar development that is developmentally pliable, and may explain variation in foliation between species, as well as identify potential avenues to treat medulloblastoma.



Disclosures: **V. Rook:** None. **R.J. Wingate:** None. **T. Butts:** None.

Poster

639. Neuronal Differentiation

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 639.16/A16

Topic: A.01. Neurogenesis and Gliogenesis

Support: KAKENHI (16K00626)

Title: Bisphenol A induces neurite extension in PC12 cells

Authors: ***K. SHIMOKE**, K. MATSUURA, H. MARUOKA;
Kansai Univ., Osaka, Japan

Abstract: Bisphenol A (BPA) is included in plastics as a plasticizer widely. BPA is an endocrine disrupting chemical (EDC) that promotes a female-inducing phenotype in genital organs via estrogen receptors. We have found that BPA and other alkylphenol compounds can cause apoptosis in PC12 cells when we add relatively high dose. This mechanism was classified as endoplasmic stress (ER)-mediated apoptosis due to involvement of accumulation of unfolded proteins with upregulation of glucose-regulated protein 78 (GRP78) / BiP (immunoglobulin heavy-chain binding protein), a marker of ER stress. In cell-based assays, we also discovered that BPA is an inducer of neurite outgrowth in PC12 cells when we add lower dose. Contrary to expectations, we also found that the neurites are unique compared with those induced by nerve growth factor (NGF). This suggests that BPA may have a direct function in differentiation of neurons. This evidence was obtained using neuronal marker proteins. In addition to formation of neurites in PC12 cells. A molecular analysis showed that acetylation of specific amino acids in histones, which induces expression of the orphan nuclear receptor nur77 gene, an immediate early gene, leading to epigenetic regulation of gene expression. Based on these results, we suggest that intracellular signaling caused by BPA is mediated via the specific gene expression epigenetically to extend the neurites.

Disclosures: K. Shimoke: None. **K. Matsuura:** None. **H. Maruoka:** None.

Poster

639. Neuronal Differentiation

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 639.17/A17

Topic: A.01. Neurogenesis and Gliogenesis

Support: INPRFM-SIC Grant 2000
CONACYT-Infraestructura 2015-Grant 254773

Title: Repetitive transcraneal magnetic stimulation reverses the alterations in the hippocampal neurogenic niche caused by chronic mild stress

Authors: *G. B. RAMIREZ-RODRIGUEZ[1], D. MENESES-SAN JUAN[2], J. J. GONZÁLEZ-OLVERA[4], L. ORTIZ-LOPEZ[3], D. REYES-HARO[5];
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Abstract: Depression is a neuropsychiatric disorder that courses with alterations in behavior and brain plasticity in regions belonging to the limbic system. Several reports have indicated that stress plays a significant role to precipitate depression. In order to reverse the alterations occurring at the behavioral and brain plasticity levels several pharmacological interventions have

been used. However, there are clinical evidences supporting the effects of repetitive transcraneal magnetic stimulation (rTMS) as a non-invasive intervention that may impact brain plasticity to reverse depression. However, the mechanisms that underlay the effects of rTMS are unknown. Thus, in this study we analyzed the impact of rTMS in female Balb/C mice exposed to chronic mild stress (CMS). Here, we found that rTMS (5Hz) applied for 28 days during the CMS protocol, reverses depressive-like behavior and produces positive changes in the cellular populations of the dentate gyrus. Moreover, rTMS increases BDNF inmunoreactity in the dentate gyrus. The data of this study strongly support the beneficial effects of rTMS and its effects on the generation of new neurons in the dentate gyrus.

Disclosures: G.B. Ramirez-Rodriguez: None. **D. Meneses-San Juan:** None. **J.J. González-Olvera:** None. **L. Ortiz-Lopez:** None. **D. Reyes-Haro:** None.

Poster

639. Neuronal Differentiation

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 639.18/A18

Topic: A.01. Neurogenesis and Gliogenesis

Support: FNRS FRIA fellowship FC 17518
FNRS grant J.0129.15
FNRS grant J.0179.16
FNRS grant T.0243.18

Title: Rhoa functions in late embryonic apical neural stem cells in the mammalian cerebral cortex

Authors: *A. COSSARD, Y. JOSSIN;
Lab. of Mammalian Develop. & Cell Biol., Univ. Catholique De Louvain, Bruxelles, Belgium

Abstract: Excitatory neurons, the major type of neurons in the cerebral cortex, are produced by Neural Stem Cells (NSCs) located in a region called the ventricular zone (VZ). Initially NSCs mainly self-renew, resulting in an expansion of their number. They then progressively switch into another type of proliferative cells called radial glia cells or apical NSCs (aNSCs) and start producing basal progenitors and neurons. The maintenance of the balance between proliferation, self-renew and differentiation is crucial to the formation of a normal cortex. Disruption of the molecular and cellular mechanisms that regulate these processes can lead to serious cortical malformations (neuronal heterotopy, microcephaly ...).
The small GTPase RhoA plays key roles in fundamental functions such as regulation of actin cytoskeleton, microtubule movement, and regulation of gene expression. It is highly expressed in the VZ of the developing cerebral cortex and its Conditional deletion in early NSCs of the

cerebral cortex induces a loss of adherens junctions associated with massive disorganization of the tissue and over-proliferation of NSCs. However, nothing is known about its function in later stage. Since early NSCs mostly self-renew while late aNSCs divide asymmetrically to produce postmitotic cells, we hypothesized that RhoA function might not be the same at different developmental stages. In this project, we investigate RhoA functions during late neurogenesis by means of an alternative approach that only affects a subset of cells in a cell autonomous manner. Using *in utero* electroporation and molecular techniques, we found that RhoA positively regulates proliferation and controls differentiation into basal progenitors or postmitotic neurons in the cerebral cortex before and therefore independently to the occurrence of tissue disorganization.

Disclosures: A. Cossard: None. **Y. Jossin:** None.

Poster

639. Neuronal Differentiation

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 639.19/A19

Topic: A.01. Neurogenesis and Gliogenesis

Support: MRC
BBSRC

Title: Pax6 regulates the development of morphology and electrophysiological properties of the mouse embryonic prethalamic neurons

Authors: *T. TIAN, I. QUINTANA-URZAINQUI, Z. KOZIć, T. PRATT, D. PRICE;
Ctr. for Discovery Brain Sci., Univ. of Edinburgh, Edinburgh, United Kingdom

Abstract: The transcription factor Pax6 is a pleiotropic player during neural development. In the central nervous system, Pax6 is mostly expressed by neural progenitors, where its functions have been most extensively studied. However, in the anterior diencephalon, the prethalamus, Pax6 is expressed in both neural progenitors and post-mitotic neurons. This distinctive expression pattern of Pax6 makes the prethalamus a unique place in which to explore the functions of Pax6 and its mechanisms of action during development.
Gene ontology analysis on our RNAseq data, which showed significant transcriptional changes of genes in the prethalamus when Pax6 is lost, indicated that Pax6 seems to regulate the process of neuronal morphogenesis. To further explore this, we dissociated the prethalamus at embryonic day 13.5 and cultured the primary prethalamic neurons for 1-9 days *in vitro* (DIV). We found that Pax6-null prethalamic neurons constantly displayed fewer neurites and a disturbed rate of neurite elongation. Additionally, we discovered that the axon initial segments (AISs) of these neurons were shorter and located further away from the soma. The AIS is where the neurons

generate action potentials, and its location and molecular composition can determine the amplitudes and firing frequencies of the neurons. We found that the components of the AISs seemed to have been altered as increased amount of voltage-gated sodium channels and AnkyrinG was found in the AISs of the Pax6-null prethalamic neurons. Therefore, our analysis suggested that the Pax6-null prethalamic neurons might display different electrophysiological properties. Whole-cell patch recording is currently underway to further confirm whether and how the electrophysiological properties are changed in the absence of Pax6.
Our results thus revealed novel and distinct functions of Pax6 in the post-mitotic cells of the mouse embryonic prethalamus- regulating neuronal morphogenesis and functionality in a cell-autonomous manner.

Disclosures: T. Tian: None. **I. Quintana-Urzainqui:** None. **Z. Kozić:** None. **T. Pratt:** None. **D. Price:** None.

Poster

639. Neuronal Differentiation

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 639.20/A20

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH-R01AA024659

Title: Novel mediators of prenatal alcohol effects in neural stem cells: Gag-like proteins as RNA chaperones for intercellular communication

Authors: *M. PINSON, A. TSENG, V. NAIR, R. C. MIRANDA;
Neurosci. & Exptl. Therapeut., Texas A&M Hlth. Sci. Ctr, Col. of Med., Bryan, TX

Abstract: Extracellular vesicles (EVs) are nanometer-sized, membrane-bound vesicles released by cells that may serve as a means of intercellular communication by transporting biological information between cells. Recently the Gag-Like Protein (GLP) Arc was identified in neuron-derived EVs, and found to transport its own mRNA between neurons. This raises the possibility that other members of the brain-enriched GLP family may function like Arc, and the ancestral retrovirus Gag protein, in their ability to interact with mRNA and self-target for membrane bound export in EVs. GLPs may chaperone RNA in intercellular transport and therefore, serve as a means for programming the multipotency and differentiation of neural stem cell (NSC) ensembles. GLPs may also mediate effects of alcohol in developing tissues. In line with this reasoning, we evaluated the expression of GLP mRNAs in neural development under basal and ethanol exposure conditions by using qRT-PCR and of proteins using immunoblot. The GLPs PEG10 and PNMA2 were knocked-down (KD) and the impact on NSC differentiation was determined by qRT-PCR and immunoblot. Furthermore, effect of KD of GLPs on cellular

metabolic activity was determined by MTT assay, on cell cycle progression Click-iT EdU flow cytometry, and apoptotic activity by Caspase-Glo 3/7 assay. Results show that transcript expression of PNMA2 increased during differentiation, suggesting a role in NSC maturation. Furthermore, ethanol exposure resulted in a dose related-increase in mRNA and protein for GLPs, PEG10 and PNMA2. Ongoing studies are evaluating the effect of GLP KD on NSC differentiation, cell cycle progression, and apoptotic activity. These data support a hypothesis that GLPs mediate compensatory mechanisms for cell survival or maturation following ethanol exposure. Further understanding how GLPs mediate and coordinate neural development may lead to interventions that moderate the harmful effects of prenatal alcohol exposure.

Disclosures: M. Pinson: None. **A. Tseng:** None. **V. Nair:** None. **R.C. Miranda:** None.

Poster

639. Neuronal Differentiation

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 639.21/A21

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant MH109747

Title: Neuron-specific alternative mRNA splicing is required for SYNGAP1 protein expression

Authors: X. FENG[1], *X. ZHANG[2];
[1]Deptment of Human Genet., The Univ. of Chicago, Chicago, IL; [2]Dept. of Human Genetics, and the Grossman Inst. for Neurosci., Univ. of Chicago, Chicago, IL

Abstract: Synaptic RAS GTPase-activating Protein 1 (SYNGAP1), a major component in the post-synaptic density, is crucial for synaptic plasticity. Mutations in SYNGAP1 are leading causes (1%) of non-syndromic intellectual disability and frequently associated with autism and epilepsy. Although *SYNGAP1* mRNA is widely transcribed in different tissues and cell types, SYNGAP1 protein is specifically expressed in the nervous system. This post-transcriptional expression difference is particularly striking during neural development, but the regulatory mechanism remains unknown. Here, we report that the polypyrimidine tract binding proteins (PTB) repress the expression of SYNGAP1 by promoting an alternative 3' splicing site usage. This mammal-conserved alternative splicing event leads to nonsense-mediated mRNA decay (NMD) in non-neural tissues and ensures neuron specific expression of SYNGAP1 protein. Our study highlights the importance of cell type specific alternative splicing in neural development.

Disclosures: X. Feng: None. **X. Zhang:** None.

Poster

639. Neuronal Differentiation

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 639.22/A22

Topic: A.01. Neurogenesis and Gliogenesis

Support: Hill Knowledge fellowship

Title: Early neurogenesis in the human cephalic ectoderm and the cranial sensory placodes

Authors: *I. BYSTRON;
Univ. of Oxford, Oxford, United Kingdom

Abstract: The preplacodal cephalic epithelium is continuous with the prosencephalic epithelium prior to the fusion of the anterior neuropore. We report here a previously unknown early neuronal population in the human cephalic ectoderm, which is distinct from the neurons originated in the cranial sensory placodes and the neural crest. Human embryos from Carnegie stages (CS) 10-17 (29-41 days post-conception) were obtained from the Human Developmental Biology Resource UK. We used a number of cell-specific and proliferative markers to reveal the phenotypic characteristics and migratory pathways of the first neurons in the cephalic ectoderm and mesenchyme. We developed a new approach to reconstruct cells in sections of the human ectoderm, diencephalon, cortical wall, and retina by rapid, high-resolution volume rendering of multichannel 3D confocal data sets from a Zeiss LSM 710 confocal microscope. The majority of precocious TU-20-positive ectodermal neurons appear to migrate tangentially within the ectoderm, and some delaminate from the epithelium to coalesce within the mecenhyme surrounding the rostral telencephalon. The fibers of the neurons in the oral ectoderm formed a dense network along the basement membrane adjacent to the ventral hypothalamus by CS13. Some neurons in the optic mesenchyma extended non-axonal processes through the prospective pigment epithelium into the neural retina. Others invade the presumptive cortical wall, perhaps providing additional signalling information to the local stem cell niche. Pioneer olfactory neurons constitute a distinct migratory population at CS 13-14. Their processes penetrate the cerebral wall by CS17. Thus the human cephalic epithelium adjacent to the forebrain contain hitherto unrecognized stem cell niches generating the first migratory neurons.
Supported by NIH and The Zvi and Ofra Meitar Family Fund

Disclosures: I. Bystron: None.

Poster

639. Neuronal Differentiation

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 639.23/A23

Topic: A.01. Neurogenesis and Gliogenesis

Title: The generation of the mystery cells of the male depends on HLH-3 function in C.elegans

Authors: *L. PEREZ, L. MARQUEZ, Z. IBRAHIM, A. ALFONSO;
Univ. of Illinois at Chicago, Chicago, IL

Abstract: The Mystery Cells of the Male (MCMs) are a newly discovered pair of neurons derived from a pair of glia in *C. elegans*. The generation of these sex-specific neurons in *C. elegans* is remarkable because it is the first documented case in which a non-epithelial cell, nor blast cell, gives rise to a neuron, and is a sexually dimorphic event occurring during L4 lethargus development. Functionally this pair of neurons integrate environmental cues to promote mating with hermaphrodites, or sexual conditioning. Our laboratory has data to suggest that *hlh-3*, which encodes a bHLH Class II proneural-like protein, has a role in the terminal differentiation of sex-specific neurons, including all sex-specific neurons of the hermaphrodites, HSNs and VCs, and a set of male specific neurons, CEMs. Since the ventral pair of CEMs are sister cells of the amphid socket glia and cousins to the MCMs, and we know that the differentiation of ventral CEMs is most affected, it seemed logical to address whether there is any defect in the generation and differentiation of the MCMs. Our analysis on markers for both MCMs and the amphid socket glia reveal abnormalities in the position and quantity of each cell type between wild type males and *hlh-3(lf*) males. Overall, we find that *hlh-3* has a role in the generation and differentiation of MCMs and that MCM-mediated male mating behavior is also compromised.

Disclosures: L. Perez: None. **L. Marquez:** None. **Z. Ibrahim:** None. **A. Alfonso:** None.

Poster

639. Neuronal Differentiation

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 639.24/A24

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant ES027822

Title: Effects of the organophosphorus insecticide chlorpyrifos on neuronal differentiation of the SH-SY5Y cell line: Involvement of cannabinoid type 1 receptors

Authors: S. W. TODD[1], E. W. LUMSDEN[1], W. R. RANDALL[2], B. K. KRUEGER[3], E. X. ALBUQUERQUE[1], ***E. F. R. PEREIRA**[1];
[1]Div. of Translational Toxicology, Dept. Epidemiology and Publ. Hlth., [2]Pharmacol., [3]Physiol., Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: The acute toxicity of the organophosphorus insecticide chlorpyrifos (CPF) results primarily from the irreversible inhibition of acetylcholinesterase (AChE). However, via mechanisms that remain poorly understood, developmental exposures to CPF levels insufficient to inhibit AChE have been associated with neurological deficits in children and animal models. This study was designed to test the hypothesis that, acting via AChE-independent mechanisms, CPF disrupts neuronal differentiation, a process that shapes the nervous system structurally and functionally from the earliest stages of embryogenesis through adulthood. To address this hypothesis, SH-SY5Y cells, a neuronal cell line used to study neuronal differentiation *in vitro*, were exposed to CPF (0.3-100 μM) for 24 h or 7 days. To minimize experimental bias and maximize rigor, we use a randomized, blind design. Each assay was done in triplicate using 3 independent cultures. Two- or three-way ANOVA followed by Tukey post-hoc test was used to statistically analyze the data. Following 24-h exposure to CPF concentrations that caused significant AChE inhibition (≥30 μM), cell viability was significantly reduced. On the other hand, following 7-day exposure to CPF concentrations that caused no detectable inhibition of AChE (1-3 μM), there was a significant reduction in the expression of nestin, a marker of neuroprogenitor cells, and a significant increase in the expression of NeuN, a marker of mature neurons. When examined by immunofluorescence, cultures exposed to these low concentrations of CPF exhibited a lower percentage of $NeuN^{-}nestin^{+}$ cells and a higher percentage of $NeuN^{+}nestin^{-}$ cells than did cultures exposed to vehicle. Since previous studies reported that CPF can interact with components of the endocannabinoid system (rev. in J Neurochem 142:162, 2017), experiments were then carried out to determine whether the effects of CPF on neuronal differentiation were mediated by cannabinoid receptor type 1 receptors (CB1Rs). In cultures that were co-treated with CPF and the CB1R antagonist AM4113, NeuN and nestin expression levels were comparable to control. CPF increased phosphorylation of a number of mitogen-activated protein kinases, including p38 - a downstream signaling pathway linked to CB1Rs. In the presence of the p38 inhibitor SB203580, CPF had no effect on nestin expression or on the percentage of $NeuN^{-}Nestin^{+}$ cells. This is the first demonstration that, acting at least in part via CB1Rs and p38, CPF induces neuronal differentiation. These findings provide a framework for future studies to determine how disruption of neurogenesis contributes to the developmental neurotoxicity of CPF.

Disclosures: S.W. Todd: None. **E.W. Lumsden:** None. **W.R. Randall:** None. **B.K. Krueger:** None. **E.X. Albuquerque:** None. **E.F.R. Pereira:** None.

Poster

639. Neuronal Differentiation

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 639.25/A25

Topic: A.01. Neurogenesis and Gliogenesis

Title: Differentiation character of HT22 cell line

Authors: *A. BATU ÖZTÜRK[1], D. YETKIN[2], N. C. ÖZTÜRK[3];
[1]Histology and Embryology, Mersin University, Hlth. Sci. Inst., Mersin University, Turkey; [2]Mersin University,Health Sci. Insitute, Mersin, Turkey; [3]Anat., Mersin University, Sch. of Med., Mersin, Turkey

Abstract: .

Disclosures: A. Batu Öztürk: None. **D. Yetkin:** None. **N.C. Öztürk:** None.

Poster

639. Neuronal Differentiation

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 639.26/A26

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant ES027822

Title: *In vitro* modeling of the disruptive effects of the organophosphorus insecticide chlorpyrifos on synaptic transmission in the developing hippocampus

Authors: *E. W. LUMSDEN, R. D. BURKE, E. X. ALBUQUERQUE, E. F. PEREIRA;
Div. of Translational Toxicology, Dept. of Epidemiology and Publ. Hlth., Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: The acute toxicity of the organophosphorus insecticide chlorpyrifos (CPF) results from the irreversible inhibition of acetylcholinesterase (AChE). However, prenatal exposures to levels of CPF that do not cause substantial AChE inhibition have been associated with neurodevelopmental disorders in children, particularly boys. Preclinical studies have also reported that developmental exposures of rodents to low levels of CPF result in sexually dimorphic learning and memory impairments (rev. in J Neurochem 142:162, 2017). Since similar

impairments can be caused by drugs that act as positive allosteric modulators of $GABA_A$ receptors, the first part of this study was designed to test the hypothesis that cognitive deficits observed in male guinea pigs prenatally exposed to subacute doses of CPF (25 mg/kg/day, gestation days 53 to 62) correlate with an increase of GABAergic transmission in hippocampal CA1 pyramidal neurons. Electrophysiological experiments revealed that the frequency of spontaneous inhibitory postsynaptic currents (IPSCs) was significantly higher in the CA1 pyramidal neurons of CPF- than vehicle-exposed male guinea pigs (n = 13 animals/group). This increase positively correlated with learning deficits the animals presented in the Morris Water maze and could not be accounted for by an increase in the number of interneurons. The second part of this study was designed to model *in vitro* the CPF-induced increase in GABAergic transmission observed *in vivo*. To this end, primary hippocampal cultures were exposed for 5-7 days to CPF (0.03-30 µM) or vehicle starting at different times after cells were plated. Seven days after the end of the exposures, synaptic activity was recorded from hippocampal neurons. A randomized, blind design was used to minimize experimental bias and maximize scientific rigor. Statistical analysis of the electrophysiological results considering treatment and cultures as independent factors revealed that the frequency of IPSCs was significantly increased in cultures that had been exposed to CPF at a time when neuroprogenitor cells (i.e., nestin-immunoreactive cells) prevailed in the system. Thus, this *in vitro* model becomes unique for studies aimed at identifying the mechanisms that underlie the developmental neurotoxicity of CPF.

Disclosures: E.W. Lumsden: None. **R.D. Burke:** None. **E.X. Albuquerque:** None. **E.F. Pereira:** None.

Poster

639. Neuronal Differentiation

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 639.27/A27

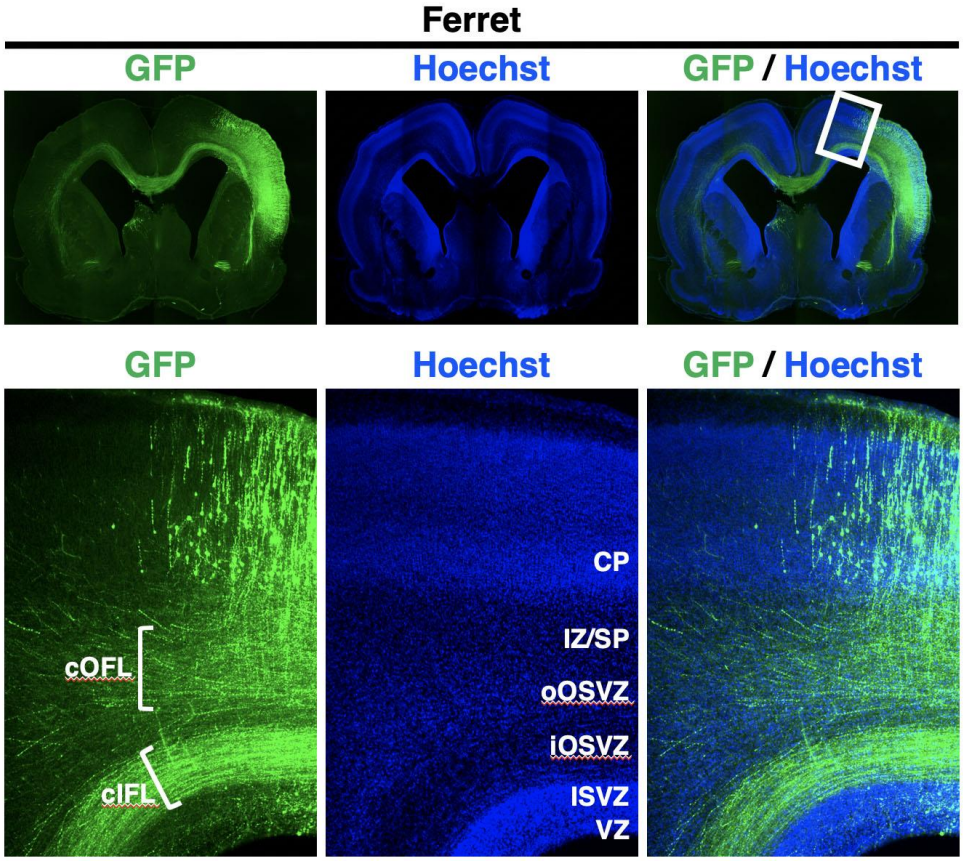
Topic: A.01. Neurogenesis and Gliogenesis

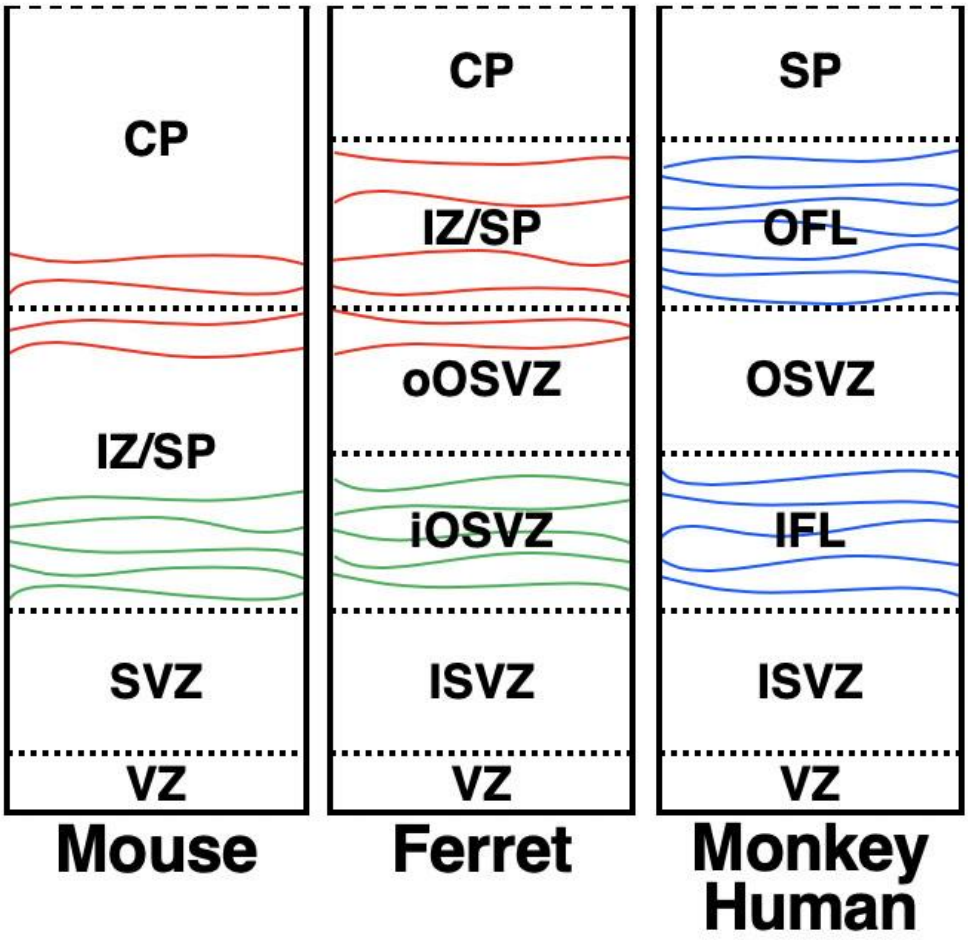
Support: Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology (MEXT)
Japan Agency for Medical Research and Development
Takeda Science Foundation
Mitsubishi Foundation
Daiichi Sankyo Foundation of Life Science
Kanazawa University SAKIGAKE project 2018
Kanazawa University CHOZEN project

Title: Characterization of fiber layers in the developing cerebral cortex of ferrets and mice

Authors: *K. SAITO, K. MIZUGUCHI, T. HORIIKE, T. A. DINH DUONG, Y. SHINMYO, H. KAWASAKI;
Dept. of Med. Neuroscience, Grad. Sch. of Med. Sci., Kanazawa Univ., Ishikawa, Japan

Abstract: Changes in the cerebral cortex of mammals during evolution have been of great interest. Ferrets, monkeys, and humans have more developed cerebral cortices compared with mice. Although the features of progenitors in the developing cortices of these animals have been intensively investigated, those of the fiber layers are still largely elusive. By taking the advantage of our in utero electroporation technique for ferrets, here we systematically investigated the cellular origins and projection patterns of axonal fibers in the developing ferret cortex. We found that ferrets have 2 fiber layers in the developing cerebral cortex, as is the case in monkeys and humans. Axonal fibers in the inner fiber layer projected contralaterally and subcortically, whereas those in the outer fiber layer sent axons to neighboring cortical areas. Furthermore, we performed similar experiments using mice and found unexpected similarities between ferrets and mice. Our results shed light on the cellular origins, the projection patterns, the developmental processes, and the evolution of fiber layers in mammalian brains.





Disclosures: **K. Saito:** None. **K. Mizuguchi:** None. **T. Horiike:** None. **T.A. Dinh Duong:** None. **Y. Shinmyo:** None. **H. Kawasaki:** None.

Poster

639. Neuronal Differentiation

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 639.28/A28

Topic: A.04. Transplantation and Regeneration

Support: NIH Grant R01NS097511-01

Title: Nanodendrimer-n-acetylcysteine enhances survival and *in vivo* migration of transplanted allogeneic glial restricted precursor cells

Authors: *S. N. TOMLINSON[1], C. L. NEMETH[1,2], M. ROSEN[1], A. WOLFE[1], A. SHARMA[3], R. SHARMA[3], M. V. JOHNSTON[1,2], R. M. KANNAN[3], S. KANNAN[4,2,3], A. FATEMI[2,1]; [1]Hugo W. Moser Res. Inst. at Kennedy Krieger, Kennedy Krieger Inst., Baltimore, MD; [2]Neurol., [3]Ctr. for Nanomedicine at the Wilmer Eye Inst., Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [4]Anesthesiol. and Critical Care Med., Johns Hopkins Univ., Baltimore, MD

Abstract: Oligodendrocyte replacement is a promising avenue for the use of glial restricted precursor cells (GRPs); however, limited cell survival reduces integration and functional recovery. Nanotherapeutic approaches can facilitate stem cell delivery while concurrently delivering factors aimed at enhancing and nourishing stem cells en route to, and at, the target site. Here, survival and migration of GRPs was assessed in a mouse model of neonatal white matter injury with different methods of G4 PAMAM dendrimer nanoparticle support. GRPs isolated from embryonic day 13.5 mice expressing eGFP were purified by A2B5 selection. Three groups of preterm equivalent (post-natal day; P5) CD-1 mice underwent right common carotid artery ligations followed by 1) a vehicle injection at P10 and an intracallosal (IC) injection of 100,000 GFP-expressing GRPs at P22; 2) a single dose of dendrimer conjugated to the antioxidant/anti-inflammatory N-acetylcysteine (D-NAC; 10 mg/kg, intraperitoneal) at P10, followed by IC GFP-GRP at P22; or 3) a vehicle injection at P10 and IC GFP-GRPs pretreated for 12h with D-NAC at P22. At 8 weeks post-transplant, GRPs were detected in 82% of mice receiving GRPs alone, 94% of mice receiving D-NAC at P10 and GRPs, and 100% of mice receiving D-NAC pretreated GRPs. Migratory capacity improved as GRPs from P10 D-NAC treated mice traveled 25% farther than untreated mice while D-NAC pretreated GRPs traveled a 75% greater distance. GRPs were also more likely to differentiate *in vivo* when combined with D-NAC. To interrogate the area of these combinatorial effects, injured animals were treated with GRPs with a fluorescent dendrimer given as a cell pre-treatment or intraperitoneally. At one-week post-transplant, intraperitoneally injected dendrimer colocalized at sites of injury, while dendrimer was detected outside pre-treated GRPs suggesting the potential for combination therapies to enhance the environment surrounding injury independent of administration route. These studies demonstrate that D-NAC nanoparticles enhance transplanted progenitor cell survival and migration, and suggest that such combinatorial therapies may allow long term engraftment without overt use of immunosuppression.

Disclosures: S.N. Tomlinson: None. **C.L. Nemeth:** None. **M. Rosen:** None. **A. Wolfe:** None. **A. Sharma:** None. **R. Sharma:** None. **M.V. Johnston:** None. **R.M. Kannan:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Own patents and is a cofounder of a company related to this technology (Ashvattha Therapeutics LLC and Orpheris Inc). **S. Kannan:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Own patents and is a cofounder of a company related to this technology (Ashvattha Therapeutics LLC and Orpheris Inc). **A. Fatemi:** 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 to Calico Labs. F. Consulting

Fees (e.g., advisory boards); Safety monitoring board for Bluebird Bio and Stealth Biotherapeutics.

Poster

639. Neuronal Differentiation

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 639.29/A29

Topic: A.08. Development of Motor/ Sensory/ and Limbic Systems

Support: Travis Roy Foundation
Swiss National Science Foundation

Title: Growth cone molecular machinery in development vs. regeneration: Subcellular transcriptome mapping in corticospinal neurons

Authors: *A. K. ENGMANN, J. HATCH, J. KIM, C. WINTER, J. D. MACKLIS;
Dept of Stem Cell and Regenerative Biology, and Ctr. for Brain Sci., Harvard Univ., Cambridge, MA

Abstract: Neurons of the central nervous system (CNS) grow axons over long distances during development, generating exquisitely precise functional circuitry. The same neurons, however, fail to regenerate following injury. Despite current knowledge about factors that prevent regeneration, including inhibitory extrinsic cues and failure to activate intrinsic growth machinery, no causal treatment exists for traumatic injuries to the CNS.
Neurons are uniquely polarized cells with extreme spatial expanse. In development and regeneration, growth cones (GCs) are the subcellular units effecting axonal growth, guidance, and circuit assembly. Until very recently, molecular states of GCs *in vivo* were experimentally not accessible. New experimental and analytic approaches developed recently in our lab enable direct access to the molecular machinery of subtype- and stage-specific GCs directly from the mouse brain. We combine specific labeling, biophysical fractionation, and newly developed fluorescent small particle sorting to purify GCs of interest. The application of this quantitative 'subcellular RNA-proteome mapping' approach to callosal projection neurons of the developing mouse cortex identified hundreds of GC-enriched RNAs/proteins [Poulopoulos *et al.*, Nature 2019].
Subcerebral projection neurons send their axons over remarkably long distances to the midbrain, brainstem and spinal cord, and play key roles in several clinical conditions. Insight into their local GC- and soma-specific transcriptomes would not only be informative but also highly translationally relevant. Due to their limited number, however, they have so far not been accessible to subcellular molecular mapping. Recent technological advancement now enables nearly full-depth RNA sequencing from as little as 100,000 GCs, collected not only in a subtype-specific manner, but also with spatial resolution across a variety of developmental stages. This

facilitates deep investigation of the molecular machinery of corticospinal GCs and somata *in vivo*. We are currently investigating the molecular states of corticospinal GCs across distinct developmental stages, generating deep data about the local changes in proteome and transcriptome that enable precise navigation of GCs all the way from the cortex caudally to the spinal cord. Additionally, we are expanding this work to regenerative GCs following spinal cord injury, aiming to identify similarities and differences between the local molecular controls of developing (growth-permissive) and regenerating (growth-abortive) corticospinal GCs.

Disclosures: A.K. Engmann: None. **J. Hatch:** None. **J. Kim:** None. **C. Winter:** None. **J.D. Macklis:** None.

Poster

640. Stem Cell Reprogramming and Screening In Vitro

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 640.01/A30

Topic: A.03. Stem Cells and Reprogramming

Title: Rat adipose stem cells: Relevance of VEGF signalling for pain relief

Authors: *A. VONA, L. DI CESARE MANNELLI, L. MICHELI, C. GHELARDINI, P. FAILLI;
Univ. of Florence, Firenze, Italy

Abstract: In oxaliplatin-induced neuropathy, vascular endothelial growth factor (VEGF) was increased in plasma. VEGF antibodies and adult rat adipose stem cells (RASCs) administration reduced neuropathic pain (Di Cesare Mannelli - Neuropharmacology, 2017). Therefore, we decided to investigate: 1) the presence of VEGF receptors (VEGFRs), 2) the intracellular signal induced by VEGF in RASCs and in "*in vitro"* neuron-like cells differentiated from RASCs.
Methods: RASCs were isolated from retrosternal fat and used at passages P1-P4. Rat endothelial cells (RCE) acted as positive control. Western blot was performed in cell homogenates. Intracellular calcium dynamic was measured using FURA-2 imaging analysis. RASCs were transformed in neuron-like cells by incubating with growth factors.
Results: 1) in RASCs and RCE the VEGFR1 was well expressed in control condition. One hour after $VEGF_{165b}$ administration (1ng/ml), VEGFR1 and trunked form of VEGFR1 (sFlt1) expression decreased in RASCs.
2) VEGF (100ng/ml) induced a small increase in intracellular calcium in RASCs and RCEs, whereas ATP induced a vigorous, oscillatory calcium signal in both cell lines. The rise of the intracellular calcium induce by VEGF was somehow slow and not synchronized in all analysed cells. Responsive cells were almost at the culture serial passage P2 (40%).
On the contrary, the rise of intracellular calcium induced by ATP was rapid and the maximum was synchronised in all cells. Moreover, ATP was very effective in RASCs at P2-P3 (76% - 81%

respectively) whereas P1 cells were less responders (8%).
RASCs can differentiate in neuron-like cells under special culture condition. Differentiated cells showed DCX and Tuj-1 positivity and GFAP negativity. Neuron-like cells presented electrically-evoked Ca^{2+} transients upon 0.1 Hz field stimulation, 100 mV voltage and 50 ms width duration in control solution. The dynamic of cytosolic Ca^{2+} increase presented Ca^{2+} transient characterized by very rapid, steeply increase and a slow return to basal Ca^{2+} levels.
Conclusion: VEGFR1 is well expressed RASCs and it stimulation can induce sFlt1 release as suggested by the decrease in soluble receptor content.
The small increase in intracellular calcium induced by VEGF suggests VEGF receptors are actively linked to intracellular calcium movement. Experiments are in progress to characterized other intracellular signaling responsible to the anti-neuropathic effect of RASCs in oxaliplatin induced pain.
Studies are in progress to better understand ionic channels at the basis of calcium transient measured in neuron-like cells and the therapeutic application of differentiated cells in different type of neuropathic pain.

Disclosures: A. Vona: None. **L. Di Cesare Mannelli:** None. **L. Micheli:** None. **C. Ghelardini:** None. **P. Failli:** None.

Poster

640. Stem Cell Reprogramming and Screening In Vitro

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 640.02/A31

Topic: A.03. Stem Cells and Reprogramming

Support: H2020-MSCA-ITN-2016, Grant Agreement No. 722779

Title: Light-induced inhibition of human primary neurons by human stem cell-derived GABAergic neurons *in vitro*

Authors: *A. GONZALEZ-RAMOS, E. WALOSCHKOVA, M. LEDRI, M. ANDERSSON, M. KOKAIA;
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Abstract: Gamma-aminobutyric acid (GABA)-releasing interneurons are responsible for the modulation of neuronal network activities in the brain by inhibiting other neurons. The alteration or absence of these cells disrupts the balance between the excitatory and inhibitory processes in the neuronal networks, leading to neurological disorders such as epilepsy. In this regard, a cell replacement-based therapy may be an alternative therapeutic approach, in particular for those epilepsy cases that currently lack effective treatment. To address this issue, a single-step method was used to generate a highly-enriched population of functional GABAergic interneurons from

human embryonic stem cells (hESCs). Using lentiviral vectors, we induced the expression of the transcription factors Ascl1 and Dlx2, that are key factors for this lineage determination. In addition, the cells were transduced by another lentiviral vector with channelrhodopsin-2 (ChR2) gene. After 35 days *in vitro* (DIV), hESC-derived GABAergic neurons showed mature electrophysiological properties and spontaneous synaptic currents that could be enhanced using 460 nm blue light to activate ChR2. We then co-cultured these cells at 14 DIV with human primary neurons to investigate whether these cells received functional afferent synapses. Thereby, we could test if the activity of the cultured primary neurons was inhibited by using blue light, which would indicate that hESC-derived GABAergic neurons do integrate into the neuronal network. This study opens the possibility to develop a new potential treatment by means of the transplantation of these inhibitory cells to obtain a precise temporal control of the neuronal network excitability in diseases like epilepsy.

Disclosures: A. Gonzalez-Ramos: None. **E. Waloschkova:** None. **M. Ledri:** None. **M. Andersson:** None. **M. Kokaia:** None.

Poster

640. Stem Cell Reprogramming and Screening In Vitro

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 640.03/A32

Topic: A.03. Stem Cells and Reprogramming

Support: R01AA024659

Title: A novel pseudogene-encoded long noncoding RNA mediates fetal alcohol effects

Authors: *N. A. SALEM[1,2], A. M. TSENG[1], A. H. MAHNKE[1], C. GARCIA[1], H. JAHROMI[1], R. C. MIRANDA[1,2];
[1]Neurosci. and Exptl. Therapeut., Texas A&M Hlth. Sci. Ctr., Bryan, TX; [2]Texas A&M Inst. for Neurosci., College Station, TX

Abstract: Prenatal alcohol exposure is a leading cause of neurodevelopmental disability. We previously found that ethanol exposure caused a loss of neural stem cells (NSCs) due to premature maturation. We asked whether ethanol could inhibit NSC self-renewal capacity, as an explanation for their ethanol-induced depletion. We assessed the regulation of the homeobox transcription factor, Oct4/POU5F1, which is important for maintaining stem cell renewal. Ethanol treatment resulted in a dose-related decrease in Oct4/Pou5f1 protein in NSCs. The Oct4 family includes a number of transcribed pseudogenes. Only one member of the murine Oct4 pseudogene family is expressed in NSCs as a long non coding-RNA lncRNA (Oct4pg9). We assessed Oct4pg9 lncRNA expression in neurospheres, along with mRNA transcripts for Oct4 and associated stem cell fate markers. We report that Oct4pg9 is expressed in NSCs at

significantly higher levels than the parent Oct4 mRNA transcript, its expression in the nucleus is ten-fold higher than in the cytoplasm. Ethanol exposure resulted in a dose-related increase in Oct4pg9 lncRNA expression. Oct4pg9 overexpression resulted in increased GLAST, DCX, NeuN and GFAP transcripts. This effect was mimicked by ethanol exposure. In contrast, Oct4pg9 knockdown results in elevated Oct4, and REST mRNA transcripts, but downregulation of DCX mRNA. These data suggest that ethanol-mediated elevation of Oct4pg9 shifts NSCs towards a neuronal/oligodendrocytic fate. Oct4pg9 overexpression decreased Oct4 3'UTR-controlled luciferase expression indicating that Oct4pg9 influences translation regulation at the Oct4 3'UTR. Our data show that Oct4pg9 associates with the miRNA chaperone, Ago2 and that capture of native Oct4pg9 resulted in preferential recovery of three miRNAs, miR-328-3p, miR-744-5p and miR-642a-5p suggesting that Oct4pg9 is a miRNA sponge. Overexpression of Oct4pg9 resulted in decreased expression of miR-328 (effect size= -0.93), an identified suppressor of tumor cell proliferation. Oct4pg9 overexpression and ethanol exposure may both increase cell proliferation in part by sequestering miR-328. Our results suggest that a novel lncRNA may regulate NSC renewal and mediate some of the teratogenic effects of ethanol through translation-regulatory mechanisms.

Disclosures: **N.A. Salem:** None. **A.M. Tseng:** None. **A.H. Mahnke:** None. **C. Garcia:** None. **H. Jahromi:** None. **R.C. Miranda:** None.

Poster

640. Stem Cell Reprogramming and Screening In Vitro

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 640.04/A33

Topic: A.03. Stem Cells and Reprogramming

Support: NIH Grant R24AI120942
NIH Grant R21AI129509-01
IHII Pilot Grant
John S. Dunn Foundation
The World Reference Center for Emerging Viruses and Arboviruses

Title: Activation of innate immune responses inhibits neurogenesis

Authors: *P. XU[1], J. GAO[1], C. SHAN[2], X. XIE[2], T. DUNN[1], N. VASILAKIS[3], P. SHI[2], S. WEAVER[4], P. WU[1];
[1]Dept. of Neuroscience, Cell Biol. & Anat., [2]Dept. of Biochem. & Mol. Biol., [3]Dept. of Pathology, [4]Dept. of Microbiology, Inst. for Human Infections and Immunity, Univ. of Texas Med. Barnch, Galveston, TX

Abstract: Objective: Globally Zika virus (ZIKV) outbreaks and their strong link to microcephaly have raised public health concerns. Studies have shown that ZIKV disrupts neural progenitor development, leading to microcephaly in mice. In human cerebral organoids, ZIKV depletes neural progenitors through activation the innate immune receptor Toll-like-Receptor 3 (TLR3). Using human neural stem/progenitor cell (hNS/PC) lines, our lab has reported that ZIKV inhibits neuronal differentiation in a cell-strain-dependent manner, which is well correlated with the alteration of global gene expression patterns, including the innate immune pathways. Nevertheless, how these immune factors affect neurogenesis is largely unknown. In this project, we sought to determine the role of innate immune genes/pathways in the hNS/PC line-dependent reduction of neurogenesis after TLR3 activation. Methods: Three hNS/PC lines were treated by ZIKV (PRVABC59) or TLR3 agonist poly(I:C) at the proliferating, priming or early differentiating stage. The mRNA levels of genes in the TLR3/IFN/MHC pathway and neurogenesis transcription factors were measured by qRT-PCR. The protein levels of pSTAT1, STAT1 and Beta-2-Microglobulin (B2M) were measured by Western blot. Newly differentiated neurons and astrocytes were detected by several makers through immunostaining. Results: Poly(I:C) robustly induced genes transcription in the TLR3/IFN/MHC pathway (TLR3, IRF7, IRF3, STAT1 and B2M) in K048 and K054 hNS/PC lines, but in G010 hNS/PC line only marginally. Moreover, these genes were transcribed in a stage-dependent manner, as they were only activated when Poly(I:C) was used in the priming and differentiating stages, but not in the proliferating stage. Correspondingly, the K048 and K054 showed a significant reduction in newly differentiated neurons, especially in the priming stage, whereas the G010 was not affected at any stage. Similarly, ZIKV (PRVABC59) robustly promoted genes transcription in the TLR3/IFN/MHC pathways in hNS/PCs, and this alternation was observed in both the proliferating and priming stages. Conclusion: TLR3 activation in neural stem cells induces innate immune responses and impairs neurogenesis in a cell-strain-dependent and a time-dependent manner.

Disclosures: P. Xu: None. **J. Gao:** None. **C. Shan:** None. **X. Xie:** None. **T. Dunn:** None. **N. Vasilakis:** None. **P. Shi:** None. **S. Weaver:** None. **P. Wu:** None.

Poster

640. Stem Cell Reprogramming and Screening In Vitro

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 640.05/DP01/A34

ControlExtraData.DynamicPosterDisplay:
Dynamic Poster
Topic: A.03. Stem Cells and Reprogramming

Title: Studying functional neurogenic plasticity from genes to spikes on a-multiscale-CMOS-chip

Authors: *H. AMIN[1], G. KEMPERMANN[1,2];
[1]German Ctr. for Neurodegenerative Dis. (DZNE), Dresden, Germany; [2]Ctr. for Regenerative Therapies Dresden (CRTD), Technische Univ. Dresden, Dresden, Germany

Abstract: Adult neurogenesis provides a continuous influx of new neurons to invigorate the brain's plasticity to adapt and change with experience. These newly-generated cells add unique properties to existing networks and contribute to particular computational functionalities of memory formation and learning process. Neuronal activity regulates genes controlling neuronal development and plastic modifications within mature networks. However, the interplay of molecular mechanisms supporting electrophysiological functions remains undefined. We report here that increasing in synaptic input conferred by heightened network-wide firing activity induces immediate-early genes (*NPAS4*, *Fos*, and *Egr1*) responses in newly neurons integrated into a resident network. We implemented a human-based on-a-chip system combined with quantitative real-time polymerase chain reaction, calcium imaging to systematically decipher the multiscale functional and molecular role of newly-generated neurons in resident networks. Indeed, this functional plasticity coordinated gene expression program is significant to experience-driven synaptic changes associated with information processing thus has implications for healthy aging and neurodegeneration.

Disclosures: H. Amin: None. **G. Kempermann:** None.

Poster

640. Stem Cell Reprogramming and Screening In Vitro

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 640.06/A35

Topic: A.03. Stem Cells and Reprogramming

Support: ERC grant 771427
wedish Research Council Consolidator Grant (2017-2022): 2016-00873
European Union Horizon2020 Marie Sklodowska Curie676408

Title: Identification and characterisation of authentic dopaminergic neurons at single cell resolution in human ventral midbrain patterned organoids

Authors: *M. BIRTELE, A. FIORENZANO, Y. SHARMA, J. NELANDER, B. MATTSSON, M. P. PARMAR;
Lund Univ., Lund, Sweden

Abstract: Parkinson's disease (PD), one of the most common neurodegenerative disorders, is characterized by a progressive loss of dopamine (DA) neurons in the ventral midbrain (VM). The inability of two-dimensional (2D) *in vitro* cultures to recapitulate the complexity of the

architecture and cell composition has made the study of human VM challenging. Despite intensive research efforts, the molecular mechanisms controlling both the development and functional maturation of DA neuron subtypes remains largely unknown.In this study, we designed a new method for expanding and differentiating human fetal cells dissociated from the VM of 7-9 weeks old human embryos. We developed athree-dimensional (3D) organoid culture system with the aim to better preserve authentic and functional DA neurons *in vitro*. Using fetal-derived organoids as valuable reference, we also conducted a comparison between fetal-derived and human embryonic stem cell(hESC)-derived VM organoids.Using single cell RNA sequencing (scRNA-seq) we compared human fetal cells from 2D and 3D *in vitro* culture systems. Despite the analysis showing that both cell preparations initially gave rise the same culture composition, the 2D system promoted proliferation of glial and oligodendrocyte progenitors, with limited surviving neuronal populations. On the contrary, 3D organoids could sustain the maturation of the neuronal population, and importantly maintained the dopaminergic neuronal compartment.Intriguingly, we have also found clear differences between fetal and hESC-derived organoids at the single cell resolution. While both cell preparations gave rise to neurons, we found that astrocytes and oligodendrocytes were detected only in fetal organoids whereas a barrier forming fibroblast-like cell type normally present in the brain was identified as a unique component of hES-derived organoids during late stage differentiation.Taken together these results represent an important step in characterizing both fetal derived- and hESC-derived authentic dopaminergic neurons through the use of novel 3D-culture conditions which better recapitulates the features of human ventral midbrain.

Disclosures: **M. Birtele:** 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.; BrainMatTrain-EU MarieCurie funding. **A. Fiorenzano:** None. **Y. Sharma:** None. **J. Nelander:** None. **B. Mattsson:** None. **M.P. Parmar:** 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.; Swedish Research Council Consolidator Grant (2017-2022): 2016-00873. New York Stem Cell Foundation Robertson Fellow (NYSCF). ERC grant 771427. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); M.P. is the owner of Parmar Cells AB and co-inventor of the US patent application 15/093,927 owned by Biolamina AB, and EP17181588 owned by Miltenyi Biotec.

Poster

640. Stem Cell Reprogramming and Screening In Vitro

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 640.07/A36

Topic: A.03. Stem Cells and Reprogramming

Support: NIH Grant AA024659

Title: Sex differences in ethanol's effects on fetal neural stem and progenitor cells

Authors: *A. H. MAHNKE, H. M. AL-MUHISEN, A. M. TSENG, N. A. SALEM, R. C. MIRANDA;
Texas A&M Univ. Hlth. Sci. Ctr., Bryan, TX

Abstract: Prenatal alcohol exposure can result in growth and neurodevelopmental deficits, collectively termed 'Fetal Alcohol Spectrum Disorders'. We have found that ethanol reprograms neural stem and progenitor cells to favor premature maturation and decrease self-renewal. Recent evidence has shown that genetic sex is an important determinant gene expression and lineage progression in the adult ventricular-subventricular zone. Here, we investigated sex differences in the developing neural stem cell niche *ex vivo*, using neurosphere cultures derived from murine dorsal neuroepithelium at GD 12.5. Separate suspension cultures were prepared from male and female tissue samples based on the qPCR assessment of the presence of the Y Chromosome (YMT region). Female neurospheres were more stem-like than male neurospheres, with higher rates of secondary neurosphere formation. In contrast, male neurospheres showed fewer secondary neurospheres but with a higher number of viable cells. This increased cell number in males is associated with a larger proportion of cells in mitotic S-phase and higher rates of DNA synthesis, indicating that male neurospheres were enriched for more lineage committed, transit amplifying-like populations. Sex-segregated neurospheres were exposed to ethanol for 5 days and were assessed for the expression of markers of neural stem cells and differentiation lineages using qPCR. Control male and female neurospheres had similar levels of stem cell and differentiation markers, with the exception of progenitor/gliogenic GFAP mRNA which was higher in the male neurospheres. Ethanol exposure at low doses (60 mg/dL) affected mRNA transcript levels only in female neurospheres, which had increased mRNA expression of stem/progenitor marker nestin mRNA and decreased expression of neurogenic and gliogenic transcripts. Ethanol exposure at chronic alcohol use levels (320 mg/dL) decreased neural, astrocytic, and oligodendrocytic markers in male neurospheres while the female neurospheres exhibited a moderate reduction in oligodendrocytic markers. Preliminary analysis of RNAseq data indicates a monotonic relationship between the number of transcripts altered at a large effect size and ethanol dose. These data provide evidence of sex differences in neural stem and progenitor cell dynamics in the developing cortex. Ethanol exposure alters the neurosphere transcriptome and further work will elucidate the contribution of sex to these ethanol-induced alterations. More research is needed to understand how these interactions between sex and alcohol shape cortical development and neurobehavioral deficits following prenatal alcohol exposure.

Disclosures: A.H. Mahnke: None. **H.M. Al-Muhisen:** None. **A.M. Tseng:** None. **N.A. Salem:** None. **R.C. Miranda:** None.

Poster

640. Stem Cell Reprogramming and Screening In Vitro

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 640.08/A37

Topic: A.03. Stem Cells and Reprogramming

Support: R01AA024659
R01HD086765

Title: Alcohol effects on the proteome of fetal neural stem cell-derived extracellular vesicles

Authors: *D. CHUNG[1], A. TSENG[1], M. PINSON[1], L. DANGOTT[2], S. WEINTRAUB[3], R. C. MIRANDA[4];
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Abstract: Prenatal alcohol exposure can result in craniofacial abnormalities, growth deficits, and is the leading cause of neurodevelopment disability worldwide. Neural stem cells (NSCs) are particularly vulnerable to alcohol (ethanol) exposure during the late first through the second trimester, when they are most extensively involved in neurogenesis. NSCs reside in a complex microenvironment rich in extracellular vesicles (EVs), which are shown to traffic protein, lipid, and RNA cargo between cells, that can serve as a mode of intercellular communication. Using fetal mouse derived cortical neuroepithelium, cultured ex-vivo as non-adherent neurosphere cultures, we previously found that ethanol exposure resulted in significant alterations of miRNA cargo in EVs.
To further assess the extent to which ethanol influenced the EV cargo, we investigated the impact of genetic sex on the proteome of EVs secreted by NSCs. EVs were isolated by ultracentrifugation from basal and ethanol-treated male and female derived NSCs, maintained as neurosphere cultures, and their proteome was assessed by liquid chromatography-tandem mass spectrometry (LC-MS/MS). Sample data were analyzed using Mascot (Matrix Science, London, UK; version 2.6.0). Scaffold (version 4.8.5, Proteome Software Inc., Portland, OR) was used to validate MS/MS based peptide and protein identifications. From our EV samples, we found over 2700 total proteins, with about 1400 proteins being represented in all the samples. For the top 25% most abundant proteins on the ratio intensity plot, the majority of proteins are within the 2-fold protein ratio of female to male. The top 100 most abundant proteins were expressed at similar levels across all samples. However, a number of proteins were expressed uniquely in male or female-derived EVs, suggesting that there may be sex-specific control over the behavior of the neurogenic niche during early fetal development. Through gene enrichment analysis, we found that our EV proteins were enriched for genes that are used for cell-cell recognition, protein

translation and transport. Based on my preliminary proteomic analysis, I also identified several RNA binding proteins (RBPs) in EVs secreted from NSCs. A number of these RBPs (e.g., HSP90AB1, HSPA8, HSP1A, and HSPD, Hsc70 and Hsp90) belong to the heat shock protein family that plays an important role in miRNA-mediated gene silencing. Consequently, our observation that ethanol elevated microRNA levels in NSC-derived EVs may be explained by alterations in miRNA binding RBPs, or alternately the miRNA binding capacity of RBPs, which are predicted to increase the loading of associated miRNAs.

Disclosures: D. Chung: None. **A. Tseng:** None. **M. Pinson:** None. **R.C. Miranda:** None. **L. Dangott:** None. **S. Weintraub:** None.

Poster

640. Stem Cell Reprogramming and Screening In Vitro

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 640.09/A38

Topic: A.03. Stem Cells and Reprogramming

Title: Effects of cocaine on an *in vitro* model of human pluripotent stem cell derived ventral midbrain neurons

Authors: *K. THANGAMANI[1], J. A. GOMEZ[1], C. HUTCHINSON[1], A. M. MAROOF[2]; [2]Dept. of Biol., [1]Univ. of Texas San Antonio, San Antonio, TX

Abstract: Addiction can be defined as a drug induced neural plasticity that leads to compulsive seeking of reward. To combat drug addiction effectively we must elucidate the cellular mechanisms that are involved upon exposure to drugs. Midbrain dopaminergic neurons are involved in acute and chronic responses to drugs. Even though this region has been studied in, much of what's been learned has not been studied in human counterparts. Therefore, the question arises, do human dopamine neurons express the pathophysiological phenotypes observed in rodent dopamine neurons when exposed to cocaine? To address this, I generated and isolated putative ventral midbrain neurons from human pluripotent stem cells (hPSCs). After characterizing these cells generated under defined differentiation conditions, I co-cultured them with primary glia to accelerate maturation of the derived neurons. After establishing stable conditions to accelerate maturation, I exposed these neurons to cocaine and determined these cell's spike rate is higher than saline treated . This model serves as a novel platform to study substance abuse in human neurons.

Disclosures: K. Thangamani: None. **J.A. Gomez:** None. **C. Hutchinson:** None. **A.M. Maroof:** None.

Poster

640. Stem Cell Reprogramming and Screening In Vitro

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 640.10/A39

Topic: A.03. Stem Cells and Reprogramming

Support: NSF GRFP
Utah Neuroscience Initiative
University of Utah
Slifka Foundation
Whitehall Foundation
Brain Foundation
NARSAD Foundation

Title: Diversity of inhibitory neurons and glial cells in human cortical organoids generated from stem cell-derived single neural rosettes

Authors: *L. A. BELL, Y. WANG, C. RUSSELL, Y. WU, C. ARMSTRONG, G. YANG, A. SHCHEGLOVITOV;
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Abstract: The neocortex is a highly complex brain structure with many human-specific features of development and function. Remarkably, this structure organizes from a pool of neuroepithelial cells organized in a tube-like structure called the neural tube. The cortex further develops to comprise a multitude of neural cell types including glutamatergic excitatory neurons and GABAergic inhibitory neurons together with a variety of glial and mural cell-types including astrocytes, oligodendrocytes, and pericytes. While excitatory neurons of the cortex arise from the dorsal pallium of the embryonic telencephalon, inhibitory neurons are traditionally thought to arise from the ventral subpallium and undergo migration to more dorsal areas. In order to study human corticogenesis, we have developed a system to generate 3D cortical organoids from a single neural rosette, a neural tube-like structure *in vitro.* Using a combination of single-cell RNA sequencing (scRNA-seq) and immunohistochemistry, we characterized the populations of cells in single rosette-derived cortical organoids (SRCOs) at different developmental stages (1 and 5 months post induction). We observed that 1-month-old SRCOs produce a variety of neural progenitors and both excitatory and inhibitory neurons. Using developmental trajectories, we identified the specific transcriptional programs that lead to the production of inhibitory neurons in SRCOs even in the absence of SHH agonists and Nkx2.1-expressing cells. After 4 months in culture, we find that SRCOs show maturation and radial organization of a variety of neural cell types including deep and superficial cortical excitatory neurons, a variety of inhibitory neurons, astrocytes, oligodendrocytes, and mural cells. Together, our results provide novel insights into

the molecular programs that are activated during different stages of human cortical development and could be disrupted in patients with developmental disorders.

Disclosures: **L.A. Bell:** None. **Y. Wang:** None. **C. Russell:** None. **Y. Wu:** None. **C. Armstrong:** None. **G. Yang:** None. **A. Shcheglovitov:** None.

Poster

640. Stem Cell Reprogramming and Screening In Vitro

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 640.11/A40

Topic: A.01. Neurogenesis and Gliogenesis

Support: Università della Campania Luigi Vanvitelli: Progetto VALERE, Vanvitelli per la ricerca

Title: Ruta graveolens stimulates neural plasticity of human and mouse embryonic mesencephalic neuronal cell progenitors

Authors: *G. CIMAGLIA, M. T. GENTILE, O. PASTORINO, L. COLUCCI-D'AMATO; DiSTABiF, Lab. of Mol. Neuropathology, Univ. of Campania "Luigi Vanvitelli", Caserta, Italy

Abstract: Neural stem cells (NSCs) proliferation and differentiation play a pivotal role in the generation of functional neuronal networks. However, NSCs as they develop and acquire the features of a mature neuronal phenotype progressively lose their ability to proliferate. Here we demonstrate that *Ruta graveolens* aqueous extract (*R. graveolens* a.e.), already shown to own selective activity on neural cells, it is capable to induce a pro-proliferative effect and to promote neural plasticity on neurons generated from two embryonic neuronal mesencephalic cell progenitors stem cell lines (mouse mes-c-myc A1 (A1) and its human counterpart ventral mesencephalic immortalized stem cell line). Both cell lines were exposed to *R. graveolens* a.e. treatment according to their experimental protocols. Both cell lines respond with an increase of neuronal cell number as shown by positivity to neuronal markers such as βIII tubulin and/or MAP-2. Even though the treated cells were fully differentiated they were still able to increase Ki67 a marker for active proliferation. Furthermore, morphologic analyses on A1 cells shown that *R. graveolens* a.e. besides enhancing the number of mature neurons also increased neurite outgrowth. Molecular analysis shows that *R. graveolens* a.e. treatment, induces expression of genes belonging to neural stem cell lineage such as rest/nrsf, nestin and light neurofilament. Therefore, we suggest that *R. graveolens* a.e. treatment might represent a powerful tool to both induce cell cycle re-entry of mature neurons and promote neural plasticity in pathological conditions were is lost.

Disclosures: **G. Cimaglia:** None. **M.T. Gentile:** None. **O. Pastorino:** None. **L. Colucci-D'Amato:** None.

Poster

640. Stem Cell Reprogramming and Screening In Vitro

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 640.12/A41

Topic: A.03. Stem Cells and Reprogramming

Support: NRF 2016R1A6A3A11936076
NRF 2018R1D1A1B07050883
CNU 2018-3498

Title: Micrornas and histone deacetylase inhibition mediated differentiation of human mesenchymal stem cells into neuronal lineage

Authors: ***S. JANG**[1,3], H.-S. JEONG[1,3], H.-H. CHO[2,3], S. PARK[1], J.-S. PARK[1,3], S.-H. PARK[1]; [1]Physiol., Chonnam Natl. Univ. Med. Sch., Hwasun-gun, Korea, Republic of; [2]Otolaryngology and Head and Neck Surgery, Chonnam Natl. Univ. Med. Sch., Gwangju, Korea, Republic of; [3]CNUH Biomed. Res. Inst., Gwangju, Korea, Republic of

Abstract: Histone deacetylase (HDAC) inhibitors play important roles in the cell homeostasis and cell cycle progression and have potentials to enhance self-renewal abilities and directed differentiation of stem cells. We previously identified a set of HDAC inhibitors can induce neurogenic differentiation of human adipose tissue-derived mesenchymal stem cells (MSCs) through canonical- and non-canonical Wnt signaling pathways. In the present study, we hypothesized that the HDAC inhibition-mediated neurogenic differentiation is regulated by the microRNAs (miRNAs) in human MSCs. By performing a miRNA-mRNA paired microarray screening, we identified and selected two candidates (miR-124 and miR-133b) among the most upregulated miRNAs after HDAC inhibitor treatment (MS275, sodium butyrate, trichostatin A, or valproic acid). After selection of the miRNAs, we investigated the ability of neurogenic differentiation of miRNAs in human MSCs by a quantitative PCR. The expressions of *TUJ1* and *MAP2* were highly increased following miRNAs treatment compared with control medium. In addition, the expression of most of the Wnt-related genes was highly increased following treatment of miRNAs. Further, the protein level of canonical- and non-canonical Wnt was upregulated after miRNAs treatment, based on western blot analysis. Using bioinformatics and functional assay, we confirmed that miR-124 and miR-133b potentially regulated Wnt signaling pathway. These findings suggest that the HDAC inhibitors enhance the neurogenic differentiation of human MSCs via the miR-124 and miR-133b and activate the neuronal gene expression and Wnt signaling pathway. In conclusion, we demonstrate a possible new

mechanism by which HDAC inhibition-induced miRNAs are required to regulate Wnt signaling and control neurogenic differentiation of human MSCs.

Disclosures: S. Jang: None. **H. Jeong:** None. **H. Cho:** None. **S. Park:** None. **J. Park:** None. **S. Park:** None.

Poster

640. Stem Cell Reprogramming and Screening In Vitro

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 640.13/A42

Topic: A.03. Stem Cells and Reprogramming

Title: Effects of CO1, an active compound from Chinese medicine, on modulating neural stem cells fate decision via mitochondrial metabolism

Authors: *Q. DU, R. DENG, C. GAO, J. SHEN;
The Univ. of HK, Hong Kong, Hong Kong

Abstract: Numerous researches demonstrate that mitochondria are central regulators of fate decision of neural stem cells (NSCs). NSC are regarded as a promising therapeutic approach to protecting and restoring damaged neurons in neurological disease. However, new research suggests that NSC reprograming is required to make this strategy effective. Here, we found one potential drug CO1, an active compound from Chinese Medicine, could modulate stem cell fate decision through mitochondrial metabolism. We tested the impact of CO1 on embryonic stem cell (ESC) proliferation and mitochondrial structural and function parameters, such as membrane potential and ATP synthesis, as well as oxidative stress indicators. The results indicated that CO1 dose-dependently increases ATP concentration, mitochondrial membrane potential, and ROS synthesis to inhibit the ESC proliferation and promotes it reprogramming into NSC. Therefore, we concluded that CO1 could efficiency develop ESC into NSC via mitochondrial activity promotion.

Disclosures: Q. Du: None. **R. Deng:** None. **C. Gao:** None. **J. Shen:** None.

Poster

641. Animal Models of Developmental Disorders

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 641.01/A43

Topic: A.07. Developmental Disorders

Support: KAKENHI JP (15K08095)

Title: Slc52a3 gene disruption affected the development of cerebral cortex in mice

Authors: *C. JIN[1,2], A. YONEZAWA[1,2], H. YOSHIMATSU[1,2], S. IMAI[1], M. KOYANAGI[1,2], K. YAMANISHI[1,2], S. NAKAGAWA[1], T. OMURA[1], T. NAKAGAWA[1], K. MATSUBARA[1]; [1]Dept. of Clin. Pharmacol. and Therapeut., Kyoto Univ. Hosp., Kyoto, Japan; [2]Grad. Sch. of Pharmaceut. Sci., Kyoto Univ., Kyoto, Japan

Abstract: Background: Riboflavin transporter 3 (RFVT3), encoded by the SLC52A3 gene, is highly expressed in the small intestine, kidney, testis and placenta. Mutations in SLC52A3 were associated with a rare neurological disorder, Brown-Vialetto-Van Laere syndrome. Our previous studies demonstrated that Slc52a3 knockout (Slc52a3-/-) mice exhibits neonatal lethality, riboflavin deficiency and metabolic disorder. Here, we investigated the inference of Slc52a3 gene disruption to embryonal development of brain using Slc52a3-/- mice. Methods: Slc52a3-/- mice were obtained from Knockout Mouse Project repository. Brains were dissected at embryonic day 13.5 (E13.5) and immediately after delivery (P0). Morphological changes in the whole brain at P0 were observed by histochemistry. Expressions of neuron and intermediate neural progenitors (INPs) makers (Tuj1 and Tbr2) were evaluated by immunohistochemical analysis. Riboflavin concentrations were measured by HPLC. Results: Brain riboflavin levels were decreased in Slc52a3-/- mice compared with WT mice. Histological and immunohistochemical analysis of brains in Slc52a3-/- newborn pups showed hypoplasia and global reduction of cerebral cortex. Slc52a3-/- pups have normal cortical lamination, but the thickness of cortical layers was significantly reduced. Evaluation of Slc52a3-/- embryos at E13.5 indicated that Tuj1-positive neurons and Tbr2-positive INPs were significantly decreased, compared with WT mice. Conclusions: Disruption of Slc52a3 gene reduced the production of INPs and neurons during the embryonic period and could influence the development of cerebral cortex in mice.

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Poster

641. Animal Models of Developmental Disorders

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 641.02/A44

Topic: A.07. Developmental Disorders

Support: NIH Grant U01NS099691
KIST Grant 2E27850

Title: Visualizing neural correlates of Tourette's-like motor tics in brain slices with genetically encoded voltage indicators

Authors: *J. RHEE[1,2], B. J. BAKER[1,2];
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Abstract: For some cases of Tourette's, Deep brain stimulation (DBS) of thalamic nuclei may be the only way to alleviate the patients' symptoms. Currently, however, there is neither a comprehensive understanding of the neural circuitry involved in Tourette's nor how DBS corrects the dysfunction. To explore whether Arclight-derived genetically encoded voltage indicators (GEVIs) can be used to detect activity resembling the neural correlates of Tourette's-like motor tics, the motor cortex was imaged to visualize both the neuronal excitation and inhibition during bath application of bicuculline in an in vitro brain slice preparation. Ensemble firing of neurons resulting in an oscillation in the motor cortex was detected, using wide-field fluorescence microscopy with 3 different GEVIs consisting of different kinetics and voltage sensitivities. All 3 GEVIs were capable of detecting oscillations: Arclight in the 5-15 Hz, Bongwoori-R3 and Bongwoori-pos6 in the 5-25 Hz range. Oscillations arose spontaneously, and correlated pixels of an oscillation showed varying patterns with no clear spatial origin.

Disclosures: J. Rhee: None. **B.J. Baker:** None.

Poster

641. Animal Models of Developmental Disorders

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 641.03/A45

Topic: A.07. Developmental Disorders

Support: NIH Grant T32 MH065215
NIH Grant MH086530

Title: Sexually-dimorphic dopamine signaling dictates the penetrance and behavioral trajectory of human dopamine transporter coding variation as revealed in studies of DAT Val559 mice

Authors: *A. STEWART[1], R. GOWRISHANKAR[1,4,5], R. PEART[2], M. J. RABIL[1], K. SPIESS[1], M. K. HAHN[1,3], R. D. BLAKELY[1,3];
[1]Biomed. Sci., [2]Honors Col., [3]Brain Inst., Florida Atlantic Univ., Jupiter, FL; [4]Neurosci. Grad. Program, [5]Intl. Scholars Program, Vanderbilt Univ., Nashville, TN

Abstract: Virtually all neuropsychiatric disorders display sex bias, with the prevalence, age of onset, and clinical symptomology differing significantly between males and females. Amongst the most strongly skewed are Attention-Deficit/Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD) for which the ratio of male:female diagnoses hovers at 4:1. Accumulating evidence indicates that genetic/gonadal sex influences a number of brain functions including the release, reuptake, and signaling response to dopamine (DA), a neurotransmitter implicated in ADHD and ASD. In an effort to identify penetrant genetic changes in DA signaling that drive ADHD risk, and generate construct-valid animal models of the disorder, the Blakely lab screened for coding variation in the DA transporter (DAT) in ADHD subjects, identifying the Ala559Val substitution in two brothers. The DAT Val559 variant has also been found in a girl with bipolar disorder and two unrelated boys with ASD. Though capable of clearing DA, the DAT Val559 mutant exhibits spontaneous outward DA leak, leading to homeostatic DA disruptions in DAT Val559 mice. We now report profound, sex-dependent phenotypic divergence in DAT Val559 mice that derives, at least in part, from circuit-specific DA D2 receptor (D2AR)-DAT coupling. In male DAT Val559 mice, presynaptic nigrostriatal D2ARs are constitutively-activated, driving enhanced DAT surface trafficking, an effect is absent in DAT Val559 females. However, females show constitutive D2AR activation of presynaptic mesolimbic D2ARs. These findings are paralleled by sex-specific differences in extracellular DA clearance as assessed by *in vivo* chronoamperometry. These sex differences in DA biology translate into a differential impact of the mutation on behavior and psychostimulant action. Male DAT Val559 mice exhibit blunted amphetamine-induced locomotion, aberrant social interaction in the tube test, and decreased spontaneous alternation in the Y-maze, phenotypes absent in their female counterparts. The DAT Val559 mutation also resulted in enhancement of amphetamine-induced c-Fos activation in the dorsal striatum of females whereas this effect is seen in the ventral striatum of males. When the rewarding properties of cocaine were assayed, male DAT Val559 animals displayed delayed conditioned place preference extinction whereas extinction was accelerated in DAT Val559 females. Overall, these studies provide striking evidence of a sexually dimorphic impact of functional DAT coding variation and reveal an important opportunity to gather insights into the sex-dependence of behavioral trajectories that attends neuropsychiatric disease risk.

Disclosures: A. Stewart: None. **R. Gowrishankar:** None. **R. Peart:** None. **M.J. Rabil:** None. **K. Spiess:** None. **M.K. Hahn:** None. **R.D. Blakely:** None.

Poster

641. Animal Models of Developmental Disorders

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 641.04/A46

Topic: A.07. Developmental Disorders

Support: Human Frontier Scientific Program (HFSP) RGP0008/2017

Title: Characterisation of William's syndrome zebrafish mutants: fzd9b and baz1b

Authors: *J. TORRES PEREZ, C. H. BRENNAN;
Sch. of Biol. and Chem. Sci., Queen Mary Univ. of London, London, United Kingdom

Abstract: Rationale and research objective: William's Syndrome (WS) is an autosomal dominant developmental disorder affecting around 1 every 7500-10000 individuals. It is caused by an haploinsufficiency on the chromosome 7 covering some 28 genes. Neurological impairments among people with WS include difficulty with visual-spatial tasks and with large number discrimination, attention deficit disorders and elevated anxiety. From the genes missing in this microdeletion, two seem key for the neurodevelopmental phenotype: frizzled class receptor 9 (fzd9) and bromodomain adjacent to zinc finger domain 1B (baz1b). Fzd9 encodes for a 7 transmembrane protein receptor from the Wnt signalling pathway. Neuronal deficiency of fzd9 leads to longer dendrites, increased number of spines and altered network connectivity. Baz1b encodes for a transcription factor which acts as neuroepigenetic switch for migration and neuronal maintenance during neurodevelopment. Deletion of this gene also leads to increased dendrite arborization and altered neuronal linkage. **Methods and results:** Here, we generated two knockout mutant zebrafish (*Danio rerio*) lines for fzd9 receptor b (fzd9b) and baz1b using the CRISPR-Cas9 technology to explore their behavioural and molecular phenotypes. All experiments were carried out in accordance with the Animals (Scientific Procedures) Act, 1985, under guidance from the Queen Mary Animal Care and Use Committee and the UK Home Office. Based on power calculations, we aimed to use around 20 larvae from each line for shoaling assay and/or for the light/dark test. Furthermore, few animals were PFA-fixed at different stages to assess the expression pattern of fzd9b and baz1b via wholemount *in situ* hybridization. Our results suggest that fzd9b and baz1b play a key role on zebrafish neurodevelopment and specially in the WS phenotype. **Conclusions:** We generated viable loss-of-function lines that show distinct phenotypes covering aspects of the WS. These lines provide a robust animal model for future research into the neurobiology of WS.

Disclosures: J. Torres Perez: None. **C.H. Brennan:** None.

Poster

641. Animal Models of Developmental Disorders

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 641.05/A47

Topic: A.07. Developmental Disorders

Support: NIH/NIAAA R21 AA026613-01

Title: Structural integrity of cholinergic neurons in the NBM-cortical pathway following behavioral intervention in adulthood in a rodent model of fetal alcohol spectrum disorders (FASD)

Authors: *K. A. MILBOCKER[1], N. K. GINN[1], Z. H. GURSKY[2], A. Y. KLINTSOVA[3]; [2]Dept. of Psychological & Brain Sci., [3]Psychological and Brain Sci., [1]Univ. of Delaware, Newark, DE

Abstract: One in twenty infants in the United States are affected by prenatal alcohol exposure (PAE) resulting in a range of disorders categorized as Fetal Alcohol Spectrum Disorders (FASD). PAE during late-stage pregnancy can produce lasting deficits of cortical-dependent behaviors in affected individuals (executive function, i.e. decision-making and inhibitory control). Evidence from human cases and animal models of FASD suggest that cognitive impairments could be mitigated by non-invasive intervention such as choline supplementation (Fuglestad et al., 2013; Idrus et al., 2017). However, it is unknown if environmental stimulations can produce changes in cholinergic function paralleled by morphological changes in cholinergic neurons.

Our study examines the effects of adult exposure to two behavioral interventions on the integrity of cortical-projecting cholinergic neurons from the nucleus basalis of Meynert (NBM) to the prefrontal cortex in a rat model of FASD. Male Long-Evans rats were exposed to binge-like alcohol (5.25 g/kg/day) on postnatal days (PD) 4-9. Control groups included sham-intubated (SI) and suckle-control (SC) rats. Pups were weaned into same-sex cages of three on PD23 (social housing, SH). On PD30, rats were either: 1) given free access to a running wheel (WR), 2) exposed to “super-intervention” consisting of twelve days of WR followed by four weeks of housing in a complex environment (EC), or 3) remained in SH from PD30-72. Immunocytochemical visualization of ChAT+ neurons in NBM was performed on brain tissue collected at PD72. Preliminary analyses of unbiased stereological estimates show a significant increase in the number of cholinergic neurons ($F(1, 27) = 6.63$, $p = 0.02$; interaction with treatment $p = 0.08$) and volume of NBM ($F(1, 27) = 4.65$, $p = 0.04$) following super-intervention. However, it appears that the intervention affects postnatal treatment groups differently, indicating decreased neuroplasticity in AE rats long-term. Chronic exercise intervention had no effect on the number or size of cholinergic neurons in the NBM in both control and AE rats.

Finally, a Hedreen and Bacon modified Karnovsky Roots histochemical stain was used to visualize AChE+ axon fibers in prelimbic medial prefrontal cortex (Cg2) of rats from all intervention groups at PD72. Neither behavioral intervention significantly altered cholinergic axon length (as measured with the Spaceballs stereological probe) or volume of Cg2 in animals of all three postnatal treatment groups. Our study suggests that cholinergic neuron integrity is largely conserved following neonatal alcohol exposure and behavioral intervention in adulthood along the NBM-cortical pathway.

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Poster

641. Animal Models of Developmental Disorders

Location: Hall A

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Program #/Poster #: 641.06/A48

Topic: A.07. Developmental Disorders

Support: Fondation pour la recherche médicale (France) Fellowship
Beatrice and Samuel A. Seaver Foundation (NY, USA)

Title: Understanding the neurodevelopment basis of DDX3X syndrome

Authors: *D. C. UNG[1,2,3], A. BOITNOTT[1,2,3], D. MENDONCA[1,2,3], K. NIBLO[1,2], E. DRAPEAU[1,2], S. DE RUBEIS[1,2,3];
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Abstract: DDX3X syndrome is a recently identified rare intellectual disability (ID) caused by mutations in the DEAD-box helicase 3 X-linked (*DDX3X*) gene. In addition to ID, affected individuals present with behavioral problems including Autism Spectrum Disorder, movement disorders, and brain anomalies including cortical malformations. Most affected individuals are females with *de novo* mutations in *DDX3X*; only a few affected males have been reported. DDX3X is an RNA helicase which regulates mRNA translation in non-neuronal cells. To date, the exact functions of DDX3X in neurons and at synapses is poorly understood. The objective of this study is to understand the molecular and cellular mechanisms of DDX3X during neurodevelopment (corticogenesis and synaptogenesis) and to explore its impact on behavior. We have generated a novel conditional knockout mouse recapitulating DDX3X syndrome. We study the effect of *Ddx3x* deficiency on corticogenesis by examining cortical lamination using immunostaining techniques with layer-specific markers at postnatal day 3 (P3) and by using a retrograde virus to label corticofugal projection neurons at P21 in *Ddx3x*-deficient ($Ddx3x^{+/-}$) and control ($Ddx3x^{+/+}$) female mice (n=6 mice/genotype). We investigate the impact of *Ddx3x*

deficiency on physical, motor, and sensory behaviors by assessing developmental milestones (P1-P21) and by testing cognitive and social behavior at the adult stage of our *Ddx3x* mouse (n=10 mice/genotype/experiment). We also apply biochemical methods to dissect the complexes mediating DDX3X-dependent translational using synapses from mouse cortices and perform an innovative method to map mRNA targeted by DDX3X (vTRAP-seq) (n=6).To study synaptogenesis, we use our mouse model to assess synapse morphology in single-embryo neuronal cultures modelling the genetics of DDX3X syndrome using a CRE-LOX strategy (n=8 embryo/genotype). We found that *Ddx3x* null male mice (*Ddx3x*$^{-/y}$) die *in utero*, compatible with the dearth of boys affected by DDX3X syndrome. *Ddx3x*-deficient females (*Ddx3x*$^{+/-}$) are viable, have reduced DDX3X protein expression in the cortex compared to controls, and have delayed developmental milestones compared to control females. DDX3X is expressed in glutamatergic projection neurons in the developing cortex and we are characterizing cortical connections and synaptogenesis in *Ddx3x*-deficient mice. In conclusion, we have generated a mouse model with construct validity for DDX3X syndrome that shows initial evidence for face validity through behavioral analyses. Through these approaches we expect to expose, with molecular and cellular resolution, the core neurobiology of DDX3X syndrome.

Disclosures: D.C. Ung: None. **A. Boitnott:** None. **D. Mendonca:** None. **K. Niblo:** None. **E. Drapeau:** None. **S. De Rubeis:** None.

Poster

641. Animal Models of Developmental Disorders

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 641.07/A49

Topic: A.07. Developmental Disorders

Support: APA
NHMRC/ARC
NHMRC
Victorian State Government Operational Infrastructure Scheme

Title: Age and sex differences in behaviors relevant to schizophrenia and addiction

Authors: *E. R. CULLITY, A. A. GUÉRIN, H. B. MADSEN, C. J. PERRY, J. H. KIM; Florey Inst. of Neurosci. and Mental Hlth., Melbourne, Australia

Abstract: Dopamine receptors 1 (D1) and 2 (D2) are important for neurodevelopmental disorders. We have shown previously that in the insula cortex, the density of D1 expressing neurons compared to D2 expressing neurons (D1:D2 ratio) is lower in adolescent male mice when compared to adolescent female, and adult male and female mice. Since addiction and schizophrenia are male dominant disorders which often have an adolescent onset, this reduced

D1:D2 ratio may be relevant in understanding the neurobiological basis of these disorders. Using a methamphetamine (meth) conditioned place preference (CPP) paradigm, I examined potential age and sex differences in meth-induced hyperactivity- relevant to psychosis in schizophrenia- as well as meth-induced place preference- relevant to addiction. Brains were perfused to investigate activation of D1- and D2-expressing cells within the insula cortex following these behaviors. I hypothesized that psychosis-like and addiction-related behaviors would be associated with a reduced D1:D2 ratio in the insula cortex, and that adolescent males would form a stronger meth CPP compared to adolescent females and adult males and females. Meth at 3 mg/kg increased locomotor activity in all mice (*n*=19-27 per age and sex group), and this effect was enhanced in adults compared to adolescents; no effects were found at 0.1 mg/kg. At 0.1 mg/kg, a higher proportion of male adolescents formed a preference to meth compared to male adults. In contrast, at 3 mg/kg, a higher proportion of male adults formed an aversion to meth compared to male adolescents. There were no age differences in females at either dose. These results suggest there is an age effect in the development of meth-induced hyperactivity, and that more male adolescents showa preference for meth compared to male adults. Collection of brain data is ongoing.

Disclosures: E.R. Cullity: None. **J.H. Kim:** None. **C.J. Perry:** None. **A.A. Guérin:** None. **H.B. Madsen:** None.

Poster

641. Animal Models of Developmental Disorders

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 641.08/A50

Topic: A.07. Developmental Disorders

Support: Research Fellowship (Shriners Hospitals for Children) : 84602
NIH(NINDS) : RO1 NS104038

Title: The role of Crb complex in hydrocephalus pathogenesis

Authors: *M. LEE, S.-H. CHO, S. KIM;
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Abstract: Hydrocephalus is a condition in which the intracerebral ventricles are engorged because cerebrospinal fluid (CSF) is obstructed, overproduced, or inadequately reabsorbed. Among the most common neurodevelopmental disorders, it can be caused by genetic mutation, infection, or brain injury. Without timely surgical intervention, it produces devastating intellectual and motor disability. However, the cellular and molecular mechanisms of hydrocephalus pathogenesis are not well understood, which precludes development of preventive

treatments. Previous genetic studies point to the importance of adhesion molecules, such as L1, and tight junction-associated proteins, such as MPDZ, in the pathogenesis of hydrocephalus in humans. Mutations in Crb2 also evoke hydrocephalus in humans, emphasizing the pathogenetic importance of the Crb complex, which includes Crb1/2/3, MPDZ/Patj and Pals1. To understand the mechanism by which Crb2 causes hydrocephalus, we developed a mutant mouse with nervous system-specific deletion of Crb2. We found that Crb2 deletion causes aqueduct stenosis with obvious hydrocephalus at birth and additional abnormalities in cerebral cortex, including periventricular heterotopic neurons. Analyses using cell-specific markers revealed that these heterotopia are primarily composed of late born neurons and astrocytes. Importantly, ependymal cells lining the ventricular aqueduct do not develop in the absence of Crb2, leading to the fusion of ventral aqueduct neuroepithelium. Together our results demonstrate that mouse Crb2 CKO recapitulates important features of human brain pathology and emphasize the important, but previously unrecognized, function of Crb2 in ependymal cell development.

Disclosures: M. Lee: None. **S. Cho:** None. **S. Kim:** None.

Poster

641. Animal Models of Developmental Disorders

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 641.09/A51

Topic: A.07. Developmental Disorders

Support: DuPont Scholarship

Title: Glia characterization in BLOC-1 deficient mice

Authors: *J. WEBSTER[1], J. LARIMORE[2];
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Abstract: Schizophrenia (SZ) is a chronic mental disorder characterized by hallucinations, disorganized speech, memory deficits, and an emotionless demeanor. It has been reported that dysbindin, a subunit of the octameric BLOC-1 complex, is reduced in the hippocampus of patients with SZ. Dysbindin regulates endosomal trafficking and has also been localized to the astroglial endfeet and endothelial cells that line capillaries in the cerebellum. Microglial activation has been implicated in neurological disorders and may regulate SZ progression. However, further characterization of glial cell function in SZ is necessary. This study will examine glia cell markers in dysbindin deficient mice in an effort to further understand disease progression in SZ.

Disclosures: J. Webster: None. **J. Larimore:** None.

Poster

641. Animal Models of Developmental Disorders

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 641.10/A52

Topic: A.07. Developmental Disorders

Title: RHEB1 activating mutations can cause aberrant neuronal development, cortical malformations and epilepsy in mouse models generated using *in utero* electroporation

Authors: *M. PROIETTI ONORI[1,2], Y. ELGERSMA[1,2], G. M. VAN WOERDEN[1,2]; [1]Neurosci., Erasmus MC, Rotterdam, Netherlands; [2]ENCORE Expertise Ctr. for Neurodevelopmental Disorders, Rotterdam, Netherlands

Abstract: RHEB1 (ras homolog enriched in brain) is a member of the GTP-binding protein family which is well known for being a key regulator of the Ser/Thr protein kinase Mammalian Target of Rapamycin (MTOR). A fine-tuned regulation of this pathway is a key determinant for proper brain development and function, and hyperactive MTOR in mouse models can lead to seizures and behavioral abnormalities. However, RHEB1 itself has never been linked to neurodevelopmental disorders in humans before. Recently, we identified a de novo mutation in the RHEB1 gene (RHEB1p.P37L) in patients with intellectual disability, macrocephaly and epilepsy, which indicates that RHEB1 might play a prominent role in neurodevelopmental disorders (Reijnders MRF, Kousi M, van Woerden GM et al., 2017). Our goal in this current research is to study the effect of RHEB1p.P37L in neuronal in vitro and in vivo assays to understand the potential role of RHEB1 in neurodevelopmental disorders and epilepsy. We made use of a screening which comprises both in vitro (mouse hippocampal cultures and multielectrode arrays (MEAs)) and in vivo (in utero electroporation and Local Field Potential measurements) techniques to assess the effect of RHEBp.P37L on neuronal development, migration and physiology. We showed that RHEBp.P37L causes hyperactivation of the mTOR pathway and we also observed, using a lentiviral approach in MEAs, that overexpression of the RHEBp.P37L mutant causes an aberrant neuronal development in vitro, with an overall increase in mean bursting rate activity (MBR: 16.2 Hz ± SEM 1.6, N=4) and burst duration (BD: 302.4 ms ± SEM 14.9, N=4) during early developmental stages, compared to control primary neuronal cultures (MBR: 6.7 ± 1.1, N=4; BD: 206.8 ± 8.9, N=4). Furthermore, using in utero electroporation, we generated a mouse model that upon overexpression of RHEBp.P37L in the somatosensory cortex at E14.5, shows the appearance of severe cortical malformations with dysplastic neurons and the presence of heterotopic nodules adjoining the ventricles. Starting from three weeks of age, all successfully targeted mice show the occurrence of spontaneous seizures (measured by electroencephalogram and local field potential), giving us the opportunity to study the involvement of RHEB1 in cortical malformations and epilepsy. This study shows

that RHEB1 activating mutations can cause intellectual disability and epilepsy, thereby making RHEB1 a potential critical therapeutic target for neurodevelopmental disorders.

Disclosures: M. Proietti Onori: None. **Y. Elgersma:** None. **G.M. van Woerden:** None.

Poster

641. Animal Models of Developmental Disorders

Location: Hall A

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Program #/Poster #: 641.11/A53

Topic: A.07. Developmental Disorders

Support: NIAAA 1 R21 AA026613-01 to AYK
NIH/NIGMS COBRE: The Delaware Center for Neuroscience Research Grant 1P20GM103653-01A1 to AYK

Title: Early postnatal alcohol exposure at both high and moderate doses reduces neuron, but not glial, number in thalamic nucleus reuniens of rat

Authors: *Z. H. GURSKY, A. Y. KLINTSOVA;
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Abstract: Individuals diagnosed with FASDs often possess cognitive deficits, with frequent impairment in "executive function" (EF) behaviors. Many behaviors included under EF umbrella require coordination of neuronal activity between the prefrontal cortex (PFC) and hippocampus (HPC). Recent non-human primate and rodent studies have demonstrated that the midline thalamic nucleus reuniens (Re) is essential in coordinating PFC-HPC activity, as selective Re inactivation impairs PFC-HPC synchrony and behavioral performance on HPC- and PFC-dependent tasks. Given its critical role in coordinating PFC-HPC activity, we initially examined immunofluorescently-labeled neurons (NeuN+) and cell nuclei (Hoechst33342-stained) in adult female Long-Evans rats exposed to 5.25 g/kg/day AE on postnatal days (PD) 4-9. We observed a significant loss of neurons in Re and reduction in volume, but no change in non-neuronal cell number. All of these measures were unaffected in the neighboring rhomboid nucleus, suggesting specificity of this damage to Re within midline thalamus. We next explored whether there is a dose-dependent loss of neurons in the nucleus reuniens. In this experiment, either "high-dose" 5.25 g/kg/day (BAC ≈340 mg/dL) or "moderate-dose" 3.00 g/kg/day (BAC ≈145 mg/dL) alcohol was delivered to male and female rats via intragastric intubation. The data suggest that both doses of alcohol produced significant neuronal (NeuN+ cell) loss in adulthood (intubated control = 67905 neurons, moderate-dose AE = 40058 neurons, high-dose AE = 38178 neurons). Neither dose resulted in altered number of microglia (immunofluorescent labeling of Iba1 protein). High-dose AE resulted in reduced Re volume (confirming the findings in previous study), but moderate-dose AE did not alter Re volume. These data indicate that moderate-dose AE is

sufficient to induce lasting damage in Re. Taken together, our data suggest that Re is highly vulnerable to AE in development, and is selectively damaged within midline thalamus, resulting in significant neuron loss at both high and moderate doses. AE at this time in development does not appear to alter the number of glial cells (i.e., non-neuronal cells or microglia) throughout life.

Disclosures: Z.H. Gursky: None. **A.Y. Klintsova:** None.

Poster

641. Animal Models of Developmental Disorders

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 641.12/A54

Topic: A.07. Developmental Disorders

Support: John S. Dunn Collaborative Research Award (R.A.U. and A.M.K.)

Title: Unraveling how gut microbiota influence form and function in the developing enteric nervous system of zebrafish

Authors: *M. A. ODEM[1], N. PEREZ-SOTO[1], S. DOWNING[2], L. THOMPSON[1], E. SINGLETON[2], A.-M. KRACHLER[1], R. A. URIBE[2];
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Abstract: The enteric nervous system (ENS) is a network of intrinsic nerve plexuses innervating the muscle layers of the gut that regulate motility, hormone secretions, water balance, and modulation of satiety via the vagal nerve. Functional maturation of the ENS is dependent on migration and differentiation of neural progenitors along the gut, and may be influenced by the luminal microenvironment. However, how the gut microbiota influence ENS form and function during early phases of development is poorly understood. The vertebrate model organism zebrafish (*Danio rerio*) may offer powerful insights into this process; the goal of this study was to investigate how absence of the gut microbiota in zebrafish affects differentiation of the ENS and to characterize potential dysfunctional phenotypes using a novel gut motility assay. First, gut motility was characterized in wild type *AB* larvae at 5-7 days post-fertilization (dpf) using novel event-detection algorithms that quantify fluorescently-contrasted muscle contractions along the regions of the gut. Next, transgenic larvae *Tg(-8.3bphox2b:Kaede)* expressing the *Kaede* fluorescent protein in enteric neuron precursors, and differentiated neurons, were used to determine how absence of the gut microbiota affects enteric neuron innervation of the gut and motility. Results from germ-free (GF) and conventionally-raised (CONV) *phox2b:Kaede* larvae suggest that enteric neurons do not properly innervate variable regions of the gut, in particular the midgut, in GF larvae at 5-7 dpf, when compared with CONV controls. Functionally, the GF larvae exhibited abnormal, irregular patterns of motility in the midgut region, suggesting absence

of the gut microbiota may negatively affect gut function, in addition to innervation. Collectively, these results suggest that microbiota may play a critical role during developmental maturation of the ENS in the midgut.

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Poster

641. Animal Models of Developmental Disorders

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 641.13/A55

Topic: A.07. Developmental Disorders

Support: Senner Endowment for Precision Health, University of Arizona Health Sciences (M.N).
National Natural Science Foundation of China (81603088) and National Key Project of Research and Development of China (2018YFC1705501) to J.Y., National Institute on Drug Abuse to R.K.); and a Neurofibromatosis New Investigator Award from the Department of Defense Congressionally Directed Military Medical Research and Development Program (NF1000099) to R.K.

Title: TAF1-gene editing alters the morphology and function of the cerebellum

Authors: *U. JANAKIRAMAN[1], Y. JIE[2], M. AUBIN[2], S. BATCHELOR[1], A. ANNADURAI[1], K. RAJESH[2], M. NELSON[1];
[1]Pathology, [2]Pharmacol., Univ. of Arizona, Tucson, AZ

Abstract: TAF1/MRSX33 intellectual disability syndrome is an X-linked disorder caused by loss-of-function mutations in the TAF1 gene. How these mutations cause dysmorphology, hypotonia, intellectual and motor defects is unknown. Mouse models which have embryonically targeted TAF1 have failed, possibly due to TAF1 being essential for viability, preferentially expressed in early brain development, and intolerant of mutation. Novel animal models are valuable tools for understanding neuronal pathology. Here, we report the development and characterization of a novel animal model for TAF1 ID syndrome in which the TAF1 gene is deleted in embryonic rats using clustered regularly interspaced short palindromic repeats (CRISPR) associated protein 9 (Cas9) technology and somatic brain transgenesis mediated by lentiviral transduction. Rat pups, post-natal day 3, were subjected to intracerebroventricular (ICV) injection of either gRNA-control or gRNA-TAF1 vectors. Rats were subjected to a battery of behavioral tests followed by histopathological analyses of brains at post-natal day 14 and day 35. TAF1-edited rats exhibited behavioral deficits at both the neonatal and juvenile stages of development. Deletion of TAF1 lead to a hypoplasia and loss of the Purkinje cells. We also

observed a decreased in GFAP positive astrocytes and an increase in Iba1 positive microglia within the granular layer of the cerebellum in TAF1-edited animals. Immunostaining revealed a reduction in the expression of the CaV3.1 T-type calcium channel. Abnormal motor symptoms in TAF1-edited rats were associated with irregular cerebellar output caused by changes in the intrinsic activity of the Purkinje cells. This animal model provides a powerful new tool for studies of neuronal dysfunction in conditions associated with TAF1 abnormalities and should prove useful for developing therapeutic strategies to treat TAF1 ID syndrome.

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Poster

641. Animal Models of Developmental Disorders

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 641.14/A56

Topic: A.07. Developmental Disorders

Support: International Foundation for CDKL5 Research
Fondazione Telethon [GGP15098]
LouLou Foundation
Marie Sklodowska-Curie grant agreement No 674901, “switchboard”

Title: The visual system as a biomarker in a mouse model of CDKL5 deficiency disorder: Functional substrates and behavioral correlates

Authors: *L. LUPORI[1], G. SAGONA[2], C. FUCHS[3], R. MAZZIOTTI[4], A. STEFANOV[5], E. PUTIGNANO[5], D. NAPOLI[1], V. MARTINI[5], G. RICCI[5], E. STRETTOI[5], E. CIANI[3], T. PIZZORUSSO[4];
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Abstract: CDKL5 deficiency disorder (CDD) is a neurodevelopmental disorder characterized by a severe global developmental delay, early-onset seizures and, notably, visual abnormalities often clinically diagnosed as Cortical Visual Impairment. Animal models of the disease have been recently generated, giving the possibility to test new therapeutic strategies as long as quantitative and longitudinal biomarkers are available. CDD mouse models display visual deficits analogous to patients and cortical visual responses can be used in mice as a robust and minimally invasive biomarker. However, a quantitative measurement of the predictive power of the visual biomarker on general behavioral cognitive dysfunctions is still missing. Moreover, the

involvement of cortical as opposed to subcortical circuits in the origin of the symptoms is poorly understood. To address these questions, we first developed a custom, automated chamber for operant conditioning to assess the impact of CDKL5 lack in the learning of a simple task. We found that mutant mice initiated significantly more trials and responded to the initiation of the trial with shorter reaction times compared to wild-type littermates. This perseveration phenotype was quantitatively correlated with the visual biomarker.We then assessed which are the circuits underlying the described visual deficits in two ways: first, we performed an in-depth morphological analysis of the visual pathway, from the retina to the primary visual cortex (V1), of CDKL5 null mice. We found that CDKL5 lack produced no alteration in the organization of retinal circuits, but, conversely, it reduced density and altered morphology of spines and decreased excitatory synapse marker PSD95 in the dorsal Lateral Geniculate Nucleus and in V1. Second, using a conditional KO model, we showed that selective cortical deletion of CDKL5 from excitatory cells is sufficient to produce abnormalities of visual cortical responses, demonstrating that the normal function of cortical circuits is dependent on CDKL5. In summary, this work proposes cortical function as a critically important target for studying CDD.

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Poster

641. Animal Models of Developmental Disorders

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 641.15/A57

Topic: A.07. Developmental Disorders

Support: FAST Grant A18-0382

Title: Behavioral characterization of a full UBE3A deletion rat model

Authors: *E. L. BERG[1], S. P. PETKOVA[2], Y. SHEN[2], S. HARRIS[3], H. A. BORN[3], A. E. ANDERSON[3], S. V. DINDOT[4], E. J. WEEBER[5], D. J. SEGAL[6], M. WÖHR[7], J. L. SILVERMAN[2];
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Abstract: Angelman Syndrome (AS) is a rare neurodevelopmental disorder caused by loss of *UBE3A* (ubiquitin-protein ligase E6-AP) expression in the brain, typically due to a deletion of

the maternal 15q11-q13 region. Symptoms of the disorder include developmental delay, impaired receptive and expressive communication skills, ataxia, motor and balance deficits, poor attention, intellectual disabilities, microcephaly, and seizures. Recent advances in genetic rat models have allowed for the development and utilization of clinically-relevant assays to quantify sophisticated outcome measures of relevance to AS across a developmental time course. We aimed to use innovative and clinically-relevant outcome measures of social communication, motor behavior, and learning and memory to identify AS-relevant functional phenotypes in the *Ube3a* mutant rat. Juvenile social communication was assessed in *Ube3a m-/p+* (with a maternally inherited deficiency) and *m+/p+* (control) rats using a heterospecific play ("tickling") assay during which subjects were manipulated by the experimenter in a standardized manner mimicking species-typical play while ultrasonic vocalizations of both low and high frequency categories were recorded. Nuanced social interaction behaviors were quantified via a separate 10 min juvenile reciprocal social interaction test in which subject rats were allowed to freely interact with a sex- and age-matched wildtype control animal. The open field test of locomotion and the rotarod test of motor learning were used to assess motor behavior, gait was analyzed using the automated DigiGait system (Mouse Specifics, Inc.), and fine motor ability was tested with an adhesive removal task. Additionally, learning and memory were assessed with the novel object recognition task as well as cued and contextual fear conditioning. This study discovered altered social communication and reciprocal social interactions in the *Ube3a m-/p+* rat model of AS. Learning and memory, as measured by the novel object and fear conditioning tasks, was undisturbed and gait parameters are currently undergoing analysis. The results herein lend support for the important role of Ube3a in social behavior and for the use of this rat model as a tool to study the neurobiology underlying the behavioral phenotypes of AS, as well as to test potential therapeutics in future experiments.

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Poster

641. Animal Models of Developmental Disorders

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 641.16/A58

Topic: A.07. Developmental Disorders

Support: L.I.F.E. Foundation Grant

Title: Latrophilin-3 (LPHN3) knockout and heterozygous Sprague Dawley rats show hyperactivity, response to ADHD medication, and cognitive deficits

Authors: *S. L. REGAN[1], C. SUGIMOTO[2], M. T. WILLIAMS[3], C. V. VORHEES[4];
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Abstract: Attention deficit hyperactivity disorder (ADHD) is a heterogeneous neurodevelopmental disorder affecting ~10% of children in the United States. Latrophilin-3 (LPHN3) is a brain specific G-protein coupled receptor that has been associated with increased risk of ADHD and cognitive deficits. CRISPR/Cas9 was used to generate a constitutive knockout (KO) rat of *Lphn3* by deleting exon 3, and this model was used to investigate the lack of LPHN3 in ADHD-related behavior, and cognition. *Lphn3* KO rats show hyperactivity, an attenuation to common ADHD medication, and significant cognitive deficits. In a second experiment we tested KO, heterozygous, and WT rats to understand if there was a gene-dose response to the behavioral phenotype. We tested the rats in home cage at P35 for 7 days and again at P50 for 9 days. On the last two days of P50 testing, rats are challenged with 0.75 mg/kg of methylphenidate (MPD) to determine if it reduces the hyperactivity of KO rats. We also tested these rats in the Morris water maze (MWM), and Cincinnati water maze (CWM) to understand if there were cognitive deficits. Results showed that KO and HET rats are hyperactive compared with the WT controls, and that this effect may be slightly attenuated by low-dose MPD. KO and HET rats also showed cognitive deficits in the MWM and CWM. The data suggest that *Lphn3* KO rats exhibit a hyperactive phenotype with severe cognitive deficits and may be a useful model to better understand one of the genetic contributions to ADHD. (Supported by a grant from the LIFE Foundation).

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Poster

641. Animal Models of Developmental Disorders

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Topic: A.07. Developmental Disorders

Support: China exchange program of the Royal Netherlands Academy of Arts and Sciences (KNAW)
Donders Centre for Neuroscience RadboudUMC junior researcher round grant

Title: Increased maternal extracellular serotonin levels beneficially influences offspring’s brain morphology and anxiety- and anhedonia-like behavior

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Abstract: Serotonin is a critical player in brain development whereby serotonin neurotrophic actions can be regulated through maternal-fetal interactions. Hence, maternal rather than offspring's serotonergic genotype may determine variation in serotonin levels in the early fetal brain, which might result in downstream effects on the development of the brain and potentially influencing behavior. Indeed, serotonin has been shown to be involved in psychiatric disorders such as autism, anxiety, and depression, but the nature of its etiology so far is unclear.
In our first study, we investigated whether changes in extracellular serotonin levels due to serotonin transporter (SERT) availability (SERT rat model) in the mother influenced the maternal care. Maternal care is a major constituent of early life environment and seems to be related to offspring's behavior and serotonin levels. We observed that one of the most prominent forms, licking-grooming their offspring, is significantly less often performed by SERT knockout (KO) dams then SERT wildtype (WT) dams. Thus, variation in licking-grooming behavior seems to be determined by maternal serotonergic genotype.
To delineate whether maternal serotonergic genotype influences offspring's development through changes in fetal serotonin levels and/or through changes in licking-grooming behavior, we set up a breeding such that both these two questions could be answered. In this study, the offspring was subjected to several behavioral assessments. Our data showed that a decrease in fetal forebrain serotonin levels (KO mother) and a decrease in licking-grooming behavior (KO care) synergistically strengthen their impact on brain morphology and behavior. More specifically, in adult offspring from SERT KO mothers, which received SERT KO care we observed a diminished anxiety (elevated plus maze test), which correlated with an increase in mineralocorticoids receptor mRNA expression in the infralimbic cortex. In addition, these offspring showed a diminished anhedonia (sucrose consumption test), which correlated with a decrease in GAD65 and BDNF VI mRNA expression in the infralimbic cortex.
These findings indicate that genetically induced increases in maternal extracellular serotonin levels has a beneficial effect on offspring's behavior via modulations of key genes involved in the functionality of the hypothalamic pituitary adrenal (HPA) axis, GABAergic transmission, and neuroplastic mechanisms. For this reason, maternal SERT genotype, influencing fetal forebrain serotonin levels and maternal care, seems to be involved in the development of psychiatric disorders.

Disclosures: S.I. Hanswijk: None. **G. Sbrini:** None. **P. Brivio:** None. **L. Heltzel:** None. **W. Li:** None. **M. Peroni:** None. **D. Cantore:** None. **M. Spoelder:** None. **M.M. Verheij:** None. **D. Peeters:** None. **A. Middelman:** None. **C. Liu:** None. **J.K. Buitelaar:** None. **F. Calabrese:** None. **J.R. Homberg:** None. **B. Natale:** None.

Poster

641. Animal Models of Developmental Disorders

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 641.18/A60

Topic: A.07. Developmental Disorders

Support: NIH Grant R01NS082283
NIH Grant P20GM103620

Title: Characterization of a novel porcine model of CLN3 Batten disease

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Abstract: CLN3 Batten disease is an autosomal-recessive neurodevelopmental disorder that results from mutations in *CLN3*. In the vast majority of cases, disease onset occurs in early childhood and is characterized by progressive loss of vision, seizures, failure in psychomotor development and is universally fatal by the third decade of life. Several mouse models of CLN3 disease have been developed that have provided insight into the pathological progression of this disease including early glial activation followed by neuronal loss, however, many aspects of the disease are not recapitulated in these mouse models. The development of an animal model that more closely recapitulates the clinical manifestations of CLN3 disease in humans is a crucial step toward implementing successful therapies for CLN3 patients. Porcine models hold the promise of a more accurate disease model given the similarities that pigs and humans share in terms of development, anatomy, and physiology, and in particular, similarities in brain development such as perinatal growth spurt and brain structure. Furthermore, the shared characteristics of the human and porcine visual system make the pig a useful resource for studying macular-associated retinal diseases that are not possible in mice. Additionally, the size of the pig would allow for the use advanced neuroimaging techniques such as MRI, CT and/or PET to model *in vivo* changes within the CNS longitudinally and track the success of potential therapeutics. Recently, we have developed a novel $CLN3^{\Delta ex7\text{-}8/\Delta ex7\text{-}8}$ porcine model of CLN3 Batten disease. Here we present initial characterization results showing behavioral, pathological, and visual deficits that mirror changes seen in human patients.

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Poster

641. Animal Models of Developmental Disorders

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 641.19/A61

Topic: A.07. Developmental Disorders

Support: NIH Grant AA1 3023

Title: Effects of developmental alcohol exposure on brain activation and functional connectivity

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Abstract: Children with fetal alcohol spectrum disorders (FASD) often have deficits associated with multisensory processing. Because ethanol disrupts activity-dependent neuronal plasticity, a process that is essential for refining connections during cortical development, it may have an effect on normal development of sensory regions and brain networks. In this study, we used a ferret model to test whether early alcohol exposure alters the activation of brain regions involved in multisensory processing using resting-state functional magnetic resonance imaging. In addition, we assessed alterations of the brain network organization.
Ferret pups were given 3.5g/Kg ethanol or saline every other day between postnatal day 10 to 30, which is similar to the 3rd trimester of human gestation regarding cortical development. 23 control (Ctr, 10 males, 13 females) and 21 ethanol-exposed (Eth, 11 males, 10 females) ferrets were imaged in juvenile. 17 Ctr (8 males, 9 females) and 15 Eth (7 males, 8 females) animals were imaged in young adulthood. The functional connectivity of the lateral rostral suprasylvian sulcal area (LRSS, an auditory-tactile area) and the rostral posterior parietal cortex (PPr, a visual-tactile area) involved in multisensory processing were assessed. Fractional amplitude of low frequency fluctuation (fALFF) and regional homogeneity (ReHo) were calculated to estimate brain activity. Graph analysis was performed to assess the network organization using a home-made ferret atlas with 60 cortical regions of interest. The effects of ethanol, age and their interaction were assessed with two-way ANOVA in males and females. Increased functional connectivity between LRSS and tactile areas was observed only in Eth males. Functional connectivity between PPr and visual regions was increased in Eth juvenile males but decreased in Eth juvenile females. ReHo of tactile regions increased only in Eth males. Eth males showed increased network clustering coefficient, local efficiency and decreased characteristic path length in juvenile, indicating increased network segregation and decreased integration. In summary, our

results indicate that early alcohol exposure alters the regional activity/interaction within sensory systems and alters the brain network organization.

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Poster

641. Animal Models of Developmental Disorders

Location: Hall A

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Topic: A.07. Developmental Disorders

Support: NIH T32 GM008151-33
NIH R01 MH117405 01A1
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Title: Dissecting the mechanism and function of DNMT3A in neural development and disease

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Abstract: Human genetic studies have linked disruption of genes encoding epigenetic regulators of transcription to autism and related neurodevelopmental disorders, but little is known about how causative mutations disrupt protein function to lead to disease. DNA methyltransferase 3a (DNMT3A) catalyzes the addition of methyl groups to cytosines in DNA, and mutations in DNMT3A are associated with neurodevelopmental disorders, including autism and intellectual disability in Tatton-Brown-Rahman Syndrome (TBRS). Though DNA methylation is classically thought to occur in mammalian cells in the CpG context, neurons have high levels of a recently-discovered form of methylation in non-CpG contexts that is established by DNMT3A. This non-CpG methylation, primarily occurring at CA dinucleotides (mCA), is critical to proper neuronal development and establishment of neuronal cell-type-specific transcription. Though mCA plays an important role regulating neuronal gene expression, little is known about how loss of DNMT3A and mCA relate to neurodevelopmental disease. We have studied disease mutations identified in patients with TBRS and Autism Spectrum Disorder and analyzed how these mutations differentially affect the ability of DNMT3A to methylate neuronal DNA through protein-domain specific mechanisms. Additionally, we have utilized several genomic, molecular, and behavioral assays to investigate how loss of DNMT3A in mice alters neuronal DNA methylation and changes neuronal function. Furthermore, we have generated mice carrying a

disease mutation identified in TBRS and we show a similar loss of disruption of DNA methylation in the brain. Together, this work defines several molecular mechanisms that may be leading to neurological disease and provides insight into the functional domains of DNMT3A. In addition, these analyses elucidate the function of DNMT3A and mCA in nervous system development and functionally link disruption of DNA methylation to neurodevelopmental disease.

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Poster

641. Animal Models of Developmental Disorders

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 641.21/A63

Topic: A.07. Developmental Disorders

Title: Uncovering the effect of MgSO4 on the NRG-ErbB pathway in embryos of maternal immune activation rat dam at different gestational days

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Abstract: Low birth weight and preterm birth proposed as risk factors for developing schizophrenia and other forms of psychosis, later in life. Administration of magnesium sulfate (MgSO4) as a neuroprotective agent to women at high risk of imminent preterm birth has become the most common clinical practice. However, the molecular mechanism of MgSO4 as a neuroprotective agent has not been fully elucidated. The NRG1-ErbB4 signaling plays a critical role in embryonic brain development, in the biology of dopaminergic and GABAergic systems and in schizophrenia, therefore, we hypothesize that pathway is associated with the neuroprotection role of MgSO4. Here, we investigate the effect of MgSO4 at either early (GD16) or late (GD20) on the expression of the ErbB, dopaminergic and GABAergic signaling pathways in maternal immune activation (MIA) embryos. Two cohorts of 20 pregnant dam rats randomly assigned into four different treatment groups: saline/saline, LPS/saline, saline/MgSO4, and MgSO4/LPS. Experimental groups were first treated i.p. with LPS or saline, and then with

MgS04 or saline every 20 minutes for four hours. Fetal brains were collected for RT-qPCR measurement. The expression of NRG1 and D2R at both gestational days were significantly elevated in the MgSO4/saline and in MgSO4/LPS groups. However, ErbB4 receptor mRNA levels at 16 GD, but not at 20 GD, were significantly elevated in the MgSO4/LPS group. The expression of NRG3, NRG2, and NRG4 at 16 GD was significantly downregulated in MgSO4/saline and MgSO4/LPS groups. Together, our preliminary results suggest that the NRG-ErbB and the D2R pathways possibly involved in the neuroprotection mechanism of MgSO4.

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Poster

641. Animal Models of Developmental Disorders

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Topic: A.07. Developmental Disorders

Support: NIH grant NH/NINDS R01NS080844
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Title: Inflammation exacerbates intrauterine growth restriction-induced cognitive deficits in juvenile rats

Authors: *L.-W. FAN[1], L.-T. TIEN[3], J. W. LEE[1], S. LU[1], N. DANKHARA[1], V. PRAKASH[1], I. ARGUELLO[2], Y. PANG[1], A. J. BHATT[1], R. D. SAVICH[1], N. B. OJEDA[1];
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Abstract: Epidemiological and experimental studies suggest that intrauterine growth restriction (IUGR) is associated with neurodevelopmental impairments. Our previous studies demonstrated that systemic inflammation during pregnancy induced the priming activation of microglia and elevated levels of pro-inflammatory cytokines, which may contribute to behavioral dysfunction in offspring. This study was designed to further examine whether maternal inflammation via lipopolysaccharide (LPS) exposure enhances cognitive deficits associated with IUGR in juvenile rats. LPS (100 µg/kg) was administered intraperitoneally into pregnant rats on day 13 of gestation (E13) and the reduced uterine perfusion (RUP) surgery was performed on day 14 of gestation (E14) to generate IUGR rat offspring. One offspring from each sex from each litter was included in each experimental group. Four groups of 8 pups per group were included in the following treatments: Saline+Sham, Saline+RUP, LPS+Sham, and LPS+RUP. The control rat offspring were from the pregnant rats which had been administered saline injection followed by

sham surgery (Saline+Sham). The body weight and locomotion of offspring were determined on postnatal day 14 (P14) and P21, and the cognitive tests were determined by Y maze (P23) and passive avoidance on P23 and P24 in a double-blind manner. To ensure scientific rigor the molecular assays and histological assessment were evaluated by triplicate, and the sample sizes were calculated to reach a statistical power of at least 0.85 for a $P<0.05$. All animals were from the same strain and same vendor. Data were analyzed by two-way ANOVA followed by the Student-Newman-Keuls test. Our results show that offspring from dams exposed to either LPS or RUP showed significantly lower birth weight compared to controls at P21. Exposure to LPS during gestation exacerbated IUGR-associated motor disturbances including increases in rearing events in juvenile rats as well as cognitive deficits including short-term memory, learning and long-term memory. Significant difference was observed between male and female rats within the same treatment group. The current study suggests that exposure to LPS during gestation enhances IUGR-associated cognitive deficits including learning and memory in both male and female juvenile rats. This model may be useful for studying mechanisms involved in the development of children's neurodevelopmental delays associated with exposure to inflammation and growth restriction during gestation, and could help to develop future potential therapeutic strategies.

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Poster

641. Animal Models of Developmental Disorders

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Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 641.23/A65

Topic: A.07. Developmental Disorders

Support: Start-up grant AY1000

Title: Role of serotonin in synaptic signaling and plasticity in tuberous sclerosis

Authors: *R. SRINIVASAN[1], W. FRANCESCONI[3], F. BERTON[4], R. KIRCHNER[5], K. P. KOSTER[2], J. BENEDICT MICHAEL[6], A. YOSHII[7];
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Abstract: Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disorder caused by mutations in TSC1 or TSC2. While it is a multi-organ disease, neurological symptoms are prominent and include epilepsy, intellectual disabilities, and autistic behaviors. Dysregulated synapse formation and plasticity is likely to play a major role in the pathophysiology of TSC. TheTSC-1 and -2 proteins form a complex that downregulates the mammalian target of rapamycin(mTOR) pathway, and a gene mutation results in mTOR over activation. mTOR is a critical regulator of protein synthesis as well as synaptic plasticity. Consequently, suppression of mTOR by rapamycin or its derivatives is one way to correct the pathophysiology of TSC. However, mTOR pathway has multiple roles and rapamycin neither specifically nor completely cures all neurological symptoms. A greater understanding of dysregulated synaptic function will enable identification of specific therapeutic targets for epilepsy and cognitive disabilities in TSC.To identify potential causes of abnormal synaptic activity, we conducted RNA-seq analysis in wild-type vs. neuron-specific TSC1 -/- and found an excess of transcripts associated with the serotonin signaling pathway in TSC1 -/- brain. Immunoblots confirmed that levels of the serotonin receptor 5-HT2C were higher and its intracellular distribution was altered in pyramidal cells ofthe TSC1 -/- cortex. We next used calcium imaging and found that TSC1 -/- cultured cortical neurons had frequent Ca 2+ bursts throughout the soma and dendrites that depended on a specific serotonin pathway while WT neurons showed random and scattered transients mostly within dendritic spines. Furthermore, daily injection of the serotonin pathway antagonist rescued the premature death of the mutant pups. Our results indicate synaptic dysregulation in TSC can be corrected by modulating serotonergic pathway and set the stage for developing a new therapeutic approach. TSC is associated with a wide range of cognitive, behavioral, and psychiatric manifestations.TSC- Associated Neuropsychiatric Disorders (TAND) is often treated with risperidone, the first FDA- approved drug indicated for behavioral problems in autistic patients. Risperidone is not only a dopamine antagonist but also possesses anti-serotonergic properties. Thus, 5HT2C inhibition as a novel, specific therapeutic strategy for neurological symptoms of TSC.

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Poster

641. Animal Models of Developmental Disorders

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Topic: A.07. Developmental Disorders

Support: DoD CDRMP NF150083 (AS)

Title: Neurofibromatosis type 1 haploinsufficient mice exhibit reduced female-induced social communicative behaviors, which were associated with abnormalities within key social brain regions

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Abstract: RASopathies are syndromes arising from genetic mutations that result in dysregulation of the RAS pathway, a ubiquitous molecular pathway involved in cellular survival, growth, and division. Neurofibromatosis type I (NF1) is a well-studied RASopathy that is caused by an inactivating mutation in a single gene (neurofibromin) responsible for RAS pathway inhibition. Patients with NF1 often possess learning or cognitive difficulties, and one third of these patients meet criteria for autism spectrum disorder (ASD). Recent studies show that a substantial number of individuals with NF1 demonstrate disruptions in communication that are independent of their attention and learning problems, in line with current and past ASD criteria. Our previous studies have shown that mice haploinsufficient for *Nf1* (*Nf1*$^{+/-}$ mice) possess long-term social memory deficits due to RAS hyperactivation. Adult mice produce ultrasonic vocalizations (USVs) in specific social contexts, and studies demonstrate that these “songs” communicate information to a partner. USVs can be reliably elicited during courtship trials and can be used as an indicator of social communication in mice. Here, we explored social communication during courtship behavior in adult male *Nf1*$^{+/-}$ and wild-type (WT) mice. Additionally, we aimed to identify male mouse brain regions involved in the male-female social communication network. We have recorded and analyzed the USVs of WT and *Nf1*$^{+/-}$ mice. Following a 5 minute habituation, male mice were allowed to interact for eight minutes with an ovariectomized WT female mouse primed with estrogen and progesterone while USVs and video were recorded. Twenty minutes following female-induced USVs, the male mice were perfused and their brains were collected for immunohistochemistry (IHC). Slices were stained using dual immunohistochemistry for phospho-ERK (pERK), a marker of cellular activity, and NeuN, a marker for mature neurons. *Nf1*$^{+/-}$ mice exhibited a reduced number and duration of USV calls, as well as a reduced complexity of syllables compared to WT. Additionally, blinded dual IHC revealed alterations in pERK activation following exposure to a receptive female in several brain regions important for social behaviors, such as basolateral amygdala and nucleus accumbens. These data will provide additional information about the neural circuits and underlying mechanisms associated with RAS-related ASD-like social communication deficits.

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Poster

641. Animal Models of Developmental Disorders

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Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 641.25/A67

Topic: A.07. Developmental Disorders

NIHR01AA0815011

Title: Effect of developmental alcohol exposure on layer 2/3 neurons in primary visual cortex

Authors: *D. KEUM[1], T. E. KRAHE[2], N. S. PULIMOOD[1], A. E. MEDINA[1];
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Abstract: Children with FASD (fetal alcohol syndrome disorder) can have deficits in visual-spatial learning and visual-motor coordination as well as display amblyopia-like visual impairments even in absence of optical and oculomotor abnormalities. Studies from our lab have demonstrated in ferrets and mice that developmental alcohol exposure leads to a long lasting deficit in neuronal plasticity in the visual cortex. However, the effects of development alcohol exposure on neuronal responses in this area remain elusive. Here we use whole-cell patch clamp to characterize neuronal responses in Layer 2/3 of the visual cortex of a mouse model of "third trimester" alcohol exposure. C57/BL6 mice from both sexes received 5g/Kg of alcohol (25% i.p.) or control saline on postnatal days (P) 5, 7 and 9. Another group of mice from the same litter remained undisturbed (Naïve). Animals were euthanized between P25-P38 and slices prepared for electrophysiology and recorded in excitatory neurons layer 2/3 of primary visual cortex. Under current clamp we analyzed the numbers of spikes reduced by 25% in alcohol exposed and 17% in saline injected mice compared to naïve animal. However, properties of cell membrane (cell capacitance, input resistance, and resting membrane potential) and spikes (threshold, half duration, rising and decay time) were not changed significantly. AMPA/NMDA ratios were analyzed under voltage clamp but there was no difference between groups. Then we analyzed spontaneous post synaptic current. Our data showed that the early exposure to alcohol significantly reduced the frequency of sPSC but did not alter the amplitude. These findings suggest that impairment in neurotransmitter release in the visual cortex may cause the deficits in neuronal plasticity previously demonstrated in this model. Stress of the injection itself also seems to affect numbers in evoked action potentials by larger current (> 200pA) range.

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Poster

641. Animal Models of Developmental Disorders

Location: Hall A

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Program #/Poster #: 641.26/A68

Topic: A.07. Developmental Disorders

Support: NIH AA019462

Title: Moderate prenatal alcohol exposure and housing manipulations alter spatial navigation behavior in adult rodents

Authors: *C. M. MAGCALAS[1], S. DAVIES[2], D. D. SAVAGE II[2], D. A. HAMILTON[1]; [1]Univ. of New Mexico, Albuquerque, NM; [2]Neurosciences, Univ. of New Mexico Sch. of Med., Albuquerque, NM

Abstract: Prenatal alcohol exposure (PAE) is associated with structural and physiological changes that impact the central nervous system and can result in persistent negative consequences in a broad spectrum of cognitive and behavioral domains including deficits in motor behavior, social behavior, and behavioral flexibility. Previous studies have characterized the influence of PAE on spatial navigation and behavioral flexibility through various behavioral paradigms including the Morris water task (MWT). The current study focuses on examining the behavioral consequences of PAE on directional and place navigation through the use of the MWT. Pregnant rat dams voluntarily consumed saccharin (SAC) water containing 0% or 5% ethanol (EtOH) for 4 hours per day during the entire gestational period. Same sex pups were pair-housed with a partner of the same prenatal treatment (Same; Sac-Sac or EtOH-EtOH) or the different prenatal treatment (Mixed; Sac-EtOH). In order to assess directional and place navigation the animals were tested in a 2-day hidden platform protocol. Day 1 of the hidden protocol consisted of 12 training trials and 1 pool shift test. Day 2 consisted of 8 training trials, 1 pool shift test (opposite of the first test), 4 training trials, and 1 probe trial. The pool shift test consisted of moving the pool to a secondary position. The platform either moves with the pool to a relative location in the pool (directional navigation) or stays in the absolute location in the room (place navigation). There were no significant differences between prenatal treatment, sex, or housing conditions in the hidden training trials. In the hidden variant there was a significant interaction in the females between preference for the absolute or relative location and PAE. This interaction was only significant in the mixed housed females and was not present in the same housed females. The SAC female rats displayed a preference for the relative platform location, which is consistent with previous findings, while EtOH female rats displayed a preference for the absolute location. Additionally, the mixed housed males showed some preference for the relative location while the mixed housed males showed almost not preference for either goal location. These outcomes suggest that animals may have distinct search patterns that may be sex specific

and can be influenced by PAE and housing manipulations. [Supported by grant AA019462 to DH].

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Poster

641. Animal Models of Developmental Disorders

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Program #/Poster #: 641.27/A69

Topic: A.07. Developmental Disorders

Title: Altered patterning and HLH transcription factors that control neurogenesis and gliogenesis in retinoic-acid-induced spina bifida in rat model

Authors: *M. ORIA, Z. LI, B. PATHAK, K. BAKRI, J. L. PEIRO;
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Abstract: During spinal cord development, multipotent progenitor cells generate three major cell lines; neurons, oligodendrocytes and astrocytes at precise time and position. Normally, neurogenesis occurs in early embryonic stage and astrocytes and oligodendrocytes later. However there have been studies indicating of astrocyte differentiation in early embryonic stages of spina bifida aperta. To date the pathophysiological mechanisms related to astrocyte differentiation with reactive astrogliosis of spina bifida aperta are poorly understood. This study characterizes the development of these reactive astrocytes from Pax6 and Olig2 multipotent progenitor cells. In comparing 20 rat spinal cords in retinoic-acid (RA) induced spina bifida and 6 sham controls at three gestational times (E15, E17, E20) we observed differentially expressed genes using standard RNA seq approach and RT-qPCR not only the transcription factors Pax6, Olig2 and Nkx2.2, but also the HLH transcription factors, Mash1, Ngn2, ID1 and ID2 that regulates the spatiotemporal neurogenesis and gliogenesis. We have also identified the presence of Olig2+ and Pax6+ multipotent progenitor cells in GFAP+ reactive astrocytes during gestation and increased numbers in the neural tissue exposed to amniotic fluid. Together, our observations demonstrate altered neurogenesis and astrogenesis patterns that contribute to neuronal dysfunction, injury, and neural loss in spina bifida aperta after birth.

Disclosures: M. Oria: None. **Z. Li:** None. **B. Pathak:** None. **K. Bakri:** None. **J.L. Peiro:** None.

Poster

641. Animal Models of Developmental Disorders

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 641.28/A70

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Children's Research Institute 1181
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Children's National Health System 44290

Title: Complex behavioral assessment of preterm brain injury models

Authors: *D. BAKALAR, H. LACAILLE, C. M. VACHER, J. O'REILLY, J. SALZBANK, P. KRATIMENOS, S. SEBAOUI, A. PENN;
Children's Natl. Hlth. Syst., Washington, DC

Abstract: Preterm birth increases the risk of attentional deficits, but the neurological basis of this process is unknown. Our lab has previously shown that pre- and post-natal inflammatory insults work synergistically, leading to interneuron subtype alterations. This includes Parvalbumin-expressing (PV) interneurons, implicated in human Attention Deficit Disorder. Here, two preterm brain injury models are compared, one resulting from external environmental insults (a two hit model combining prenatal maternal inflammation with postnatal hypoxia) and the other resulting from intrinsic environmental factors (Akr1c14-Cyp19Cre mouse which has a placental deficit of the anti-inflammatory hormone Allopregnanolone). We screened mice for behavioral deficits using an IntelliCage (an automated group behavioral testing platform) and custom analysis pipeline focused on attention and inhibition. Module 1 assessed activity levels, anxiety, circadian rhythm, and working memory. Module 2 assessed Place Learning and Reversal Learning. Module 3 used the Simple Reaction Time Task, previously validated against the 5-Choice Serial Reaction Time task, to assess attention, impulsivity, and compulsivity. Finally, a Delay Discounting task was used to measure impulsive choice and reward motivation. A custom-written Python analysis program cleans the data, extracts relevant values and produces a pandas DataFrame on which statistics can be run, allowing for full automation of all modules. Preliminary data in both mouse models show no changes in baseline behavior, and intact place learning and memory. However, attentional deficits are evident, implicating the medial prefrontal cortex. This region will be assessed at a molecular and cellular level with a specific focus on inflammatory processes and PV-interneurons.

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Poster

641. Animal Models of Developmental Disorders

Location: Hall A

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Program #/Poster #: 641.29/A71

Topic: A.07. Developmental Disorders

Support: NCN grant UMO-2018/29/B/NZ3/02675
NCN grant UMO-2018/29/N/NZ3/02682.

Title: Deficiency of Amotl1 leads to schizophrenia-like phenotype in mice

Authors: J. KRZEMIEN, K. O. ROJEK, M. WINIARSKI, P. BOGUSZEWSKI, E. KNAPSKA, ***T. J. PROSZYNSKI**;
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Abstract: The Angiomotin family comprises of three scaffold proteins Amot, Amotl1, and Amotl2 that have been implicated in the regulation of cell polarity, migration, and proliferation. We have recently reported that Amot together with Yap1, the Hippo pathway transcription co-activator, are critical for proper dendritic arborization and mice locomotor coordination (Rojek KO, et al. (2019) PLoS Biol 17(5): e3000253). However, the function of two other Angiomotins, Amotl1 and Amotl2 in neurons has not been investigated.
In the present study, we show that Amotl1 localizes to the synaptic compartments in neurons. In contrast to Amot mutants, mice with systemic or neuron-specific knockout (KO) of Amotl1 do not show impairments of motor coordination. Instead, Amotl1 mutants exhibit hyperactivity in the open field (n=10) and decreased anxiety reflected by the time spent in the center of the open field and reduced digging in the marble burying test (n=9). Amotl1 ablation causes alteration in mice sociability, which was assessed by a three-chamber experiment (n=8), and mice nesting behavior (n=6). Abnormal social behavior was independently studied in the Eco-Hab experiment (n=10), in which behavior of individual animals within the larger group is measured over prolonged time and analyzed in an automatic manner (Puścian A., et al. (2016) eLIFE 5: e19532). Amotl1 mutants, however, did not show tendency to increased repetitive behavior (e.g. self-grooming). Morphological analysis of Amotl1 KO brains by MRI and histochemical methods revealed a 50% increase in volume of lateral ventricles and cerebrospinal fluid (n=4). Similar features are observed in animal models of schizophrenia.
We identified a novel synaptic protein Amotl1, the deletion of which causes behavioral deficits thus it could be a potential molecular target for the development of new therapeutics for neurological disorders.
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Poster

642. Autism: Neurons, Circuits, and Behavior

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 642.01/A72

Topic: A.07. Developmental Disorders

Support: New York State Office for People with Developmental Disabilities

Title: The effects of maternal high fat diet on ultrasonic vocalizations during maternal separation by BTBR and B6 mouse pups

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Abstract: The etiology for most cases of autism spectrum disorder (ASD) is unknown at this time. There is strong evidence for the genetic role in ASD but environmental factors also have a modifying role. One potential environmental factor is the maternal diet during fetal development. Obesity before and during prenatal development increases the vulnerability of affective disorders including schizophrenia and ASD. Prenatal maternal obesity has been shown to be a risk factor for ASD and other developmental disabilities (Krakowiak et al. *Pediatrics* 2012; 129; e1121). BTBR $T^{+ tf}$ Itpr/J (BTBR) mice have been used as a model for ASD because of low sociability and high levels of repetitive behaviors. These experiments examined the effects of a maternal high fat diet on pup ultrasonic vocalizations (USV) in C57BL/6J and BTBR offspring on P4, 6 & 8. Female C57BL/6J and BTBR mice were placed one of three diets (regular mouse chow, high fat diet, control diet) for 2 weeks prior to mating and remained on each diet throughout these experiments. One male and female pup per litter were tested for USVs for 5 min. Overall, the BTBR pups made more calls compared to the B6 pups. Across all three time points, the high fat diet BTBR pups made more calls than the pups from the control and chow diets. Across all 3 diets, BTBR pups made longer calls compared to B6 pups, regardless of diet. Differences in prenatal nutrition led to minor differences in pup vocalization behavior.

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Poster

642. Autism: Neurons, Circuits, and Behavior

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Topic: A.07. Developmental Disorders

Support: KAKENHI Grant 15K14356

Title: Comprehensive profiling and localization of gene expression in the cerebral cortex and striatum of BTBR mice, a mouse model of autism spectrum disorder by comparing with those of C57BL6/J, a highly social mouse strain

Authors: *S. MIZUNO[1], J. HIROTA[1], H. IWASAKI[2], S. OKABE[3], Y. SANO[1], T. FURUICHI[1];
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Abstract: Autism spectrum disorder (ASD) is a neurodevelopmental disorder, of which prevalence rate is approximately 1%, and that is characterized by two core symptoms: 1) impaired social interaction and communication, and 2) restricted and repetitive behavior. Genetic factors strongly contribute to the risk for ASD. Recent studies reported that ASD have high degree of genetic heterogeneity and are probably caused by complex interaction between multiple genes. However, it is unclear how a combination of different gene variations causes a common mind symptom. Here, we compared brain gene expression between two mouse strains BTBR T+tf/j (with low sociability and used as a model for ASD) and C57BL/6J (B6) (with high sociability). For this purpose, we applied DNA microarray analysis (Agilent, SuperPrint G3 Mouse Gene Expression Microarrays: 27,122 genes, 4,578 lncRNAs) to perform genome-wide expression profiling in the cerebral cortex and striatum because of the possible involvement of the corticostriatal pathway in ASD core symptoms. As a result, we could identified 1,081 downregulated genes and 359 upregulated genes. Among these genes, 45 genes have already been reported as ASD gene candidates (ASD-linked genes registered in AutDB), and 268 genes are non-coding RNA (ncRNA). First, we focused on Fmr1 and Cpeb4 (RNA-binding protein genes known candidate for ASD) and searched their binding target genes among 45 ASD-related genes differently expressed between BTBR and B6. The results showed that there were 4 and 15 targeted genes for Fmr1 and Cpeb4, respectively in ASD-related genes differently expressed in BTBR. Second, we investigated functional interaction networks of ncRNAs using a database starBase v3.0 in which 19 ncRNAs among those differently expressed in BTBR were registered in this program. The results showed that these 19 ncRNAs possibly interact with 135 target genes including 6 ASD candidate genes and thereby may affect their expression and/or function. Third,

we performed gene ontology (GO) enrichment analysis using DAVID 6.8. The results highlighted 96 annotations (GO terms) including neuron/synapse, immune, chromosome/DNA-related ones. Lastly, we performed clustering of ASD candidate genes differently expressed in BTBR based on their spatial gene expression profiles in mouse brain regions using the Allen Brain Atlas tool. The results showed that many genes were classified into a region cluster including prefrontal, motor and temporal cortex. Taken together, our comprehensive gene expression study indicates a transcriptomic feature that distinguishes between BTBR and B6 mice, which may contribute to their difference in sociability.

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Poster

642. Autism: Neurons, Circuits, and Behavior

Location: Hall A

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Program #/Poster #: 642.03/A74

Topic: A.07. Developmental Disorders

Title: Overexpression of metabotropic glutamate receptor 5 in the striatum and prefrontal cortex of BTBR mouse model of autism spectrum disorder

Authors: F. MATRISCIANO[1], V. LOCCI[1], E. DONG[1], ***D. R. GRAYSON**[2], A. GUIDOTTI[1]; [1]Psychiatry, Univ. of Illinois Chicago, Chicago, IL; [2]Psychiatry, Univ. of Illinois at Chicago, Chicago, IL

Abstract: Autism Spectrum Disorder (ASD) is a complex neuropsychiatric syndrome for which there is not presently a cure. The metabotropic glutamate receptor 5 (mGluR5) is involved in synaptic plasticity and learning and memory mechanisms during development and represents a suitable target for neurodevelopmental disorders associated with intellectual disabilities such as ASD. Our study focused on the expression, function, and signaling of mGluR5 using the BTBR T+tf/6J (BTBR) mice that exhibit behavioral endophenotypes relevant to the behavioral symptoms associated with ASD. C57BL/6J (B6) mice were used as controls. First, we measured the mGluR5 mRNA levels in selected brain regions of BTBR mice involved in cognition and motor programing such as frontal cortex, hippocampus, striatum and cerebellum. Both mRNA and protein levels of mGluR5 were significantly higher in striatum of BTBR compared to B6 mice. Higher levels of mGluR5 mRNA and protein were also detected in frontal cortex. The striatum of BTBR mice was characterized by decreased levels of mGlu2 receptors which are neuroprotective against excitotoxicity mechanisms induced by high levels of glutamate. Other mGluR mRNAs were unchanged. Because the canonical signaling pathway associated with the activation of mGluR5 coupled receptors is Pi hydrolysis, we also performed measurements of PI hydrolysis. Compared to controls, and we found significantly higher basal levels of inositol-

monophosphate accumulation in the striatal tissue of BTBR mice after systemic *in vivo* lithium exposure. In addition, we found increased levels of the early inducible gene *Mef2c,* and *Arc* which are responsible for AMPA receptor endocytosis at dendrites. Behaviorally, BTBR mice showed deficits in novel object recognition, social interaction and stereotypic behavior, such as self-grooming, which is one of the major behavioral features of these animals. A single injection of the selective allosteric glutamate antagonist MTEP (10 mg/kg, i.p) fully reversed the stereotypic behavior and reduced the high levels of Arc mRNA. A higher variability in the response to MTEP was observed in the social interaction test, suggesting that in addition to altered expression of mGluR5, additional mechanisms may be involved in the control of altered social behavior. Our results showed that in BTBR mice, which exhibit biochemical, behavioral and pharmacological endophenotypes reminiscent of those observed in ASD subjects, that mGluR5 receptor expression is elevated and likely responsible for some of these behaviors.

Disclosures: F. Matrisciano: None. **V. Locci:** None. **E. Dong:** None. **D.R. Grayson:** None. **A. Guidotti:** None.

Poster

642. Autism: Neurons, Circuits, and Behavior

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Program #/Poster #: 642.04/A75

Topic: A.07. Developmental Disorders

Support: FRF 13-1617

Title: Perinatal fluoxetine exposure results in social deficits and reduced monoamine oxidase gene expression in mice

Authors: C. M. BOND, **J. C. JOHNSON**, V. CHAUDHARY, M. L. MCWHORTER, *N. S. WOEHRLE;
Wittenberg Univ., Springfield, OH

Abstract: BACKGROUND Currently, 8.7% of pregnant American women fill antidepressant prescriptions, and approximately 80% are for selective serotonin reuptake inhibitors (SSRIs). Perinatal antidepressant drug exposure increases risk for autism spectrum disorder, yet the molecular and neurobehavioral effects of maternal antidepressant drug use on offspring remain poorly understood. METHOD In this study, we examined social interaction behavior and whole brain monoamine oxidase A (*MAOA*) gene expression in the offspring of female mice administered the SSRI fluoxetine non-invasively throughout gestation and early lactation. We tested mice in the three-chambered social test (TCST) as juveniles and again as young adults. Gene expression was measured using droplet digital PCR (ddPCR). RESULTS We found deficits in sociability and social novelty-seeking behavior in the juvenile offspring of SSRI-

treated mice, and these behaviors persisted into young adulthood. Furthermore, we found decreased *MAOA* expression in the brains of offspring of SSRI-treated mice. CONCLUSIONS Our findings suggest that exposure to antidepressants during the prenatal and early postnatal period negatively affects social development. Moreover, reduced *MAOA* expression may play a role in the mechanistic pathway linking SSRI exposure and behavioral deficits symptomatic of autism.

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Poster

642. Autism: Neurons, Circuits, and Behavior

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Topic: A.07. Developmental Disorders

Support: NIH T32 GM008014 (NIGMS)

Title: The role of cerebellar granule cells in autism spectrum disorder related behaviors

Authors: *B. DENTEL, E. GIRMASH, E. OH, L. ANGELES-PEREZ, C. REN, P. TSAI; Neurol., UT Southwestern, Dallas, TX

Abstract: Autism Spectrum Disorder (ASD) affects 1 in 59 children and is a heterogenous disorder for which there are no targeted therapies. Individuals with ASD not only experience the 2 core deficits in social and repetitive behaviors but also experience severe comorbid conditions including anxiety. The underlying neural substrate underlying these behavioral disruptions in ASD are not well understood. Accumulating evidence has increasingly implicated the cerebellum in patients with ASD, including many studies which demonstrate significant changes in cerebellar volume in individuals with ASD. While previous studies have highlighted the vital modulatory role of Purkinje cells of the cerebellum in ASD-related behaviors, granule cells (GCs) make up the majority of cerebellar volume, while many ASD-linked genes are exclusively expressed in GCs. However, as little is known about the contribution of GCs to ASD-related behaviors, we hypothesize an important role for cerebellar GCs in the regulation of ASD-relevant behaviors. To investigate this hypothesis, we generated a GC-specific deletion of *Tsc1*, one of the genes mutated in Tuberous Sclerosis, a neurodevelopmental disorder associated with high rates of ASD in an *Atoh-1*^{creER2}*Tsc1*$^{fl/fl}$ mouse. We first assessed recombination of this mouse by crossing an *Atoh-1*^{creER2}*Tsc1*$^{fl/fl}$ mouse to a *Rosa* cre TdTomato Reporter mouse. All pups were injected on p0 with 350mg/kg tamoxifen. At 6 weeks of age, we examined animals for behaviors relevant to ASD (tests performed from least to most stressful). The experimenter was blinded to genotype during all behavioral testing with only males tested in this cohort. Mutants

were compared with Cre negative, tamoxifen-exposed littermate controls (n=13 per cohort). We examined ASD-relevant behaviors and whereas we identified no social deficits or repetitive behaviors, mutants' performance in reversal learning was significantly worse than control littermates, pointing to deficits in behavioral inflexibility. Upon further investigation we also found that mutant mice displayed anxiety-like behaviors in the open field and light/dark box testing. Acute slice recordings were also performed on GCs. Mutant cells were less excitable and had decreased excitatory postsynaptic currents (EPSCs). This model demonstrates that hypofunction of GCs in the cerebellum contributes to ASD-related behaviors.

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Poster

642. Autism: Neurons, Circuits, and Behavior

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Topic: A.07. Developmental Disorders

Support: Research Opportunity Fund #DRDP-ROF2016

Title: Impacts of social and environmental deprivation on fine motor development in mice: Implications for ASD

Authors: S. PICKERNELL, K. CLARK, A. PELLE, *D. P. DEVINE;
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Abstract: People with Autism Spectrum Disorder (ASD) present with many co-morbid features, which include sensori-motor integration deficits. As children with ASD fail to interact appropriately with their social and physical environment, we used a rodent model to investigate the potential that inadequate environmental engagement may impair development of sensori-motor integration and fine motor skills. We raised 170 C57Bl6 mice from weaning in physically and socially enriched environments, or environments that were physically impoverished, but included social mates, or environments that were both physically and socially impoverished. The mice were then tested in a vermicelli handling task to assess the impact of impoverishment on development of sensori-motor integration. The total amount of pasta consumed was scored for each mouse and a defined set of fine motor handling behaviors was assessed. The enriched mice ate significantly more pasta and exhibited greater fine motor dexterity than did the mice in both the impoverished housing environments. Overall, these results support the theory that social and environmental deprivation leads to failures in sensori-motor development.

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Poster

642. Autism: Neurons, Circuits, and Behavior

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Title: Developmental trajectories in social reward and salience brain networks: A combined behavioral and structural MRI study in infant rhesus macaques

Authors: *S. E. SAAVEDRA[1], M. WALLACE[1], T. JONESTELLER[1], M. BAUTISTA[1], J. WESSON[1], M. H. KYLE[1], L. LI[2,5], M. A. STYNER[6], J. RAPER[1,2], J. BACHEVALIER[1,3], M. SANCHEZ[1,4], Z. KOVACS-BALINT[1];
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Abstract: Non-human primate (NHP) translational models are critical for understanding social deficits in neurodevelopmental disorders, such as Autism Spectrum Disorder (ASD). Development of primate infant attachments/bonds depends on the mother and are necessary for the maturation of social competency. The goal of this study was to identify early social predictors shaping later social competence and to map the developmental trajectories of social reward and salience neurocircuits that support the maturation of early prosocial behaviors and attachments in infant rhesus macaques.
Longitudinal structural MRI scans were acquired at 2, 4, 6, 8, 12, 16, 20, 24 wks from 25 male macaques living with their mothers in social groups, and again at 12 months in a subset of 4 animals. T1- and T2-MRI images were acquired using a 3T MRI scanner and analyzed for volumetric changes in social reward and salience brain regions, i.e. amygdala (AMY), nucleus accumbens (NACC), anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), ventromedial prefrontal cortex (vmPFC) and insula (INS). Measures of infants' social development were collected from a subset of subjects (n = 4), using: (1) a rhesus ethogram, (2) rating scales of atypical social behaviors (adapted from the Social Responsiveness Scale used for ASD diagnosis

in humans) and (3) maternal rating scales (to examine the contribution of maternal care to developmental outcomes).
AMY volume -core region for social salience- increased rapidly from 4-8 and after 16 wks. The INS -crucial in social cognition and in mapping interoception that initiates processing of salient emotional information and explicit motivation- showed rapid gray matter volume increase from 4-8 wks, and sharp white matter (WM) volume decrease from 4-12 wks. These neural changes were paralleled by a decline in frequency and duration of mother-infant affiliative behaviors (including face-to-face interactions and contact) by 8 wks, when infants increase independence-seeking behavior and engage in social play with peers. We are currently analyzing changes in other brain regions in these networks (ACC, OFC, NACC) and increasing the sample size.
Our findings suggest that during the first 24 wks, particularly the first 8 wks, social salience and reward brain networks undergo robust structural changes, presumably to support the infant's adjustment to independence and increasing emotional awareness of appropriate social interaction. Understanding how normative social behavior and the underlying social brain networks develop can help elucidate the roots of brain-behavior pathogenesis of human social deficits.

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Poster

642. Autism: Neurons, Circuits, and Behavior

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 642.08/A79

Topic: A.07. Developmental Disorders

Title: A new objective electrophysiological technique as a measure of central auditory processing in a rat model of autism spectrum disorder

Authors: R. SINHA[1], D. MISHRA[2], **R. MITTAL**[2], D. SHAHAL[2], J. MITTAL[2], *S. A. PENA[1], J. BOHORQUEZ[4], A. A. ESHRAGHI[3];
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Abstract: Objective: Autism Spectrum Disorders (ASD) comprise complex neuropsychiatric disorders associated with high healthcare burden. One of the most commonly reported sensory processing impairments in individuals with ASD is the abnormalities in central auditory processing (CAP). ASD patients consistently exhibit atypical behaviors in response to auditory stimuli and central auditory processing disorder (CAPD), which refers to a complex and

heterogeneous group of auditory-specific disorders. There is still not a reliable electrophysiological technique to determine CAPD in ASD patients. The aim of this study was to develop an electrophysiological technique that can be used as an objective measure of CAP in anesthetized rat model.
Methods: We developed a method to determine the Objective Gap Detection Threshold (OGDT) in rats. Quasy steady state response (QSSR) elicited by noise modulated by 40Hz gaps of different durations were analyzed in time and frequency domains using wild-type (WT) and rat model of ASD. The detection was performed in frequency domain, by applying the Hotelling's T2 test to the 40Hz complex fundamental frequency component. The OGDT is estimated by analyzing the confidence ellipses of the 40Hz spectral component.
Results: Our results suggest that WT rats were able to detect noise gaps as low as 2 ms. On the other hand, we observed that the rats with ASD phenotype were detecting noise gaps of 12, 10 and 8ms and not detecting thresholds lower than the 6ms gap. We also observed the "vanishing" of response into the background noise when a 4ms noise gap is applied. The 6ms OGDT result was verified by the statistical T2 test and is consistent with the previous animal studies with awake rats. The OGDT values were significantly increased in our rat model of ASD in agreement with findings observed in humans having ASD.
Conclusions: We have developed an electrophysiological method to determine OGDT as a measure of CAPD in an anesthetized rat model. This technique eliminates the need for being alert and awake during the test bringing a new dimension especially in animal experiments regarding central auditory evaluation. The availability of novel objective techniques to determine CAPD will help in its early detection in patients diagnosed with ASD or suspicion of being on the spectrum leading to early intervention and hence better clinical outcomes.

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Poster

642. Autism: Neurons, Circuits, and Behavior

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Title: The role of Foxp1 and Foxp2 in striatal D1 spiny projection neurons

Authors: *N. I. AHMED, A. G. ANDERSON, G. KONOPKA;
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Abstract: Speech and language deficits and autism spectrum disorder have been observed in individuals with mutations in either *FOXP1* or *FOXP2*. These transcription factors can work together to regulate gene expression and one part of the brain where they are co-expressed is the striatum. Heterozygous reduction of *Foxp1* in mice results in hyperexcitability of dopamine 2 receptor spiny projection neurons (D2 SPNs) of the striatum without a significant effect on dopamine 1 receptor SPNs (D1 SPNs). Furthermore, behavioral studies have found motor learning impairments upon the conditional deletion of *Foxp1* from D2, but not D1, SPNs. We therefore hypothesize that *Foxp1* and *Foxp2* may be able to compensate for each other in the D1 SPNs. To test this hypothesis, we have deleted *Foxp1*, *Foxp2*, or both from the D1 SPNs in mice and are examining the effects of loss of these transcription factors on behavior and gene expression. We have found that D1 specific conditional knockout mice of *Foxp1* or *Foxp2* alone do not show deficits in motor learning as assessed by a rotarod assay. However, deleting both *Foxp1* and *Foxp2* from D1 SPNs leads to significant impairments in this assay. Ultrasonic vocalization recordings of these mice at early postnatal time points also show a trend in decreased bout number in the double conditional knockouts. Using single-nuclei RNA-sequencing, we are examining cell type-specific effects on gene expression that include non-cell-autonomous molecular changes with loss of these genes. These data offer novel insights into the extent to which *Foxp1* and *Foxp2* can coordinate molecular pathways important for striatal function and may provide a better understanding of the molecular underpinnings of speech and language impairments associated with *FOXP1* or *FOXP2* mutations.

Disclosures: N.I. Ahmed: None. **A.G. Anderson:** None. **G. Konopka:** None.

Poster

642. Autism: Neurons, Circuits, and Behavior

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Topic: A.07. Developmental Disorders

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Title: Modulation of ASD-like behavior in the MIA mouse model

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Abstract: We investigate how the immune system can modulate ASD-like behavior using a mouse model of neurodevelopmental disorders in which offspring are exposed to maternal

immune activation (MIA) during embryogenesis, resulting in deficits in sociability in adulthood. We demonstrate that the social behavior deficits of MIA mice can be modulated through the immune system. At the neural level, increasing immune activities produced a reduction in neural activity in the dysgranular zone of the primary somatosensory cortex (S1DZ). S1DZ hyperactivity was previously implicated in the manifestation of MIA behavioral phenotypes. At the molecular level, we demonstrate that modulation of blood brain-barrier (BBB) permeability, potentially allows immune molecules to act directly upon the brain. Our data suggest that peripherally-induced immune molecules can affect the expression of neurodevelopmental disorders by abrogating hyperactivity in the central nervous system.

Disclosures: M.D. Reed: None. **S. Kim:** None. **Y. Yim:** None. **H. Kim:** None. **H. King:** None. **G. Welch:** None. **M.T. Harnett:** None. **A. Waisman:** None. **L. Tsai:** None. **J.H. Huh:** None. **G.B. Choi:** None.

Poster

642. Autism: Neurons, Circuits, and Behavior

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 642.11/A82

Topic: A.07. Developmental Disorders

Support: NIH-NIGMS R35 GM119831
NIH-NIGMS T32 GM007377
NIH-NIMH F31 MH119789-01
UC Davis MIND Institute IDDRC U54 HD079125

Title: Altered RNA processing in CHD8 haploinsufficient mice

Authors: *A. A. WADE, C. P. CANALES, I. ZDILAR, A. L. GOMPERS, L. SU-FEHER, A. S. NORD;
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Abstract: CHD8 is a chromatin remodeler encoded by a high-risk autism gene. Studies in mouse models show that CHD8 has important roles in gene regulation, but mechanisms underlying this function have yet to be fully elucidated. While significant data point to the role of this protein in maintaining open chromatin for transcription, new evidence shows *Chd8* haploinsufficiency has downstream consequences on co-transcriptional RNA processing. We used RNA sequencing in mouse brain to further test how gene isoform expression is altered with heterozygous mutation to *Chd8*. We also used chromatin immunoprecipitation followed by liquid chromatography with tandem mass spectrometry in wild-type mouse cortex to profile Chd8 interaction partners and propose explanations for how Chd8 function could be related to RNA processing. In our

transcriptomic analysis, we found several alternatively-spliced RNA transcripts in *Chd8* mutant mice. Furthermore, differentially-spliced transcripts commonly encode synapse-relevant proteins, suggesting a relationship between perturbed splicing and synaptic dysfunction with *Chd8* haploinsufficiency. Preliminary proteomic data also suggest a physical association between Chd8 and splicing proteins, further implicating a relationship between Chd8 and co-transcriptional gene regulation. These studies offer a novel mechanism for pathology associated with heterozygous *Chd8* mutations but warrant additional *in vivo* validation and characterization before definitive conclusions can be made. As *Chd8* haploinsufficiency could represent generalized convergence of synaptic dysfunction and abnormal gene regulation in autism, understanding these perturbations could provide insight into the biological underpinnings of neurodevelopmental disorders.

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Poster

642. Autism: Neurons, Circuits, and Behavior

Location: Hall A

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Program #/Poster #: 642.12/A83

Topic: A.07. Developmental Disorders

Title: Altered gene expression in the embryonic rat brain following maternal poly I:C exposure during pregnancy

Authors: E. KAMIMURA[1,2,3], H. ZHU[1], A. SAEFULLOH[1,3], S.-I. HORIKE[2,3], ***S. YOKOYAMA**[1,3];
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Abstract: Maternal immune activation (MIA) during pregnancy with various infectious agents has been reported to increase risk for offspring's neurodevelopmental disorders, such as schizophrenia and autism spectrum disorders (ASD). Previous studies have established several rodent MIA models that manifest various abnormal behaviors characteristic of these disorders. In particular, offspring from the polyriboinosinic-polyribocytidilic acid (poly I:C) model has been demonstrated to exhibit the core symptoms of ASD including impairments in social communication and repetitive behavior, as well as schizophrenia-like behaviors including deficits in sensorimotor gating, working and social memory, and increased anxiety. However, little is known about the molecular and cellular mechanisms underlying these abnormal behaviors. In the present study, we therefore studied changes in gene expression of embryonic

brain obtained from the poly I:C model. Pregnant Wister rats at embryonic day 12 (E12) were injected intravenously with poly I:C (4 mg/kg) or saline. After 3 or 7 days (at E15 or E19), rats were deeply anesthetized with isoflurane, and embryonic brains were removed; the experimental procedures approved by the Guideline for the Care and Use of Laboratory Animals in Kanazawa University. Total cellular RNA was then extracted and subjected to microarray analysis. We compared gene expression differences between E15 and E19. Overall 610 common up-regulated genes and 529 common down-regulated genes were identified. Further analysis revealed that significant (fold change of at least 2.0, $p < 0.05$) changes were observed in 194 genes: 153 for up-regulation and 41 for down-regulation. Gene ontology analysis showed that genes representing the olfactory pathway are enriched: 30 up-regulated and one downregulated genes encoded olfactory receptors. These results suggest that poly I:C treatment alters multiple pathways other than immune-related genes, thereby increasing risk for neurodevelopmental disorders.

Disclosures: **E. Kamimura:** None. **H. Zhu:** None. **A. Saefulloh:** None. **S. Horike:** None. **S. Yokoyama:** None.

Poster

642. Autism: Neurons, Circuits, and Behavior

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Program #/Poster #: 642.13/A84

Topic: A.07. Developmental Disorders

Support: NIH Grant R01 MH108659
SFARI Pilot Grant 32322
postdoctoral fellowship from the Stanford Child Health Research Institute

Title: Dysregulation of the blood-brain barrier and neurovasculature induced by prenatal immune disturbances

Authors: *H. MOON, B. A. BABINEAU, J. UMANS, H. NGUYEN, T. D. PALMER; Stanford Univ., Stanford, CA

Abstract: Dysfunction of the blood-brain barrier (BBB) and neurovasculature has been implicated in the etiology of neurodevelopmental disorders such as autism spectrum disorder (ASD) and schizophrenia (SCZ). At a cellular level, BBB-associated endothelial cells regulate selective movements of ions, nutrients, metabolites, and immune cells. Prior genetic profiling from SCZ patient-derived endothelial cells uncovered dysregulation of the angiogenic pathways. Elevated peripheral neuroinflammatory biomarkers and immune cell infiltration in SCZ patients' brains suggested aberrant BBB permeability. Downregulation of *Claudins* and *Occludin*, BBB-associated tight junction proteins, has been detected in the SCZ brains. Genetic studies also

confirmed that a *CLAUDIN-5* SNP is linked to SCZ psychosis and *CLAUDIN-5* haploinsufficiency is associated with 22qDel syndrome. Intriguingly, BBB abnormalities in rare ASD cases were reported in a recent GWAS study identifying *LAT-1* mutations. Together, these previous findings suggest that BBB dysfunction may underpin the pathogenesis of neurodevelopmental disorders. However, the exact cellular mechanisms by which BBB disruptions cause the neuropathology of aforementioned diseases have not been elucidated. We hypothesized that neuroinflammation may result in endothelial cell dysregulation and BBB disorganization, leading to neocortical defects. To investigate mechanisms by which neurovasculature disruptions impair fetal brains, we prenatally challenged mice with immune activators. Maternal immune activation elicited cytokine responses in the maternal periphery, placentas, and fetal brains. Through further fetal brain expression analyses, we demonstrated downregulation of multiple target genes encoding tight junctions, adherens junctions, and metalloproteinases at the BBB. These modulating effects were also accompanied by suppression of the transcriptional factors of neural progenitors' self-renewal and mislocalization of neural subtypes. In prenatally exposed neocortex, the blood vessel formation was altered with aberrant neurovascular patterning. Our study identified novel molecular pathways which regulate BBB formation during neocortical development. This study also highlights that these networks are vulnerable to prenatal immune disturbances during the critical time points of development. These findings provide new evidence that modulation of the BBB integrity and homeostasis may serve as a new therapeutic strategy to mitigate neuroinflammation by restoring endothelial cell functions and regulating crosstalk between the brain and peripheral system.
(2289 total counts)

Disclosures: **H. Moon:** None. **B.A. Babineau:** None. **J. Umans:** None. **H. Nguyen:** None. **T.D. Palmer:** None.

Poster

642. Autism: Neurons, Circuits, and Behavior

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Program #/Poster #: 642.14/A85

Topic: A.07. Developmental Disorders

Support: Neurochlore
Fondation Bettencourt Schueller

Title: Pyramidal neuron growth and increased hippocampal volume during labor and birth in autism

Authors: R. CLOAREC[1,2], ***B. RIFFAULT**[1,2], A. DUFOUR[1,2], H. RABIEI[1,2], L.-A. GOUTY-COLOMER[1,2], C. DUMON[1,2], D. GUIMOND[1,2], P. BONIFAZI[3,4], S. EFTEKHARI[1,2], N. LOZOVAYA[1,2], D. C. FERRARI[1,2], Y. BEN-ARI[1,2];

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Abstract: Birth is among the most complex biological mechanisms in mammals and epidemiological studies suggest that birth-related alterations could lead to a higher incidence of autism spectrum disorders and other developmental disorders. Astonishingly, we have little information on how the brain is prepared for and endures this critical step. Experimental observations suggest that labor and birth are critical periods playing an important role in the pathogenesis of brain disorders. Furthermore, several indirect lines of evidence obtained in humans suggest that brain growth velocity slows during the third trimester, possibly in an effort to avoid an exacerbated brain volume during vaginal delivery, and this is followed by a spurt of growth after birth that correlates with synapse density. To understand whether and how the brain is prepared to meet the challenge of labor and birth, we performed experimental studies in control and *in utero* VPA injected rats (VPA model of autism) comparing brain and neuronal parameters shortly before and after birth. We report that in control animals neuronal morphology shortly before and after birth was similar, suggesting a "growth stop signal" in preparation for labor and birth. However, this stop signal is alleviated in VPA animals as illustrated by the increase in the length of apical dendrites of CA3 hippocampal pyramidal neurons during this period. Using the iDISCO clearing method, we further show that hippocampal, especially the CA3 region, and neocortical volumes are increased during labor and birth and that the cerebral volume distribution shifts from normal to lognormal in VPA animals. Maternal administration during labor and birth of the NKCC1 chloride transporter antagonist bumetanide, which reduces [Cl−]i and attenuates the severity of autism, abolished the neocortical and hippocampal volume changes and reduced the whole-brain volume in VPA-treated animals. These results suggest that the abolition of the oxytocin-mediated excitatory-to-inhibitory shift of GABA actions during labor and birth contributes to the pathogenesis of autism spectrum disorders by stimulating growth during a vulnerable period.

Disclosures: R. Cloarec: A. Employment/Salary (full or part-time):; Neurochlore. **B. Riffault:** A. Employment/Salary (full or part-time):; Neurochlore. **A. Dufour:** A. Employment/Salary (full or part-time):; Neurochlore. **H. Rabiei:** A. Employment/Salary (full or part-time):; Neurochlore. **L. Gouty-Colomer:** A. Employment/Salary (full or part-time):; Neurochlore. **C. Dumon:** A. Employment/Salary (full or part-time):; Neurochlore. **D. Guimond:** A. Employment/Salary (full or part-time):; Neurochlore. **P. Bonifazi:** None. **S. Eftekhari:** A. Employment/Salary (full or part-time):; Neurochlore. **N. Lozovaya:** A. Employment/Salary (full or part-time):; Neurochlore. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurochlore. **D.C. Ferrari:** A. Employment/Salary (full or part-time):; Neurochlore. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurochlore. **Y. Ben-Ari:** A. Employment/Salary (full or part-time):; Neurochlore. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurochlore.

Poster

642. Autism: Neurons, Circuits, and Behavior

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 642.15/A86

Topic: A.07. Developmental Disorders

Support: Jerome Lejeune Foundation Research grant #1674
Marie Curie Career Reintegration Grant PCIG09-GA-2011-293589

Title: Effects of cannabinoid drugs in preclinical models of autism spectrum disorder

Authors: S. SCHIAVI, A. MANDUCA, *V. TREZZA;
Roma Tre Univ., Rome, Italy

Abstract: The terms “Autism spectrum disorder” (ASD) define a group of pervasive neurodevelopmental disorders characterized by altered sociability, compromised communication and stereotyped/repetitive behaviors. No effective and specific treatments are yet available for ASD, and none of the off-label medications currently prescribed to ASD patients selectively ameliorates their deficits in the core social and communicative domains. Different lines of evidence support a role for the endocannabinoid system in ASD: 1. altered endocannabinoid activity has been observed in autistic patients, and 2. endocannabinoids are known to modulate behavioral traits that are typically affected in ASD. On this basis, we tested the hypothesis that changes in the endocannabinoid tone contribute to the altered phenotype observed in genetic and environmental preclinical models of ASD, with focus on behavioral features that resemble core and associated autistic symptoms. We used two validated rat models which display most of the core autistic-like behavioral features and which reflect the critical role played by both environmental and genetic factors in the pathogenesis of ASD: the environmental model based on prenatal exposure to the antiepileptic valproic acid (VPA), and the genetic model based on FMR1 protein deletion. In the course of development, VPA-exposed rats and and FMR1 KO rats showed specific core and secondary autistic-like traits, confirming the face validity of these animal models of ASD. At the neurochemical level, VPA-exposed rats and FMR1 KO rats showed changes in different components of the endocannabinoid system in multiple brain regions, from infancy to adulthood. Interestingly, pharmacological manipulation of endocannabinoid neurotransmission rescued the behavioral deficits displayed by these animal models of ASD. Altogether, these findings reveal that abnormalities in brain endocannabinoid activity may underlie the deleterious impact of environmental and genetic risk factors on ASD-relevant behaviors, and that the endocannabinoid system may represent an interesting therapeutic target in ASD.

Disclosures: S. Schiavi: None. **A. Manduca:** None. **V. Trezza:** None.

Poster

642. Autism: Neurons, Circuits, and Behavior

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Title: Single-cell analysis of Foxp1-driven mechanisms essential for striatal development

Authors: *A. ANDERSON, A. KULKARNI, M. HARPER, G. KONOPKA;
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Abstract: The striatum is a critical forebrain structure for integrating cognitive, sensory, and motor information from diverse brain regions into meaningful behavioral output. However, the transcriptional mechanisms that underlie striatal development and organization at single-cell resolution remain largely unknown. Foxp1, a transcription factor strongly linked to autism and intellectual disability, is enriched in the striatum compared to the rest of the brain with high expression in spiny projection neurons (SPNs) of the direct (dSPNs) and indirect pathways (iSPNs). Here, we show that Foxp1 regulates organizational features of striatal circuitry in a cell-type-dependent fashion. Using single-cell RNA-sequencing (scRNA-seq), we examine the cellular diversity of the early postnatal striatum and find that deletion of *Foxp1* in distinct SPN populations alters both the cellular composition and neurochemical architecture of the striatum. We identify Foxp1-regulated target genes within distinct SPN populations and connect these molecular changes to functional and behavioral deficits relevant to phenotypes described in patients with *FOXP1* mutations. Additionally, we combined our early postnatal scRNA-seq dataset with other striatal single-cell datasets spanning embryonic to adult time points and built a developmental trajectory map of striatal cells. We then examined the global molecular changes that occur in glial and other striatal cell-types with deletion of *Foxp1* in SPNs. These data reveal cell-type-specific transcriptional mechanisms underlying distinct features of striatal circuitry and identify Foxp1 as an important regulator of striatal development.

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Poster

642. Autism: Neurons, Circuits, and Behavior

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Program #/Poster #: 642.17/B2

Topic: A.07. Developmental Disorders

Support: K08 MH014743-01A1
University of Michigan Start-Up Funds (JD)

Title: Sex differences in infant processing of social cues in the valproic acid-induced autism-like rat phenotype

Authors: *A. M. WHITE[1,2,3], X. AN[4,1,2], J. DEBIEC[1,2,3];
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Abstract: Disrupted processing of social cues and altered social behaviors are among the core symptoms of autism spectrum disorders (ASDs). Animal models are particularly useful tools for modeling aspects of ASDs, as they can help identify the neurobiological underpinnings of some of these symptoms. One such model is the prenatal valproic acid (VPA) exposure autism-like phenotype. Developing rat fetuses exposed to VPA at embryonic day (E) 12.5 show reduced play behavior, social exploration, and social interactions as juveniles and adults. However, less is known about how VPA-treated rats respond to social cues in infancy. Here, we examined the behavioral response to social odors in infant rats exposed to 500 mg/kg VPA or saline at E12.5. In early infancy, (postnatal day (P) 6-7), pups underwent an odor preference test (OPT) in an arena that contained clean bedding at one end and contained soiled bedding laden with social olfactory cues from the pup's homecage at the other end. VPA-treated pups spent significantly less time and made fewer entries into the section of the arena that contained soiled bedding than saline-treated pups (p's < 0.05). When examining these results by sex, we observed that female VPA-treated pups spent significantly less time in the section of the arena that contained soiled bedding than saline-treated pups ($p < 0.05$), but this effect was not present in male pups ($p > 0.05$). Both female and male VPA-treated pups made fewer entries into the section of the arena which contained soiled bedding than female and male saline pups. Regardless of sex, VPA and saline-treated pups did not differ in their total distance traveled during the test ($p > 0.05$), so the differences we observed are unlikely to be due to motor deficits in the VPA-treated pups. When we examined behavior in the OPT in older pups (P13), we did not observe any significant differences between VPA and saline-treated pups. We also did not observe any differences between treatment groups when we analyzed our pups by sex. In accordance with previously published data, our data suggest that in early infancy, VPA-treated pups may have impaired social recognition and/or may be less motivated to approach social odors. This is especially

important because early infancy is a period of intense attachment learning, which relies on social cues. Our results may inform about the underlying behavioral characteristics of ASDs, including sex differences reported by clinical studies, and could shed light on potential opportunities for intervention.

Disclosures: A.M. White: None. **X. An:** None. **J. Debiec:** None.

Poster

642. Autism: Neurons, Circuits, and Behavior

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

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Topic: A.07. Developmental Disorders

Support: Nancy Lurie Marks/ Landreth Family Foundation

Title: Neuroanatomical consequences of prenatal exposure to ASD-specific maternal antibodies in rat's offspring

Authors: *M. WOLF-OCHOA[1], C. FALCONE[1], M. R. BRUCE[2], M. D. BAUMAN[3,4], J. VAN DE WATER[2,4], V. MARTÍNEZ CERDEÑO[1,4];
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Abstract: Autism spectrum disorders (ASD) are a set of neurodevelopmental disorders classified by core impairments in social interactions and communication that are accompanied by the presence of repetitive and stereotyped behaviors. Despite increasing prevalence rates and awareness, the causes for idiopathic ASD are unknown. One potential non-genetic contributing factor to ASD is immune system dysregulation, which has been frequently described in individuals with ASD. Immunoglobulin G (IgG) antibodies transfer at high concentrations during mid-gestation in humans. Under normal conditions, antibodies are unable to cross the blood-brain barrier (BBB) to access the brain. However, the BBB is permissive during early brain development thus permitting maternal antibodies access to the fetal brain. A strong association between maternal AB reactivity towards fetal brain proteins and risk of ASD has been previously identified. Early studies identified patterns of reactivity to fetal brain proteins at approximately 37 and 73 kDa that were uniquely found among mothers of children with ASD. Several preclinical animal models have been conducted to determine pathogenic importance of these particular maternal AB, finding ASD-like behavioral alterations in offspring exposed to the AB from mothers of children with ASD. However, all of the animal models to date have utilized passive transfer techniques in which pregnant animals were injected during mid-gestation with human IgG isolated either from mothers of typically developing children or from mothers of

children with ASD. Herein, we propose to use our antigen-driven animal model of maternal AB related (MAR) autism. In this model, rat embryos are continuously exposed to the maternal AB throughout gestation, better representing the MAR ASD environment. We investigated the neuroanatomical and neuropathological consequences of prenatal exposure to the ASD-specific maternal AB in offspring. We quantified the number of the main neural cell populations in the cerebral cortex (neurons, astrocytes, oligodendrocytes) in the brain of adult MAR offspring (Ongoing). We analyzed the synaptic component by quantifying the number of pre- (V-glut+) and post-synaptic (PSD95+) structures in the cerebral cortex of the MAR ASD rat, and found a decrease in the number of pre- and post-synaptic structures. We evaluated the status of the immune cells of the brain, microglial cells, and did not find a change in their number. We are currently analyzing state of activation. Understanding the underlying etiology of ASD is crucial. The identification of risk factors and mechanisms would allow for earlier identification, treatment, and prevention.

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Poster

642. Autism: Neurons, Circuits, and Behavior

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 642.19/B4

Topic: A.07. Developmental Disorders

Support: Voelcker Biomedical Research Foundation

Title: Therapeutic potential of granulocyte-colony stimulating factor for core autism behaviors

Authors: *G. G. GOULD[1], S. FEDORCHAK[1], L. F. FERREIRA[1], B. RICE[1], N. PATHAPATTI[1], B. SAYGIN[1], M. LEONARD[1], S. T. SCHULTZ[1], E. B. KRAIG[2], L. C. DAWS[1];
[1]Cell. & Integrative Physiol., U Texas Hlth. Sci. Ctr. at San Antonio, San Antonio, TX; [2]Cell Systems and Anat., U Texas Hlth. Sci. Ctr. at San Antonio, San Antonio, TX

Abstract: The need for more effective and comprehensive treatments for core autism symptoms remains critical. In about 20% of autism cases, excessive serotonin transporter (SERT) function is evident, and hyperactive SERT seems to underlie behavior deficits paralleling autism in rodents. Pro-inflammatory cytokines can impact SERT function and vice versa. Signs of altered immune response and inflammation are evident in many autism patients, so therapeutics that modulate inflammatory immune response can have therapeutic potential. Granulocyte-colony stimulating factor (G-CSF) is an endogenous cytokine that is a hematopoietic growth factor stimulating neutrophil production. G-CSF has neurotrophic, anti-inflammatory and anti-apoptotic

functions in the central nervous system that were unknown prior to its approval for human use as an adjuvant to chemotherapy for cancer patients. As such G-CSF is emerging as a potential therapeutic to protect or restore memory and cognitive flexibility. We hypothesized G-CSF might ameliorate autism-like behaviors in black and tan brachury (BTBR) mice, wherein other researchers found evidence of elevated neuro-inflammatory markers. The mean baseline serum G-CSF in BTBR is 85 ± 26 pg/ml lower than in C57BL/6J mice. To better understand G-CSF's role in shaping autism-relevant behaviors, we studied them in adult male BTBR after G-CSF (5 d, 125 µg/kg/day) or saline injections. Behavior tests started 3 days after final injection were social preference and marble burying. Two days later dominance was tested, and 3 days later water T-maze tests commenced for 5 days, followed by 3 days of reversal to assess cognitive flexibility. To ensure rigor and reproducibility, a priori power analysis was performed and treatment-blind observers collected behavior data**.** G-CSF treatment did not alter dominance, preference for social interaction or novelty or marble burying relative to saline controls. Yet interestingly G-CSF treatment reduced errors and time to locate the platform on reversal day 1 in the water T maze. Hence weeks after treatment subacute G-CSF enhanced BTBR cognitive flexibility, wherein initial serum G-CSF levels are relatively low. To reveal potential underlying mechanisms we examined SERT and dopamine transporter binding in brains from behavior-tested mice in terminal field areas using [^{125}I] RTI-55 with selective blockade. SERT density was increased in the hippocamus following G-CSF treatments. Future studies of G-CSF treatment effects on BTBR autism-relevant behaviors under different treatment regimens paired with cytokine panel measures will help to elucidate the mechanisms of action involved in the brain.

Disclosures: G.G. Gould: None. **S. Fedorchak:** None. **L.F. Ferreira:** None. **B. Rice:** None. **N. Pathapatti:** None. **B. Saygin:** None. **M. Leonard:** None. **S.T. Schultz:** None. **E.B. Kraig:** None. **L.C. Daws:** None.

Poster

642. Autism: Neurons, Circuits, and Behavior

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 642.20/B5

Topic: A.07. Developmental Disorders

Support: RGPIN-2013-436204

Title: Effects of prenatal stress and/or forebrain Atrx deficiency in C57BL/6 male mice on maternal care, brain development, and emotional, cognitive and social behaviors in the adult offspring

Authors: *G. J. RODRIGUES[1], K. LEE[2], H. MAILLET[2], D. GOGUEN[2], I. C. G. WEAVER[2]; [1]Psychology and Neurosci., Dalhousie, Halifax, NS, Canada; [2]Psychology and Neurosci., Dalhousie Univ., Halifax, NS, Canada

Abstract: Introduction: Early childhood experience and degree of parental-infant attachment influence the developing brain, notably in brain areas that support stress regulation, cognition and social behaviors. Animal models examining gestational stress suggest that sustained changes in gene expression in response to prenatal stress and/or natural variations in mother-pup interactions during the first week of postnatal life is mediated by changes in chromatin structure and DNA methylation. Although the exact mechanism is not completely understood, the chromatin remodeling factor ATRX is stably regulated by maternal care. We compared the affiliative behavior of mothers toward Atrx hemizyogous (Atrx+/-) and wild-type (Atrx+/+) offspring during the first week of life as a function of prenatal experience (gestational restraint stress verses no restraint stress).
Methods: Restraint-stress and behavioral phenotyping assays to measure the frequency of mother-pup interactions of C57BL/6 mice as well as open-field, Morris water maze and social investigation performance in the adult male and female Atrx+/+ and Atrx+/- offspring. RT-qPCR arrays for gene activity, western blotting for signaling proteins and immunohistochemistry for structure and function in transgenic mice and chromatin immunoprecipitation confirmed by sodium bisulfite-pyrosequencing to profile DNA methylation and chromatin modifications.
Results: Mothers provided less active maternal care and spent less time in contact with Atrx+/- offspring by comparison to Atrx+/+ offspring— similar to gestational-stressed mothers. Stress during pregnancy and maternal behaviour influenced Atrx expression, and Atrx genotype influenced maternal behaviour toward the whole litter. As adults, offspring prenatally stressed and/or reared with Atrx+/- males showed altered Atrx gene regulation, reduced forebrain growth and increased anxiety, social avoidance and cognitive deficits—including Atrx+/+ female mice.
Conclusion: Our findings demonstrate an unexpected role for ATRX in prenatal and early postnatal mouse development involving experiences of social and affiliative interactions, such as parenting, with a persistent effect on DNA methylation, hippocampus development, cognition, and anxiety-related and social behaviors in the adult offspring.

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Poster

642. Autism: Neurons, Circuits, and Behavior

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Topic: A.07. Developmental Disorders

Support: R01 CA74177
NF150083

Title: The basolateral amygdala plays an integral role in modulating social memory deficits in neurofibromatosis type 1 mice

Authors: *H. P. DROZD[1], J. L. LUKKES[2], A. R. ABREU[2], E. T. DUSTRUDE[2], D. W. CLAPP[3], A. SHEKHAR[2], A. I. MOLOSH[4];
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Abstract: Neurofibromatosis type 1 (NF1) is an autosomal dominant disease affecting approximately 1 in 3000 people. NF1 results from a mutation in one copy of the neurofibromin gene (*NF1*), a negative regulator of the RAS-MAPK/ERK pathway. In addition to neurocutaneous lesions and tumors, individuals with NF1 show increased incidence of specific learning disabilities, attention deficit hyperactivity disorder, and autism spectrum disorder (ASD), with 20-30% meeting diagnostic criteria for ASD. ASDs represent a heterogeneous group of disorders characterized by deficits in social interaction and communication and restricted behaviors or interests. We have previously shown that male mice haploinsufficient for the neurofibromin gene ($Nf1^{+/-}$) demonstrate deficits in long-term social memory and hyperactivation of the RAS-MAPK/ERK pathway in the basolateral amygdala (BLA). Reduction of RAS-MAPK/ERK activity directly in the BLA of $Nf1^{+/-}$ male mice using p21 protein-activated kinase inhibitor rescued long-term social memory deficits. To further elucidate the role of the BLA in social learning, we injected a calmodulin-kinase II (CaMKIIα) adeno-associated virus (AAV) that expressed eYFP (control; AAV5-CaMKIIα-eYFP) or channelrhodopsin-2 expressing AAV (ChR2; AAV5-CaMKIIα-ChR2(H134R)-eYFP) into the BLA of adult C57/BL6J wild-type (WT) male mice. Additionally, we injected control and archaerhodopsin-3 AAVs (eArch; AAV5-CaMKIIα-eArch3.0-eYFP) in the BLA of adult $Nf1^{+/-}$ male mice. Four weeks later, mice were photostimulated in the BLA for forty-five minutes after acquisition of a social memory in the three-chamber social preference test. Twenty-four hours after BLA photostimulation, long-term social memory in the social preference test was assessed. During acquisition of short-term social memory, all mice displayed preference for the novel mouse. However, twenty-four hours after BLA photostimulation, BLA ChR2-expressing WT mice exhibited equal preference for a novel mouse compared to the familiar mouse in the social preference test. Dual immunofluorescence was used to map pERK, c-fos, and eYFP expression in the BLA of control-, ChR2-, and eArch-injected mice. Increased pERK activation immunoreactivity was observed in ChR2-expressing WT mice after BLA photostimulation compared to control WT mice. In contrast, long-term social learning deficits observed in $Nf1^{+/-}$ control mice were restored in BLA eARCH-expressing $Nf1^{+/-}$ mice when the BLA was inhibited with green light. These data provide evidence for the significant role of the BLA in regulating long-term social memory in an experimental model of NF1.

Disclosures: **H.P. Drozd:** None. **J.L. Lukkes:** None. **A.R. Abreu:** None. **E.T. Dustrude:** None. **D.W. Clapp:** None. **A. Shekhar:** None. **A.I. Molosh:** None.

Poster

642. Autism: Neurons, Circuits, and Behavior

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 642.22/B7

Topic: A.07. Developmental Disorders

Support: NIGMS-GM113109 NIH
KSU Start up Funds
KSU USRG

Title: Set shifting deficits in valproic acid model of autism in Long Evans rats

Authors: *Z. MCKINNELL[1], B. CHALLANS[2], T. MAZE[2], A. RAMOS[2], A. PRITCHARD[2], B. PLAKKE[3];
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Abstract: According to the CDC approximately 1 in 59 children will be diagnosed with autism spectrum disorder (ASD), which is characterized by social deficits, impairments in communication, restrictive/repetitive behavior, and deficits in cognitive flexibility. Research focused on understanding the underlying neural network of this disorder is an important step in developing more efficient treatment strategies for individuals that struggle with this disorder. The Valproic acid (VPA) model of autism is a widely used model of autism in animals (Mabunga et al., 2015), where VPA treated offspring exhibit alterations in social and repetitive behavior. In tasks testing cognitive flexibility, people with ASD tend to exhibit a higher shift cost, which means it is more difficult to shift attention on trials where the rule changes (Van Eylen et al., 2011). In order to examine cognitive flexibility within the VPA model we ran offspring through the attentional set-shifting task, which is the rodent equivalent of the Wisconsin Card Sorting Task (Birrell et al., 2000). To control for order effects, a Latin square counterbalancing technique was used to ensure that each pair of exemplars would be experienced in each phase of the task across rats (Tait et al., 2018). All offspring from controls and VPA litters were kept for a total of 82 rats. Both males and females were run to investigate sex differences. Rats went through the set shifting task after reaching adulthood, after postnatal day 60. VPA rats made significantly more errors during the intra-dimensional shift (IDS) than control rats. Preliminary analyses also indicated there is a main effect of sex across multiple phases including on simple discrimination and IDS. Additionally, fewer VPA rats formed an attentional set, evidence that they had difficulty learning the rules of the task. One of the symptoms of ASD is cognitive/behavioral rigidity, such that individuals who struggle with the disorder have problems changing their pattern of behavior. This was reflected within this study by the large amount of VPA rats who did not form an attentional set. The sex difference results are supported

by studies in humans where ASD females perform worse in cognitive flexibility tasks when compared to males in the same task (Memari et al., 2013). Overall, these results provide further support that males and females may suffer from different symptoms and present a different profile that encompasses their experience with ASD.

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Poster

642. Autism: Neurons, Circuits, and Behavior

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 642.23/B8

Topic: A.07. Developmental Disorders

Title: Behavioral characterization of mice deficient for the mammal-specific microRNA 379-410 cluster

Authors: *A. Ö. SUNGUR[1,2], M. LACKINGER[3], L. STEMMLER[1], R. GROSSE[1,3], R. K. W. SCHWARTING[1,2], G. SCHRATT[3,4], M. WÖHR[1,2];
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Abstract: microRNAs (miRNAs) represent a group of small, noncoding RNA molecules that play a major role in the posttranscriptional regulation of gene expression. Members of a large placental mammal-specific miRNA cluster, namely miR379-410 encompassing 38 miRNAs, have been implicated in a variety of neurodevelopmental disorders. We have conducted comprehensive behavioral phenotyping on mice deficient for the miR379-410 cluster throughout development. Recently, we have shown that deletion of this cluster in mice leads to hypersocial behavior and increased emission of ultrasonic vocalizations (USV), which is accompanied by altered excitatory synaptic transmission, and exaggerated expression of ionotropic glutamate receptor complexes in the hippocampus. Mutant mice further displayed more pronounced anxiety-like behavior across the entire lifespan, in the absence of cognitive deficits. To further investigate the contribution of miR379-410 cluster to communication deficits present in neurodevelopmental disorders, here we have performed detailed analysis on acoustic features of isolation-induced pup USV. In addition to increased call rate, mice lacking miR379-410 cluster displayed increased peak amplitude and frequency modulation when isolated from the mother and littermates. In adulthood, mutant mice displayed increased self-grooming but reduced marble burying behavior. We also tested for mania-like elevated drive by studying effects of the psychostimulant d-amphetamine (AMPH) on locomotor activity. Mutant as well as wildtype mice reacted to AMPH treatment by a significant increase in locomotor activity, and no genotype

differences were evident, indicating lack of mania-like behavior in miR379-410 mutants. Taken together, the present study confirms and extends previous findings, showing that deletion of miR379-410 cluster leads to altered communication and repetitive behavior, without affecting psychostimulant-induced hyperactivity.

Disclosures: A.Ö. Sungur: None. **M. Lackinger:** None. **L. Stemmler:** None. **R. Grosse:** None. **R.K.W. Schwarting:** None. **G. Schratt:** None. **M. Wöhr:** None.

Poster

642. Autism: Neurons, Circuits, and Behavior

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 642.24/B9

Topic: A.07. Developmental Disorders

Support: FAPESP 2017/08377-7
UNINOVE CAPES PROSUP

Title: Study of post-pubertal social vocalization in pre-adolescent males and females coming from maternal hypothyroidism: Link for neurodevelopmental aspects in autism-related conditions?

Authors: *D. M. SANTOS[1], J. D. SILVA[1], G. GIANNOCCO[2], M. RIBEIRO[3], C. A. PENATTI[4];
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Abstract: Subtle maternal thyroid dysfunction and its most common condition, subclinical maternal hypothyroidism (MH), 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 oral communication of the new born and pre-adolescence individuals and regarding their sex differences subjected to MH during pregnancy. Using a C57black6 mouse model of discrete MH, we investigated the social interaction of both male and female matched-offspring before puberty across animal behavioral paradigms to look for differences in motor locomotion, anxiety, maternal care and preference, and vocalization based on innate social behavior display for that mouse strain and species. In addition, we checked the expression levels of three mRNA of genes related to verbal communication in models of ASD. Behavioral testing did not show overall differences in locomotor behavior based on open field paradigm when applicable to males and females. We show that first generation male but not first generation female offspring from

hypothyroid dams has increased anxiety levels tested at pre-pubertal age post-natal (PN) day 30, using *plus-maze* paradigm when compared with control offspring. Regarding oral communication, one group of males born from hypothyroid dams displayed increased total vocalizations only in early age (PN 6 and 7) when compared with age-matched control males. In later ages (PN 15 and 21), the difference of the vocalization patterning between the experimental groups was lost. In order to look for specific differences in the display of maternal behavior, we developed the paradigm of foster mother's place-preference. Despite the observational preference for the foster moms going more frequently towards the maternal hypothyroid-born offspring in males, there were no significant differences in overall choice among all male and female offspring. Our preliminary results on mRNA expression within prefrontal cortex of oral communication-related genes did not show differences. Therefore, our findings suggest that subtle or subclinical MH during early pregnancy may facilitate complex and variable social behavior disarrangements in maternal care, anxiety in infancy and childhood and verbal communication deficits in a sex-dependent manner. We thus speculate that the animal model in subtle or subclinical MH has much to mimic the highly variable neuropsychological manifestations in ASD and may favor the understanding in children's development among the ASD individuals.

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Poster

642. Autism: Neurons, Circuits, and Behavior

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Program #/Poster #: 642.25/B10

Topic: A.07. Developmental Disorders

Support: The Nancy Lurie Marks Family Foundation
SBIR
American Autoimmune Related Diseases Association (AARDA)
Barbara Zucker Early Faculty Career Award

Title: The role of maternal anti-CASPR2 antibody in autism spectrum disorder: A second hit model

Authors: *C. BAGNALL-MOREAU[1], R. BERLIN[2], P. T. HUERTA[2], B. T. VOLPE[3], B. DIAMOND[3], L. BRIMBERG[4];
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Abstract: Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by core deficits in social interaction, impaired communication and stereotypic behavior. Numerous studies highlight the role of the maternal immune system in fetal neurodevelopment, and perturbations in the prenatal environment are associated with an increased risk of ASD. Maternal cytokines and autoantibodies have been demonstrated to disrupt fetal brain development and contribute to an ASD-like phenotype in primate and rodent offspring. Work from our lab have previously found that antibodies targeting Contactin Associated Protein-Like 2 (Caspr2) are frequently found in the serum of women with anti-brain antibodies and a child with ASD. Furthermore, mice exposed *in utero* at gestational day E13.5 to human anti- Caspr2 antibody (namely C6), cloned from a mother with anti-brain antibodies and an ASD child resulted in an ASD like phenotype in male, but not female offspring. In the current study, we have characterized a new model in which female mice are immunized with the extracellular domain of human Caspr2 and produce anti-Caspr2 antibody. Male offspring of these immunized females also present with a neurodevelopmental phenotype, similar to what has been seen following a single exposure *in utero* to C6. Since the affected offspring of women harboring anti-Caspr2 antibody can be male or female, and some mothers with anti-Caspr2 antibody and an ASD child also have a typically developing child, we propose to use this model to explore the additional immune factors that predispose to the development of an ASD-like phenotype in offspring of dams harboring anti-Caspr2 antibody. We hypothesize that immunological activation during pregnancy may serve as a 'second hit' and exhibit a synergistic effect with anti-Caspr2 antibody to promote ASD phenotype in female and male offspring. Caspr2 or adjuvant-only immunized dams are injected with recombinant IL-6 or saline on gestational day E12.5 to mimic maternal inflammation. We are assessing cortical laminar organization of fetal brains at E14.5 and E18.5. The expression and activation of cytokine signaling pathway proteins is also being assessed in the placenta and fetal brain by qPCR and western analysis. We expect that the gender bias observed in offspring will be altered when a combination of risk factors is present. Furthermore, these studies will explore the contribution of the placenta to fetal brain development during maternal infection and antibody exposure. These studies will increase our understanding of the triggers of neurodevelopmental impairment and possibly suggest novel approaches to protecting the fetal brain.

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Poster

642. Autism: Neurons, Circuits, and Behavior

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 642.26/B11

Topic: A.07. Developmental Disorders

Support: CAPES scolarship

Title: Early-life developmental profile of ultrasonic vocalizations in the valproic acid model of autism

Authors: *R. S. BESSA, R. N. ROMCY-PEREIRA;
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Abstract: Autism is a heterogeneous developmental disorder in which neural circuits involved in social cognition and sensory processing are dysfunctional. In animal models of autism, ultrasonic vocalizations (USV) are thought to be a measure of communication skill related to social deficits. In rodents, prenatal exposure to valproic acid (VPA) produce autistic endophenotypes including social deficits, repetitive behaviors and reduced USV emissions. In the present study, we aimed to analyze the dynamic of USV production in VPA-treated rats from P7 to P21. Adult female Wistar rats received a single dose of VPA (500mg/kg, ip. in saline) at gestational day 12.5. At P7, P14 and P21 isolated pups had USV measured in an acoustic isolated box set with dim red light and an ultrasonic microphone (Dodotronics; Ultramic250K) positioned 45 cm above. For 5min, USVs were recorded with a sampling rate of 250 kHz. USVs were analyzed in MATLAB with an entropy-based method for USVs identification and clustered/classified using a deep learning-based algorithm DeepSqueak. Our results showed that all control animals at all ages vocalized when isolated. In contrast, 84%, 96% and 96% of VPA rats vocalized at P7, P14 and P21, respectively. In addition, VPA pups produced less USVs at P7 and P14 compared to controls, with no difference at P21. Total vocalization time was similar between VPA and control. However, the distribution of call durations changed across ages. At P7 and P14, 90% of the USVs consisted of <130ms and <170 ms-long USVs, respectively for control animals, whereas for VPA animals, 90% of USVs consisted of <200ms and 270ms-long emissions at P7 and P14. At P21 both groups showed shorter emissions - 90% of the USVs up <70ms. USVs at P7 had principal frequency around 45 kHz and at P14 and P21 were distributed around 45 kHz and 68 kHz. USV bout clusters were analyzed theough inter-USV interval (IUI). At P14, VPA animals had shorter intervals than controls, with three distribution peaks at 100ms, 200ms and 300ms whereas controls had peaks at 150ms, 270ms and 400ms. USVs were also classified in 11 pre-defined types using a supervised learning algorithm and the relative frequency of occurrence for each type were analyzed at all ages investigated. At P7, control animals emitted more ‘Complex Trill’ than VPA animals. No difference was found at P14 and P21. Transition probabilities between USV classes were also computed. P14 was the age that animals in both groups showed the most significant differences. In conclusion, our results confirm some of the previous findings of the literature and extends our understanding of development of isolation USV emissions in VPA-treated rats.

Disclosures: R.S. Bessa: None. **R.N. Romcy-Pereira:** None.

Poster

642. Autism: Neurons, Circuits, and Behavior

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 642.27/B12

Topic: A.07. Developmental Disorders

Support: NIMH (1R01MH107515-01A1, JDD)
IDDRC (NIH/NICHD U54 HD087011)

Title: Shank3b loss in the mouse results in deficits to motivation for social reward

Authors: *K. B. MCCULLOUGH, S. E. MALONEY, C. WEICHSELBAUM, J. DOUGHERTY;
Washington Univ., Saint Louis, MO

Abstract: Loss-of-function polymorphisms in the *SHANK3* gene cause Phelan-McDermid syndrome, a neurodevelopmental disorder characterized by global developmental delay, intellectual disability, speech delay, poor motor function, and Autism Spectrum Disorder (ASD). ASD is defined in part by deficits in social communication and social interaction, yet a long-standing hypothesis is that the root deficit may actually be in social motivation. Previous work in mice with genetic disruption of the *Shank3b* gene has shown subtle social approach deficits yet normal direct social interactions, with pathologically repetitive grooming behaviors. We recently developed a novel behavioral assay for assessing social motivation for social reward in the mouse, the social operant task. Here, we tested social motivation function in the *Shank3b* heterozygous (*Shank3b*$^{+/-}$) and homozygous (*Shank3b*$^{-/-}$) mutants. *Shank3b*$^{-/-}$ mutants failed to work for access to a social partner, whereas the *Shank3b*$^{+/-}$ mutants and wild type littermates demonstrated intact motivation for access to a social partner as well as increased effort under more constrained parameters. To understand if the deficits observed in the *Shank3b*$^{-/-}$ mutants were due to underlying deficits in the global reward circuitry or learning and memory function, we also conducted cocaine conditioned place preference and Barnes maze testing. We further examined these mice in the sucrose operant task to understand if the motivational impairments were specific to the social domain. Recent work has helped to define the role of oxytocin in social reward, and altered oxytocin function has been implicated in ASD. Therefore, were interested in understanding the role of oxytocin in this phenotype. Our study shows for the first-time deficits in social motivation in the *Shank3b* mutant mouse model. On the whole, our work allows us to better understand how motivation and reward are involved in the social deficits characteristic of ASD and other neurodevelopmental disorders.

Disclosures: K.B. McCullough: None. **S.E. Maloney:** None. **C. Weichselbaum:** None. **J. Dougherty:** None.

Poster

642. Autism: Neurons, Circuits, and Behavior

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Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 642.28/B13

Topic: A.07. Developmental Disorders

Support: NIH grant EY022122

Title: Shank3 is required for late-phase juvenile ocular dominance plasticity in mice

Authors: *C. GROVES KUHNLE, V. TATAVARTY, S. D. VAN HOOSER, G. TURRIGIANO;
Dept of Biol., Brandeis Univ., Waltham, MA

Abstract: In order to better understand how autism-associated genes impact the experience-dependent development of visual cortical circuits, we investigated the role of *Shank3* - an Autism Spectrum Disorder associate gene - in ocular dominance plasticity. Ocular dominance plasticity after monocular lid suture has been divided into two stages that consist of 1) an early-phase (1-3 day) decrease in responsiveness to the closed eye, and 2) a late-phase (3-7 day) homeostatic increase in overall responsiveness. The late phase of OD plasticity is thought to rely on synaptic scaling, and previous studies in our lab have shown that *in vitro* cultures in which Shank3 has been depleted by RNAi fail to exhibit homeostatic synaptic scaling either up or down. We thus hypothesized that that late-phase ocular dominance plasticity would be reduced in *Shank3*-knockout animals. Wildtype mice showed the expected decrease in response to drive from the closed eye at 3 days and the subsequent strengthening of response to both eyes at 6 days. In contrast, while Shank3 knockout animals exhibited the expected decrease in cortical responsiveness to the closed eye during short monocular deprivation (MD) of 3 days (similar to their wildtype colony mates), they lacked the normal homeostatic increase in responsiveness after 6 days MD. These data show that the homeostatic component of experience-dependent plasticity is absent in Shank3 knockout mice, and suggest that loss of homeostatic plasticity may contribute to circuit dysfunction in these mice.

Disclosures: C. Groves Kuhnle: None. **V. Tatavarty:** None. **S.D. Van Hooser:** None. **G. Turrigiano:** None.

Poster

642. Autism: Neurons, Circuits, and Behavior

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 642.29/B14

Topic: A.07. Developmental Disorders

Support: NIMH Grant 1R01MH107515-01A1 (JDD)
NICHD Grant U54 HD087011 (IDDRC)

Title: Development of a quantitative measure of social motivation in mice and its regulation by oxytocin

Authors: *S. E. MALONEY[1], K. B. MCCULLOUGH[2], C. T. WEICHSELBAUM[2], J. D. DOUGHERTY[3];
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[3]Genetics, Psychiatry, IDDRC, Washington Univ. Sch. of Med., St Louis, MO

Abstract: Humans and other social species find social interaction inherently rewarding. Facets of social motivation are critical to the development and maintenance of healthy social functioning. Autism spectrum disorder (ASD) is defined in part by deficits in social communication and social interaction, yet a long standing hypothesis is that the root deficit may actually be in social motivation. Recent work has helped to define the role of oxytocin in social reward, and altered oxytocin function has been implicated in ASD. We seek to understand if abnormalities in social motivation for social reward underlie the core social phenotypes in ASD, and to what extent oxytocin is playing a role. While current behavior assays in mice can answer questions regarding direct social interactions or sociability, assays for assessing social motivation (how much work an animal is willing to do for social reward) are not well established. Thus we developed a task to directly examine motivation for social interaction. To do this, we modified standard mouse operant conditioning chambers to create an automated system in which social motivation is directly assessed by quantifying nose pokes performed for access to a social partner. Specifically, a correct nose poke opened a door to reveal a social partner separated by steel bars and allowed for a 12-sec interaction. Quantification of nose pokes allowed for examination of motivation to interact with a social partner compared to only the opening the door (control). Behavioral tracking also enabled quantification of social interactions including total time interacting, time spent per reward and latency to interact. We first demonstrated adult wild-type C57BL/6J female and male mice will work for access to a social interaction, increase that work under more constrained parameters, and exhibit an increased work breakpoint for access to a social interaction compared to only opening the door. We also observed sex differences: male mice exhibited increased motivation for access to a conspecific compared to females. We next investigated the role of the oxytocin system in this task. We administered an

oxytocin antagonist continuously through an IVC cannulation with subdermal pump during social operant testing and again quantified social motivation in male and female mice. Here, we have established a behavioral paradigm for social motivation that can be used to examine operant responses to social reward in mouse models of ASD. Further, we have tested the role of the oxytocin system in this paradigm that can be leveraged in the future to determine whether oxytocin can be used to modulate social motivation performance in ASD models.

Disclosures: S.E. Maloney: None. **K.B. McCullough:** None. **C.T. Weichselbaum:** None. **J.D. Dougherty:** None.

Poster

643. Sensorimotor Development and Disorders

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 643.01/B15

Topic: A.08. Development of Motor/ Sensory/ and Limbic Systems

Support: FAPESP Grant 2013/205497
CNPq Grant 301333/2017-3
FAEPA Grant 818/2014

Title: Assessment of somatossensory development after neonatal pain

Authors: *V. S. FAZAN[1], L. S. SANADA[2], E. C. CARMO[2], N. L. B. MACHADO[2];
[1]Surgery and Anat., [2]Sch. of Med. of Ribeirao Preto, Ribeirão Preto, Brazil

Abstract: Advances in medicine have increased the survival of preterm neonates that are constantly submitted to invasive procedures, causing repetitive painful experiences in the neonate period. However, morphological consequences of early painful experiences in the central and peripheral nervous system remain fairly explored. We aimed to evaluate the possible alterations in the sural nerves of male and female adult Wistar rats, after painful stimulation in the neonatal period. We also aimed to assess the glial activity in cortical areas related to pain processing (pre-frontal, anterior insular, anterior cingulated, primary and secondary somatossensorial area, primary and secundary motor area). Wistar rats were followed from birth to 180 days of life, separated in 8 groups: 1) Control-male neonate group; 2) Control-female neonate group; 3) Pain-male neonate group; 4) Pain-female neonate group; 5) Control-male adult group; 6) Control-female adult group;7) Pain-male adult group; 8) Pain-female adult group. Neonatal pain was induced by repetitive needle insertion in one heel twice per day for 15 days starting at birth. The control groups were stimulated with a cotton swab, twice per day for 15 days starting at birth. Both male and female Wistar rats (N=48) received either neonatal injury or control stimulation and they were tested behaviorally for mechanical withdrawal thresholds of the paw and muscle, and for gait alterations. The animals were then weighed, anesthetized, and

they had their right and left sural nerves dissected and fixed in glutaraldehyde. After that, the animals were perfused and their brains dissected. After preparation with conventional histological techniques with epoxy resin, cross-sections of the right and left sural nerves were obtained for analysis by light microscopy. The morphometry was performed with the aid of an image analysis software. The brains were used for immunohistochemistry of glial cells in the cortical areas (pre-frontal, anterior insular, anterior cingulated, primary and secondary somatossensorial area, primary and secundary motor area). The statistical analysis was performed using specific statistical tests. Differences were considered significant when $p<0.05$. It was observed that the nociceptive stimuli in the neonatal period were able to produce hyperalgesia and changes in gait pattern; additionally, pain in neonatal period increased glial cells in the cortical areas and it altered the morphology and morphometry of sural nerve, which persisted into adulthood. Therefore, pain in the neonatal period can cause persistent sensorymotor changes.

Disclosures: V.S. Fazan: None. **L.S. Sanada:** None. **E.C. Carmo:** None. **N.L.B. Machado:** None.

Poster

643. Sensorimotor Development and Disorders

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 643.02/B16

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH-R01-GM104987
NIH-R21-HD089731

Title: Relation between movement and respiration in preterm infants

Authors: *I. ZUZARTE[1], D. PAYDARFAR[2], D. STERNAD[3];
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Abstract: An estimated 15 million babies (>10% of all births) are born preterm (<37 week gestational age). Apnea resulting from prematurity and instability of the respiratory system is a common condition in preterm infants that is implicated in several acute and long-term complications. Few studies have investigated whether respiration is coupled to infants' movements. For clinical applications, prediction of apneas would be of high significance to counteract the onset of apneas or alarm clinical personnel. This study proposes the hypothesis that infant movements are a predictive marker for apneic episodes; specifically, we examine this relation in preterm infants' breathing cycle. Movements were estimated based on artifacts in

physiological signals with a custom-developed wavelet-based algorithm. Respiratory activity was measured in 13 infants using respiratory inductance plethysmography. In an additional 8 infants, respiration and partial pressure of carbon dioxide (PCO_2) were measured by a nasal cannula circuit with side-stream capnometry to avoid direct mechanical effects of movement on respiration. Respiratory and movement data of the 13 preterm infants were investigated and correlated with the frequency and characteristics of apneas during movement. Results of a previous study were validated, while also highlighting critical limitations due to restricted selectivity of the included data samples. To overcome these limitations, we analyzed the stability of respiration with respect to the onset and offset of movement in 8 preterm infants, using standard deviation of inter-breath intervals and Poincaré maps of the respiratory activity. A significant difference ($p < 0.05$) was observed in the stability of respiration following movement onset using both methods. Movement increased the variability of inter-breath intervals and PCO_2, while also causing a significant reduction in the end-tidal carbon dioxide ($ETCO_2$). Low $ETCO_2$ has been shown to be associated with decreased cerebral hypoxia, one of the primary causes of preterm apnea. Moreover, results showed that the degree of destabilization of respiration was dependent on the duration of movement. These findings support that bodily movements of the infants might serve as predictors of life-threatening events, useful for effective clinical management and for risk stratification of infants.

Disclosures: I. Zuzarte: None. **D. Paydarfar:** None. **D. Sternad:** None.

Poster

643. Sensorimotor Development and Disorders

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 643.03/B17

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NWO Vidi-grant FirSTeps 016.156.346
ERC Starting Grant Learn2Walk 715945

Title: Dynamic connectivity and changes in coordination during walking

Authors: *J. N. KERKMAN, A. BEKIUS, A. DAFFERTSHOFER, N. DOMINICI;
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Abstract: We studied the locking between the arms and legs displaying spontaneous switches from a 2:1 to 1:1 frequency ratio when walking speed increases. Is this transition induced by biomechanical factors or caused by active motor control processes? To answer this question, we studied dynamic connectivity within and between groups of muscles.
Sixteen healthy subjects (five males, eleven females, mean age 25.3 ± 2.4 years) walked on a treadmill with their arms swinging along their body while kinematics and surface

electromyography (EMG) was recorded. We grouped EMG signals in muscle synergies using non-negative matrix factorization (NMF). We also estimated intermuscular coherence between all muscle pairs to estimate connectivity between muscles at different frequency bands. Again, NMF was used to group the coherence spectra. Both outcome measures were combined into minimally-connected multiplex networks. We compared these networks within and between modules and examined their changes as a function of walking speed.
As expected, the coordination between arms and legs changed from 2:1 to 1:1 when treadmill speed increased. Muscle synergy analysis disclosed five relevant synergies. The corresponding temporal activation patterns differed between speeds in both temporal structure and amplitude. The muscle synergy network turned out to consist of two modules of which one was mainly located at the legs and the other at the pelvis and the upper body. However, the NMF of the coherence spectra yielded four networks enclosed distinct frequency bands: 1-3 Hz, 3-8 Hz, 8-18 Hz, and 18–60 Hz. The corresponding multiplex network contained four modules enclosing both arms, trunk, right leg, and left leg. The community structure of the muscle synergy and coherence networks differed primarily in the organisation of arms and legs. The coherence networks revealed an increased connectivity in the lower frequencies between trunk and legs and the arms appeared uncoupled from the rest of the body when looking at higher frequencies after the switch from a 2:1 to a 1:1 coupling between arms and legs.
Taken together, the change in coordination between arms and legs was accompanied by changes in muscle synergies. Both synergy and coherence networks underwent changes in their functional and structural community structure. In particular the latter may indicate the involvement of different neural pathways in the control of muscle synergies at different walking speeds. This seems to support the concept that the switch in coordination is not merely due to biomechanical factors.

Disclosures: **J.N. Kerkman:** None. **A. Bekius:** None. **A. Daffertshofer:** None. **N. Dominici:** None.

Poster

643. Sensorimotor Development and Disorders

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 643.04/B18

Topic: A.08. Development of Motor/ Sensory/ and Limbic Systems

Title: Assessing the impact of chewing on motor function in children and adolescents

Authors: *J. PREBOR[1], B. SAMULSKI[2], S. MORRISON[3];
[1]Kinesiology and Rehabil., Old Dominion Universtiy, Norfolk, VA; [2]Kinesiology and Rehabil., [3]Physical Therapy and Athletic Training, Old Dominion Univ., Norfolk, VA

Abstract: Previous research has shown that, for young and older adults, walking is constrained by a person's chewing rate with step frequency altering in line with the speed of chewing. However, it is unclear whether this coupling relation occurs in younger populations or if the gait-chewing relationship extends to other rhythmical motor tasks like finger tapping. Consequently, the aim of the study was to assess the impact chewing at different speeds (i.e. fast, slow, and preferred) on walking performance and finger tapping as a function of age from childhood to adolescence. The responses from 16 individuals, ranging from 10-17 years of age were assessed. To determine chewing rates, surface EMG recordings from the masseter muscle were used.. For the gait assessments, individuals walked at their preferred speed over a 20ft Protokinetics pressure sensitive walkway. For finger tapping, participants were asked to tap on a force sensor with their index finger at their preferred speed. Our results demonstrated that chewing was strongly related to the performance of both the finger tapping and walking tasks. For gait, cadence and step time changed as a function of the chewing rates while step length was relatively unaffected. Similarly, the speed of finger tapping altered in line with changes in the persons chewing rates. Interestingly, the robustness of the link between chewing and the other motor tasks appeared to be mediated by the participant's age, with older children exhibiting stronger coupling between tasks compared to the younger individuals. Taken together, these results illustrate that the oral motor task of chewing has a strong driving influence on other neuromotor functions. This influence appears to be more pronounced in adolescents indicating less synchronization in younger children. Younger children were also highly variable in their motor responses. These distinctions between younger and older children may be supported by previous research of motor development where younger children have less established motor patterns. These differences in motor patterns with age have been linked to increased activity in the frontal cortex and cerebellum in children as compared to adults. As a result, the movement responses of the younger persons appear to be less automatic, more variable and exhibit decreased synchronization between motor effectors. The findings from this study suggest rhythmical motor dual tasks are less established in early childhood and affected by increasing age.

Disclosures: **J. Prebor:** None. **B. Samulski:** None. **S. Morrison:** A. Employment/Salary (full or part-time):; Old Dominion University.

Poster

643. Sensorimotor Development and Disorders

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 643.05/B19

Topic: A.08. Development of Motor/ Sensory/ and Limbic Systems

Support: NIH Grant R01HD039343
NIH Grant R01NS058667

Title: Motor drive to the paretic lower limb in children with hemiplegic cerebral palsy: A pilot study

Authors: *V. GOYAL[1,2], T. SUKAL-MOULTON[1,3], J. P. A. DEWALD[1,2];
[1]Physical Therapy and Human Movement Sci., [2]Biomed. Engin., [3]Pediatrics, Northwestern Univ., Chicago, IL

Abstract: Individuals with a unilateral brain injury experience a loss of corticofugal projections from the lesioned hemisphere to the contralateral side of the body. In adults with hemiparetic stroke, it is postulated that upregulation of corticobulbospinal pathways causes an abnormal coupling between the extensors in the lower limb (hip adduction with hip/knee extension and ankle plantarflexion), leading to a loss of independent joint control. However, previous work showing spontaneous mirror movements in the paretic upper extremity suggests that children with hemiplegic cerebral palsy (HCP) from an early-onset brain injury (a pre-natal injury before the early third trimester or a peri-natal injury during birth) may additionally rely on retained ipsilateral corticospinal pathways. To investigate potential differences in descending drive to the lower extremity, we use a novel device previously developed for adult stroke studies to quantify abnormal joint torque coupling at the hip. The device includes two load cells and is able to capture high-resolution and simultaneous isometric multi-joint torque measurements. We include three participants without HCP (three females aged 9.1, 13.2, and 13.9 yrs) and two participants with HCP (a 10.5 y/o male with a pre-natal injury and a 16.8 y/o male with a peri-natal injury) in our pilot study. Testing was done in the non-dominant/paretic lower limb. Participants were first instructed to generate maximum voluntary torques in hip extension and abduction. Participants were then instructed to combine submaximal hip extension efforts (20%, 40%, 60%) with maximal hip abduction torque generation, a grouping outside the stereotyped hip extension/adduction pattern. Hip abduction torque was normalized to the max for comparison. Participants without HCP were able to generate 81±4% hip abduction max during 20% hip extension, 76±5% hip abduction max during 40% hip extension, and 81±2% hip abduction max during 60% hip extension. Both participants with HCP demonstrated comparable values at 71-80% hip abduction max during 20% hip extension, 82-100% hip abduction max during 40% hip extension, and 79-96% hip abduction max during 60% hip extension. These results indicate no abnormal coupling between hip extension and adduction and support the hypothesis that children with HCP from early-onset brain injury do not employ corticobulbospinal pathways for motor control of the paretic lower limb. Future work will include children with HCP from late-onset brain injury to quantify possible coupling between hip extension and adduction to confirm the hypothesis that this cohort may instead rely on corticobulbospinal pathways for motor control.

Disclosures: V. Goyal: None. **T. Sukal-Moulton:** None. **J.P.A. Dewald:** None.

Poster

643. Sensorimotor Development and Disorders

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 643.06/B20

Topic: A.08. Development of Motor/ Sensory/ and Limbic Systems

Support: Research in Autism, Intellectual and Developmental Disabilities (RAIND

Title: A novel two-body sensor system to study spontaneous movements in infants during caregiver physical contact

Authors: *P. PATEL[1], Y. SHI[2], F. HAJIAGHAJANI[2], S. BISWAS[2], M.-H. LEE[1];
[1]Kinesiology, [2]Electrical and Computer Engin., Michigan State Univ., East lansing, MI

Abstract: Spontaneous movements, which refer to repetitive stereotyped limb movements in the absence of any external stimulus, have been found to be reflective of neurodevelopmental status during infancy. These movements are modulated by both individual and environmental factors, including physical contact with the caregiver. However, it is a challenge to measure spontaneous movements during physical contact because infant-generated movements are coupled with caregiver-generated movements. Here, we propose the use of a novel two-body sensor system to distinguish infant-generated movements in the presence of physical contact with the caregiver. Data from seven typically developing infants and their caregivers were recorded during different simulated home activities, which involved different combinations of physical interaction, caregiver's movement and infant positions. The two-body sensor system consisted of two wearable accelerometers - one placed on the infant's arm and one on the caregiver's arm, and we developed a Kalman-filter based algorithm to isolate the infant-generated movements. In addition, video was recorded for qualitative analysis. Results indicated that spontaneous movement activity was higher when there was no physical contact with caregiver. When there was physical contact, spontaneous movements were also increased when the caregiver was still and when the infant was held horizontally. These results show that the novel two-body sensor system and the associated algorithms were able to isolate infant-generated movements during physical contact with the caregiver. This approach holds promise for the automated long-term tracking of spontaneous movements in infants that may provide critical insight into developmental disorders.

Disclosures: P. Patel: None. **Y. Shi:** None. **F. Hajiaghajani:** None. **S. Biswas:** None. **M. Lee:** None.

Poster

643. Sensorimotor Development and Disorders

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 643.07/B21

Topic: A.08. Development of Motor/ Sensory/ and Limbic Systems

Title: Acetaminophen exposure during the juvenile period impairs motor coordination in C57Bl/6 mice

Authors: *J. V. GEORGE[1], G. GUNAWAN[1], A. A. WISLOTSKY[1], P. T. ORR[1,2];
[1]Neurosci. Program, [2]Psychology Dept., Univ. of Scranton, Scranton, PA

Abstract: Although acetaminophen (APAP) or paracetamol is a common over-the-counter analgesic and antipyretic, it is associated with an increased likelihood of hyperkinetic disorder following prenatal exposure in humans and is associated with hyperactivity and deficits in motor coordination after prenatal exposure in mice. Currently, it is not known if similar effects are found after APAP exposure during the juvenile period. This study investigated whether chronic APAP exposure affects locomotion and anxiety in juvenile mice. C57BL/6 mice were injected with 50 mg/kg APAP or vehicle every third day after weaning until sacrifice. At 6 (cohort 1) or 8 (cohort 2) weeks of age, mice were tested on open field, marble burying, Von Frey tactile sensitivity, and accelerated rotarod. There were no significant sex differences; thus, analyses were combined across sex. Regardless of age, acetaminophen impaired performance in the rotarod. Vehicle- and acetaminophen-treated mice improved across the ten rotarod trials at 20 rpm/min ($F(9, 234) = 8.463$, $p < .001$) on the first day. However, mice receiving acetaminophen spent significantly less time on the rod across all ten trials ($F(1, 26) = 4.308$, $p < .05$). There was no trial by condition interaction ($F(9, 234) = .649$, $p > .05$). Overall, these results suggest that recurrent acetaminophen exposure during the juvenile period impairs motor coordination, which is consistent with our previous results in prenatally exposed mice.

Disclosures: J.V. George: None. **G. Gunawan:** None. **A.A. Wislotsky:** None. **P.T. Orr:** None.

Poster

643. Sensorimotor Development and Disorders

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 643.08/B22

Topic: A.08. Development of Motor/ Sensory/ and Limbic Systems

Title: Prenatal acetaminophen exposure alters FAAH expression in newborn C57Bl/6 mice

Authors: G. GUNAWAN[1], S. N. WIERBOWSKI[1], *P. T. ORR[1,2];
[1]Neurosci. Program, [2]Psychology Dept., Univ. of Scranton, Scranton, PA

Abstract: Previous work has demonstrated that prenatal acetaminophen (APAP) is associated with increased risk of hyperkinetic disorders in humans and hyperactivity in mice. There are multiple potential mechanisms which could mediate these effects, including conversion to AM404, a cannabinoid reuptake inhibitor, via fatty acid amide hydrolase (FAAH) and inhibition of cyclooxegenase-2 (COX-2). We administered 15 mg/kg/day of APAP or regular tap water to pregnant C57Bl/6 mice throughout once gestation was detected and collected brain tissue from pups within 48-72 hours of birth. Western blotting was used to detect changes in FAAH and Cox-2 in these samples. There was no significant difference in Cox-2 levels between groups ($t(27) = .322$, $p > .05$), but pups prenatally exposed to APAP showed a significant upregulation in FAAH ($t(24) = 1.987$, $p = .029$). These result suggest that FAAH may be an important mediator of the effects of long-term APAP exposure, although more mechanistically-focused work is still needed.

Disclosures: P.T. Orr: None. **G. Gunawan:** None. **S.N. Wierbowski:** None.

Poster

643. Sensorimotor Development and Disorders

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 643.09/B23

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH Grant 1R01NS104423-01A1

Title: Cerebellar GluRδ2 deficiency in mice recapitulates key clinical features of essential tremor

Authors: *C.-L. NI[1], M.-K. PAN[3], Y.-S. LI[1], S.-B. WANG[4], E. P. CORTES[5], J. G. VONSATTEL[2], E. D. LOUIS[6], P. L. FAUST[2], S.-H. KUO[1];
[1]Dept. of Neurol., [2]Departments of Pathology and Cell Biol., Columbia Univ., New York, NY; [3]Dept. of Med. Res., Natl. Taiwan Univ. Hosp., Taipei, Taiwan; [4]Dept. of Pediatrics, Taipei Tzu Chi Hosp., Taipei, Taiwan; [5]Dept. of Pathology, Icahn Sch. of Med. at Mount Sinai, New York, NY; [6]Dept. of Neurol., Yale Univ., New Haven, CT

Abstract: Essential tremor (ET) is one of the most common movement disorders, the prototypical disease model for motor rhythm control and for clinical application of focused

ultrasound. However, the pathophysiology of ET remains poorly understood. Here we report that GluRδ2 protein deficiency in the cerebellar Purkinje cells can recapitulate key features of ET. We identified a reduction of GluRδ2 expression in the postmortem cerebellum of ET patients. *Grid2*^{dupE3} mice, a mouse model with GluRδ2 insufficiency, developed ET-like tremor that is adult-onset, chronic and progressive kinetic (action-only) tremor and responsive to ET medications including primidone, propranolol and ethanol. GluRδ2 rescue via intra-cerebellar viral transfection confirmed the necessity and specificity of GluRδ2 in tremor generation of *Grid2*^{dupE3} mouse model, while shRNA knockdown of GluRδ2 in adult, wild type mouse cerebellum sufficiently recapitulates ET-like tremor. Our findings identified that GluRδ2 insufficiency can be a molecular mechanism of tremor pathophysiology. An animal model of ET-like tremor with matched human-to-animal molecular mechanism may open a window for translational research in ET and motor rhythm control.

Disclosures: C. Ni: None. **M. Pan:** None. **Y. Li:** None. **S. Wang:** None. **E.P. Cortes:** None. **J.G. Vonsattel:** None. **E.D. Louis:** None. **P.L. Faust:** None. **S. Kuo:** None.

Poster

643. Sensorimotor Development and Disorders

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 643.10/B24

Topic: A.08. Development of Motor/ Sensory/ and Limbic Systems

Support: CONACYT grants No 243247 and 243333
VIEP-BUAP grant 2019 to Cuerpo Académico en Neuroendocrinología BUAP-CA-288

Title: Maternal care impact spontaneous and dopaminergic-induced yawning and penile erection frequencies in Sprague-Dawley rats

Authors: *J. EGUIBAR[1], C. CORTES[2], A. TRUJILLO[3], A. UGASTE[2], M. DORANTES-NIETO[2];
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Abstract: We select an inbred a high-yawning (HY) subline from Sprague-Dawley (SD) with 20 yawns/h that is one order of magnitude higher with respect to SD with just of 2 yawns/h. HY male rats are more active in the open-field arena indicating are less emotional reactive and also less anxious in elevated plus maze with respect to SD rats. Importantly, HY dams showed a disorganized maternal care. In base of that the aim of this study was to analyze the influence of maternal care on yawning and penile erections through in- and cross- fostering in both rats. All subjects (Ss) were maintained under standard conditions. Saline (NaCl 0.9%) and (-)-quinpirole

were administered by s.c. injection in the dorsal neck region. Yawning and penile erection recorded 1h in a Plexiglass cage and video recorded and measured using The Observer XT (Noldus) by two trained observers.Spontaneous yawning and penile erection frequency were significantly higher in HY with respect to SD rats independently of the maternal care received ($P < 0.05$); as well as after s.c. injection of (-)-quinpirole ($P < 0.05$). Importantly, in-fostered male rats had highest responses, with a peak response at 50 and 100 μg/Kg of (-)-quinpirole, with respect to saline-treated rats ($P < 0.05$). In conclusion, males that are in-fostered increase the spontaneous and dopaminergic-induced yawning and penile erections. These results showed that maternal care has a strong impact in the expression maternal care has a strong impact in the expression of yawning a well know behavior related to emotion and empathy.

Disclosures: J. Eguibar: None. **C. Cortes:** None. **A. Trujillo:** None. **A. Ugaste:** None. **M. Dorantes-Nieto:** None.

Poster

644. Nicotinic Acetylcholine Receptors: Structure and Regulation

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 644.01/B25

Topic: B.02. Ligand-Gated Ion Channels

Title: TMEM35/NACHO recognizes α7 nicotinic receptor transmembrane domains but cannot rescue mixed chimeras

Authors: *R. H. LORING, S. K. IYER, K. ADHIKARI, Z. WANG, S. ORUGANTI, L. HANSEN, V. RAMESH;
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Abstract: Alpha7 nicotinic receptor (α7 nAChR) subunits have four transmembrane domains (TMDs) and assemble in cells as pentamers, but require chaperone proteins to properly fold and assemble. The two best characterized α7 chaperones are Resistance to Inhibitors of Cholinesterase 3 (RIC3) and TMEM35 (Transmembrane protein 35, also known as Nicotinic Acetylcholine Regulator, or NACHO). Others established that chimeric receptor subunits consisting of α7 extracellular and intracellular domains, but with serotonin 5HT3 receptor TMDs do not require chaperones for folding and expression. Gee et al. (Br. J. Pharm. (2007) 152: 501) showed that chimeras consisting of rat α7 non-TMDs and mouse 5HT3 TMDs express well without RIC3 but that RIC3 could not rescue expression when the chimera TMDS were mixed. We investigated whether TMEM35 could rescue expression of mixed chimeras by producing receptor subunits consisting of human α7 non-TMDs and mixed amounts of mouse 5HT3 and human α7 TMDs. TMEM35 is not required for cell surface expression of 5HT3 TMD1-4 chimeras when transfected into HEK cells and measured by α-bungarotoxin binding, but native α7 (α7 TMD1-4) requires RIC3 or TMEM35, with optimum expression at a chaperone ratio of

1:3 respectively. However, TMEM35 did not significantly rescue expression when TMDs were mixed (α7 TMD1-3+5HT3 TMD4, or 5HT3 TMD1-3+ α7 TMD4). These data suggest that like RIC3, the site of action of TMEM35 is most likely in the α7 TMD regions, and that mixing TMDs from α7 and 5HT3 receptors results in chimeric subunits that do not properly fold or assemble.

Disclosures: R.H. Loring: None. **S.K. Iyer:** None. **K. Adhikari:** None. **Z. Wang:** None. **S. Oruganti:** None. **L. Hansen:** None. **V. Ramesh:** None.

Poster

644. Nicotinic Acetylcholine Receptors: Structure and Regulation

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 644.02/B26

Topic: B.02. Ligand-Gated Ion Channels

Support: Texas A&M University

Title: Expressing extracellular domain α4β2 nicotinic acetylcholine receptors depends on proximal proline of first transmembrane domain

Authors: A. M. PERSON, ***G. B. WELLS**;
Mol. and Cell. Med., Texas A&M Univ. Col. of Med., College Station, TX

Abstract: Background: The smaller size and reduced transmembrane sequence of extracellular domain (ECD) receptors from α7, α4, α3, β2, and β3 nicotinic receptor (nAChR) subunits might allow higher resolution structural studies and lead to better understanding of functional roles of the ECD and transmembrane domains. A long-term goal is to insert a protease site at the interface between the ECD and first transmembrane domain (M1), leading to *in vitro* liberation of water soluble ECD nAChRs. Characteristics of the interface that control expression of ECD nAChRs, however, are not well understood. Proximity of the conserved Cys-loop with proximal residues of M1 in crystallographic structures leads to the hypothesis that this interaction controls expression of ECD α4β2 nAChRs. We previously found that 1) substituting valine for the proximal proline of M1 blocks expression of ECD α4β2 nAChRs and 2) duplicating proximal M1 residues at the interface functionally unlinks the ECD from M1. We combined these findings to study the role of the interfacial proline with the upstream ECD and with the downstream M1 for expressing ECD α4β2 nAChRs.
Objective: Determine whether the interfacial proline needs to be adjacent to the ECD, to M1, or to both domains for expressing ECD α4β2 nAChRs.
Methods: Human α4 and β2 cDNAs were truncated after M1 (α4M1 and β2M1). Five residues of proximal M1 were inserted at the interface, producing an extended ECD with duplicated interfacial prolines separated by nine residues (α4PP and β2PP). Duplicated prolines were

mutated to valine or serine, leading to α4PV, α4VP, α4PS, α4SP, β2PV, β2VP, β2PS, β2SP. Subunits were expressed in *Xenopus laevis* oocytes. Immunoblotting and immunoisolated [^{3}H]epibatidine binding sites assessed expression of subunits and ECD α4β2 nAChRs. **Results**: Expression of α4PP/β2PP and α4M1/β2M1 nAChRs were comparable. Mutating the second proline (α4PV/β2PV and α4PS/β2PS) did not adversely affect expression. In contrast, mutating the first proline to valine (α4VP/β2VP) severely reduced expression. Unexpectedly, mutating the first proline to serine (α4SP/β2SP) did not adversely affect expression. **Conclusions:** These results support the hypothesis that interaction between the Cys-loop and proximal M1 is important for expressing ECD α4β2 nAChRs. Valine appears to be acting as a negative effector of ECD α4β2 nAChR expression when substituted for the interfacial proline. Serine can substitute for the interfacial proline, suggesting that proline is not required at the interface for expressing ECD α4β2 nAChRs. Functionally unlinking the ECD from M1 facilitates studying how the interfacial region contributes to the structure of ECD nAChRs.

Disclosures: A.M. Person: A. Employment/Salary (full or part-time):; Texasa A&M University. **G.B. Wells:** A. Employment/Salary (full or part-time):; Texas A&M University.

Poster

644. Nicotinic Acetylcholine Receptors: Structure and Regulation

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 644.03/B27

Topic: B.02. Ligand-Gated Ion Channels

Support: Marshall Research Corporation

Title: Effects of nicotine + morphine on reward-related behavior and nicotinic acetylcholine receptor regulation in mouse midbrain

Authors: *A. J. AVELAR, A. T. AKERS, S. Y. COOPER, B. J. HENDERSON;
Biomed. Sci., Marshall Univ., Huntington, WV

Abstract: In the United States about 480,000 deaths/year are caused by cigarette smoking. Nicotine is the addictive component of cigarettes. Also, in the United States about 50,000 overdose deaths/year occur due to opioid abuse. Morphine is an opioid drug that is prescribed to treat pain, but is often abused. Co-use of more than one drug is very common, therefore, it is vital that we study the effects of drug combinations to understand how co-use alters the brain. Especially given the fact that in America, > 90% of heroin and opioid dependents are heavy smokers. The objective for this study is to determine how combined nicotine + morphine alters reward-related behavior and nicotinic acetylcholine receptor (nAChR) expression in the midbrain. Our hypothesis is that co-use of nicotine + morphine leads to enhanced GABA neuron disinhibition of VTA dopamine neurons. Female and male (adults, 3-5 months old) C57BL/6J

background strain animals with or without α4-mCherryα6-GFP nAChRs were used in conditioned place (CPP) preference assays to examine reward-related behavior with 0.5 mg/kg nicotine + 10 mg/kg morphine (intraperitoneal injections). To examine changes in nAChR number in midbrain neurons we used a previously characterized α4-mCherryα6-GFP (nAChR) mouse line (C57BL/6J background). We used confocal microscopy to analyze the density of α4-containing (α4*), α6*, and α4α6* nAChRs in ventral tegmental area (VTA), substantia nigra pars compacta (SNc), and substantia nigra pars reticulata (SNr). In our CPP assays, a Two-way ANOVA (factors: treatment and sex) showed a significant effect of sex ($F(1, 42) = 5.75$; $p = 0.02$) on reward-related behavior, suggesting a sex-dependent dose effect with morphine. In our microscopy assays, nicotine + morphine treatment downregulated α4* nAChRs on SNr GABA cells. We observed little or no effect of nicotine + morphine on nAChRs expressed on VTA and SNc dopamine neurons. Although the drug treatments tested using CPP did not affect reward behavior, we will next test additional doses of morphine. However, our CPP data does support that sex is an important variable in the effects of drugs on reward-related behavior. This study is ongoing and will contribute new knowledge of how co-use of nicotine + morphine affects reward-related behavior and receptor regulation in the midbrain. We have no conflicts of interest.

Disclosures: **A.J. Avelar:** None. **A.T. Akers:** None. **S.Y. Cooper:** None. **B.J. Henderson:** None.

Poster

644. Nicotinic Acetylcholine Receptors: Structure and Regulation

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 644.04/B28

Topic: B.02. Ligand-Gated Ion Channels

Title: Identification of multiple accessory proteins for nAChR alpha6 containing receptors

Authors: *S. GU, J. A. MATTA, W. B. DAVINI, G. B. DAWE, B. LORD, D. S. BREDT; Janssen Pharmaceuticals of Johnson & Johnson, San Diego, CA

Abstract: Nicotinic acetylcholine receptors (nAChRs) are well-recognized therapeutic targets and play crucial roles in many physiological processes. These receptors are also regulated by interactions with diverse accessory proteins and the full repertoire of these accessory proteins remains uncertain. In the case of α6-containing nAChR, functional reconstitution in transfected cells is especially challenging. Therefore, neuronal accessory proteins are likely necessary for functional expression in vivo. To search for these unknown accessory proteins, we developed a genome-wide cDNA screening assay that scores accessory proteins candidates through agonist evoked functional response. Using this assay, we identified the accessory proteins, NACHO, BARP, LAMP5 and SULT2B1 for α6-containing nicotinic acetylcholine receptors. Co-expressing these proteins with α6 nAChR enables its functional reconstitution in a heterologous

expression system. Knockout of NACHO or BARP markedly decreases α6 mediated function in the striatum. The discovery of these accessory proteins will facilitate drug-targeting of the mesolimbic dopaminergic system and enable physiological studies of α6 containing nAChRs.

Disclosures: **S. Gu:** A. Employment/Salary (full or part-time):; Johnson and Johnson. **J.A. Matta:** A. Employment/Salary (full or part-time):; Johnson and Johnson. **W.B. Davini:** A. Employment/Salary (full or part-time):; Johnson and Johnson. **G.B. Dawe:** A. Employment/Salary (full or part-time):; Johnson and Johnson. **B. Lord:** A. Employment/Salary (full or part-time):; Johnson and Johnson. **D.S. Bredt:** A. Employment/Salary (full or part-time):; Johnson and Johnson.

Poster

644. Nicotinic Acetylcholine Receptors: Structure and Regulation

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 644.05/B29

Topic: B.02. Ligand-Gated Ion Channels

Title: A stably transfected, doxycycline inducible, HEK-293 model for the characterization and screening of alpha3 beta2 neuronal nicotinic acetylcholine receptors

Authors: A. SEGO, R. RICHTER, M. WRIGHT, R. WAGNER, C. MERRILL, M. KROPELNICKI, R. JOHNSON, ***S. N. SUDWEEKS**;
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Abstract: Nicotinic acetylcholine receptors (nAChR) of various forms are found widely throughout the body (i.e., in skeletal muscle, central nervous system, and the peripheral nervous system). Like other members of the cys-loop family of receptors, nAChRs are composed of five protein subunits, each with four transmembrane domains. Neuronal nicotinic acetylcholine receptors, created from combinations of the α2-10 and β2-4 subunits, can form in many arrangements and stoichiometries. Each arrangement can have varying binding affinities and channel kinetics, resulting in great modulatory capacity for these receptors. mRNA for the α3 and β2 subunits is found in surprisingly high abundance in CA1 interneurons in the *stratum radiatum* and *stratum oriens* of the rat hippocampus. α3 and β2 subunit mRNA injected into *Xenopus laevis* ooctes at different ratios (1:5 and 5:1) demonstrates at least two α3β2 subtypes. In order to further study the α3β2 nAChR in a more physiologically relevant mammalian environment, with consistent control over subunit expression ratios, we created a stably-transfected doxycycline-inducible HEK-293 cell line. This line has been stably transfected with the human α3 and β2 nAChR subunits and NACHO, a chaperone protein which has been shown to mediate the assembly of several nAChRs. This new model is able to induce expression of α3 and β2 subunits in various ratios, which should prove to be valuable tool in the characterization and screening of the α3β2 nAChR subtypes.

Disclosures: **A. Sego:** None. **S.N. Sudweeks:** None. **R. Richter:** None. **M. Wright:** None. **R. Wagner:** None. **C. Merrill:** None. **M. Kropelnicki:** None. **R. Johnson:** None.

Poster

644. Nicotinic Acetylcholine Receptors: Structure and Regulation

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 644.06/B30

Topic: B.02. Ligand-Gated Ion Channels

Support: Oxford Brookes University -PhD-3

Title: Identifying determinants of agonist selectivity in nicotinic acetylcholine receptors: Impact of non-aromatic residues

Authors: ***T. MINGUEZ**[1], A. S. F. OLIVEIRA[2], D. K. SHOEMARK[3], B. E. NIELSEN[4], C. BOUZAT[4], R. B. SESSIONS[3], A. J. MULHOLLAND[2], S. WONNACOTT[5], T. GALLAGHER[2], I. BERMUDEZ[1];
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Abstract: The α4β2 and α7 receptors are the most abundant nicotinic acetylcholine receptors (nAChRs) in the brain. Here, they contribute to a wide variety of behaviours, including cognition, reward and mood. They have also been implicated in a number of brain dysfunctions such as cognitive deficit, addiction to tobacco smoking and depression. Activation of these receptors by agonists, particularly partial agonists is a valid strategy to intervene therapeutically in the aforementioned dysfunctions. The design of an α7- or α4β2-specific agonist is however problematic, mainly because of the highly conserved nature of the aromatic box that binds agonists in both subtypes of receptors. Using docking and molecular dynamics simulations combined with single point mutations, two-electrode voltage clamping and single channel recordings, we have interrogated the structural determinants that may contribute to the differences in the functional potency of cytisine at the α4β2 (logEC50 = -5.27 ± 0.09 at the $(\alpha4\beta2)_2\alpha4$ stoichiometry) and α7 (logEC50 = -4.61 ± 0.15) nAChRs. Comparison of the crystal structure of the α4β2 nAChR with a homology model of the α7 nAChR indicated that non-aromatic residues in loop B differ in the α4 and α7 subunits: α4-KFGSWTYDK *vs.* α7-KFGSWSYGG. Because these differences may affect how agonists interact with the conserved tryptophan (W) residue of loop B, we made α7 loop B α4-like and tested the functional consequences of this modification at the whole- and single-channel level. α7 receptors with an α4-like loop B have higher sensitivity to activation by cytisine (logEC50 = -5.07 ± 0.19, n = 11), compared to wild type (two-tailed Student's *t*-test). Single-channel analysis showed that in loop B mutant α7 receptors, cytisine induced longer activation episodes, named as bursts (τ_{burst} (ms) =

1.25 ± 0.30, n = 4), whereas those were brief and infrequent in α7 WT (τ_{burst} (ms) = 0.72 ± 0.12, n = 6, two-tailed Student's *t*-test). Together, our findings highlight the importance of the environment surrounding the tryptophan conserved aromatic residue of loop B impacts on the interaction of agonists with this residue.

Disclosures: T. Minguez: None. **A.S.F. Oliveira:** None. **D.K. Shoemark:** None. **B.E. Nielsen:** None. **C. Bouzat:** None. **R.B. Sessions:** None. **A.J. Mulholland:** None. **S. Wonnacott:** None. **T. Gallagher:** None. **I. Bermudez:** None.

Poster

644. Nicotinic Acetylcholine Receptors: Structure and Regulation

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 644.07/B31

Topic: B.02. Ligand-Gated Ion Channels

Title: Effects of MMB4 and 2-PAM on alpha1-, alpha7-, and alpha3-type nicotinic acetylcholine receptors

Authors: *S. E. WOLFE, P. M. BODNER, M. G. KRICHTON, J. B. MACHAMER, P. M. MCNUTT;
USAMRICD, Gunpowder, MD

Abstract: Organophosphate (OP) nerve agents, such as soman and sarin, act by deactivating acetylcholinesterase (AChE) via phosphorylation, causing acetylcholine (ACh) to accumulate in the synaptic cleft and overstimulate cholinergic receptors. The resulting cholinergic toxidrome includes vomiting, confusion, seizures, neurotoxicity and respiratory failure. Current treatment for OP poisoning includes the use of oximes to reactivate AChE, such as pyridine-2-aldoximechloride (2-PAM). However, 2-PAM works against a comparatively narrow range of OP nerve agents and has dose-limiting toxicities. Oximes that antagonize a broader range of OP nerve agents, such as MMB4, HI-6 and HLo7, are currently under consideration as next-generation oxime replacements for 2-PAM. However, preclinical animal trials have found that each oxime exhibits toxicities that include respiratory depression. Hypothesizing that respiratory depression results from antagonism of nicotinic acetylcholine receptors (nAChRs), we used patch-clamp electrophysiology of dissociated mouse flexor digitorum brevis (FDB) muscle fibers to characterize agonist-induced α1 nAChR currents in the presence of oximes. To further evaluate whether each oxime antagonizes multiple peripheral nicotinic receptors, human embryotic kidney (HEK) cells were transfected with cDNA for human and mouse α1-, α7-, and α3-type nAChRs, and agonist-evoked currents were evaluated in the presence of increasing concentrations of each oxime. Preliminary data suggest that (1) nAChR antagonism is a class effect of quaternary ammonium oximes, (2) each oxime has differing potencies against various nAChRs, and (3) 2-PAM is the most toxic oxime among the oximes tested.

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Poster

644. Nicotinic Acetylcholine Receptors: Structure and Regulation

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 644.08/B32

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH RL5GM118990
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NIH P20GM103395
URSA Spring Project Award S18-40

Title: An investigation into the effects of two epilepsy-implicated point mutations within human nicotinic acetylcholine receptors containing accessory subunits

Authors: *J. MCKAY, T. J. SMITH, M. M. WELTZIN;
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Abstract: Nocturnal frontal lobe epilepsy (NFLE) is a group of familial and sporadic seizure disorders associated with mutations in nicotinic acetylcholine receptor (nAChR) subunits. NFLE is characterized by nighttime seizures that are frequently uncontrollable with available antiepileptic therapies. More effective therapies may be those that selectively target NFLE-associated nAChRs, such as the α3α4β2 and α4α5β2 subtypes, which are enriched in the epilepsy-implicated thalamocortical pathway compared to other brain regions. NFLE-associated intracellular cytoplasmic loop point mutations in the α4 or β2 subunits enhance the function of the pentameric α4β2 nAChRs. An accessory subunit can replace an α4 or β2 subunit, resulting in dramatic effects on receptor properties. We determined the outcomes of incorporating an accessory subunit in NFLE-containing nAChRs by substituting in an α3 or α5 accessory subunit in wildtype or NFLE-containing α4β2 nAChRs. To control receptor stoichiometry, we used wildtype or NFLE-containing concatenated β2 and α4 subunits that are linked with six alanine-glycine-serine repeats. Wildtype and NFLE-containing α4α5β2 and α3α4β2 nAChRs were expressed by co-injecting the concatenated β2-α4 dimer with the accessory subunit in 2:1, 1:5, and 1:50 ratios into *Xenopus laevis* oocytes. Agonist-induced currents were measured using nAChR-expressing oocytes and two-electrode voltage-clamp electrophysiology to determine differences in receptor peak function, efficacy, and potency for physiologically relevant ligands. Preliminary results show no variations in acetylcholine potency between wildtype and NFLE-containing receptors. Initial tests indicate that the α4α5β2 subtype has a decreased functional response to the partial agonist Sazetidine-A compared to the high agonist sensitivity α4β2

isoform. Notably, we observed a 2.4-fold increase in receptor function for the NFLE-mutated α4α5β2 nAChR versus wildtype receptors. This increase in function is similar for the low agonist sensitivity α4β2 isoform, identifying that the NFLE gain-of-function effect is still present despite containing fewer mutated α4 subunits. Characterizing receptors with restricted expression patterns may identify novel therapeutic targets.

Disclosures: J. McKay: None. **T.J. Smith:** None. **M.M. Weltzin:** None.

Poster

644. Nicotinic Acetylcholine Receptors: Structure and Regulation

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 644.09/B33

Topic: B.02. Ligand-Gated Ion Channels

Title: A functionally conserved mechanism of modulation via a vestibule site in pentameric ligand-gated ion channels

Authors: D. C. BERTRAND[1], K. KAMBARA[2], M. BRAMS[3], K. PRICE[4], S. C. LUMMIS[4], E. PARDON[5], A. GHARPURE[6], C. GOVAERTS[7], J. STEYAERT[5], R. E. HIBBS[8], *C. ULENS[9]; [1]Hiqscreen, Vesenaz - GE, Switzerland; [2]Hiqscreen Sarl, Vesenaz, Switzerland; [3]KULeuven, Leuven, Belgium; [4]Univ. of Cambridge, Cambridge, United Kingdom; [5]Vrije Univ. Brussel - VUB VIB, Brussels, Belgium; [6]UTSoutwestern, Dallas, TX; [7]Univ. Libre Bruxelles, Brussels, Belgium; [8]Neurosci., UT Southwestern Med. Ctr., Dallas, TX; [9]KU Leuven, Leuven, Belgium

Abstract: Pentameric ligand-gated ion channels (pLGICs) or Cys-loop receptors belong to a class of ion channels involved in fast synaptic signaling in the central and peripheral nervous systems. Molecules acting as allosteric modulators target binding sites which are remote from the neurotransmitter binding site, but functionally affect the coupling of ligand binding to channel opening. Allosteric modulators hold therapeutic potential as they finely tune channel function while preserving the normal fluctuations of neurotransmitter release at the synapse. In this study, we focus our attention to an allosteric binding site in the ion channel vestibule, which has converged from a series of studies on prokaryote and eukaryote channel homologs. We developed antibody fragments, called nanobodies, which are functionally active as allosteric modulators and solved co-crystal structures of the prokaryote channel ELIC bound either to a positive (PAM) or a negative (NAM) allosteric modulator. In combination with cysteine-scanning mutagenesis, we extrapolate the functional importance of the vestibule binding site to eukaryote ion channels, suggesting an evolutionarily conserved mechanism of allosteric modulation. Together, our work contributes to a better understanding of strategies to target new allosteric binding sites in pLGICs.

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Poster

644. Nicotinic Acetylcholine Receptors: Structure and Regulation

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 644.10/B34

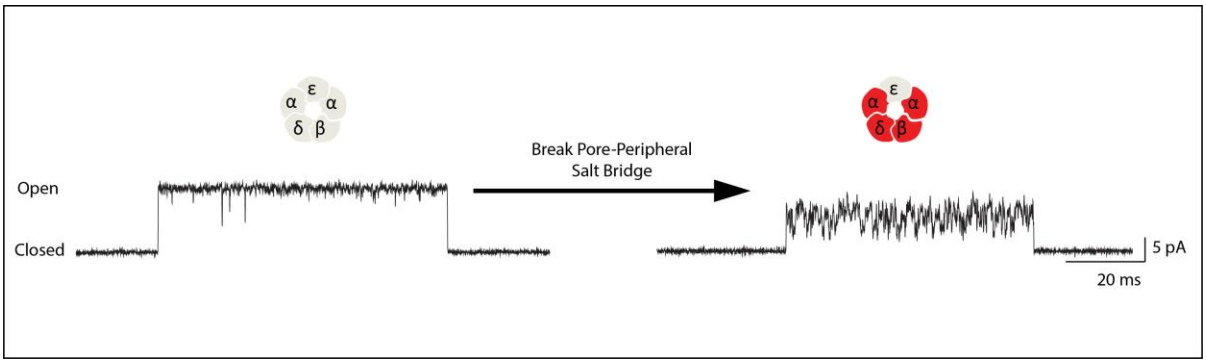
Topic: B.02. Ligand-Gated Ion Channels

Support: NIH Grant NS031744

Title: Structural foundations for ionic current stability and gating efficiency in cys-loop receptors

Authors: *J. R. STRIKWERDA, S. M. SINE;
Mayo Clin., Rochester, MN

Abstract: Cys-loop receptors mediate rapid synaptic excitation and inhibition throughout the central and peripheral nervous systems. They are pentamers comprised of five homologous subunits that assemble in a ring to form a central ion pore. Their principal functions are to rapidly open in response to bound agonist, select either cations or anions, and promote their rapid flow across the cell membrane. Here, for the acetylcholine receptor (AChR) from the neuromuscular junction, we investigate the structural bases for its efficient gating and high and uniform ion throughput. In particular, the ion pore is formed by five alpha-helices, one from each subunit. Near its cytoplasmic end, the pore constricts to its narrowest point and subtype specific residues select the ions for translocation. In this region, there is a highly conserved and yet uninvestigated intra-subunit salt bridge between the pore-lining alpha-helix and the most peripheral alpha-helix, which may stabilize the pore architecture in this critical region. Using site-directed mutagenesis we neutralize the charge on one member of the salt bridge in the human muscle AChR, and study the mutant receptors heterologously expressed in human embryonic kidney cells. Receptors with disrupted salt bridges exhibit decreased channel open times and increased closed times compared to wild type receptors. Furthermore, open channel currents show a marked increase in fluctuations and a decrease in amplitude. These open channel current fluctuations increase as the number of mutant subunits is increased. These results suggest that the inter-domain salt bridge is a universal stabilizer of the ion pore, enabling rapid and uniform ion flow, and that it serves to enhance the gating efficiency of the receptor. Future work will develop a residue-level mechanism behind the inter-domain salt bridge’s contribution to gating efficiency and open channel current stabilization.



Disclosures: **J.R. Strikwerda:** None. **S.M. Sine:** None.

Poster

644. Nicotinic Acetylcholine Receptors: Structure and Regulation

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 644.11/B35

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH Grant UL1GM118991
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Title: A study of a dog-variant rabies virus glycoprotein derived peptide interactions with nicotinic receptors subtypes

Authors: *S. THAO, C. SPAIN, K. HUEFFER, M. WELTZIN;
UAF, Fairbanks, AK

Abstract: The zoonotic virus, rabies (genus *Lyssavirus*, family *Rhabdoviridae*), kills approximately 60,000 people each year. Animals infected with rabies show changes in locomotor, breathing, and aggression behaviors. These behaviors are controlled by brain regions that express unique nicotinic acetylcholine receptors (nAChRs) subtypes and isoforms. nAChRs are cholinergic receptors that bind to exogenous and endogenous proteins and ligands, including the neurotransmitter acetylcholine (ACh). The rabies virus glycoprotein (RVG) is predicted to bind to nAChRs in a similar manner to snake toxins, but detailed analysis has not been performed.
The purpose of this study is to determine the activity of RVG using a derived peptide on various nAChR subtypes and isoforms involved in the modified behavior of animals infected with rabies.

We used a RVG-derived peptide of the putative glycoprotein region that interacts with nAChRs. nAChR subtypes and isoforms were expressed using biased cRNA subunit injection ratios. The electrophysiology technique, two-electrode voltage clamp, was used to collect concentration-response data to measure the potency of RVG peptide inhibition on acetylcholine activated nAChRs. Results show that there are differences in RVG peptide inhibition potencies between each nAChR subtype tested. Interestingly, this study shows that the RVG peptide has higher inhibition potency for the α7 nAChR subtype. Results will likely identify new molecular targets (nAChR subtypes or isoforms) for the RVG, and will expand our understanding of basic mechanisms in host-pathogen interactions that result in neurological disorders. Identification of specific nAChR subtype interactions with the RVG peptide could lead to the development of new antiviral pharmacological approaches to improve survival of this severe infectious disease, which so far has evaded successful therapy once rabies infection symptoms occur.
Key words: Nicotinic acetylcholine receptors, cholinergic receptors, rabies, glycoprotein, electrophysiology

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Poster

644. Nicotinic Acetylcholine Receptors: Structure and Regulation

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 644.12/B36

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH Grant GM57481
NIH Grant NS095899
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Title: Heteromeric neuronal nicotinic acetylcholine receptors with mutant beta subunits acquire sensitivity to alpha7-selective positive allosteric modulators

Authors: *C. STOKES[1], S. GARAI[3], A. R. KULKARNI[3], L. N. CANTWELL[3], C. M. NOVIELLO[4], R. E. HIBBS[4], N. A. HORENSTEIN[2], K. A. ABBOUD[2], G. A. THAKUR[3], R. L. PAPKE[1];
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Abstract: Homomeric α7 nicotinic acetylcholine receptors (nAChR) have an intrinsically low probability of opening that can be overcome by α7-selective positive allosteric modulators (PAMs), which bind at a site involving the second transmembrane domain. Mutation of a methionine that is unique to the sequence of α7 at the 15' position of this domain to leucine, the

residue in most other nAChR subunits, largely eliminates the activity of such PAMs. We tested the effect of the reverse mutation (L15'M) in heteromeric nAChR receptors containing α4 and β2, the nAChR subunits that are most abundant in brain. Receptors containing these mutations were found to be strongly potentiated by the α7 PAM TQS but insensitive to the alternative PAM PNU-120596. The presence of the mutation in the β2 subunit was necessary and sufficient for TQS sensitivity. The primary effect of the mutation in the α4 subunit was to reduce responses to ACh applied alone. Sensitivity to TQS required only a single mutant β subunit, regardless of the position of the mutant β subunit within the pentameric complex. Similar results were obtained when β2L15'M was co-expressed with the alternative α subunits α2 or α3 and when the L15'M mutation was placed in β4, co-expressed with α2, α3, or α4. Interestingly, the ACh responses of muscle-type receptors with the L15'M mutation in γ, ε, or δ subunits were decreased by co-application of TQS, and functional receptors were not observed when β1L15'M subunits were co-expressed with other muscle nAChR subunits. GAT107, the active isomer of the ago-PAM 4BP-TQS, did not produce allosteric activation of heteromeric β2L15'M containing receptors, and was less effective as a PAM than it is on α7 nAChR. An alternative PAM, GAT927, which like TQS has a bulky aromatic base group, was extremely efficacious on α4β2L15'M receptors and produced activation when applied without ACh. The unique structure-activity relationship of PAMs and the α4β2L15'M receptor compared to α7 and the availability of high resolution α4β2 structures may provide new insights into the fundamental mechanisms of nAChR allosteric potentiation.

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Poster

644. Nicotinic Acetylcholine Receptors: Structure and Regulation

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 644.13/B37

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH Grant R01 GM57481

Title: Allosteric and orthosteric activation of alpha7 nicotinic acetylcholine receptors by tri-substituted 2-aminopyrimidines

Authors: ***R. L. PAPKE**[1], G. A. CAMACHO HERNANDEZ[2], C. STOKES[1], M. QUADRI[3], L. CORRIE[4], N. A. HORENSTEIN[5], P. W. TAYLOR[2];
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Abstract: Positive allosteric modulators (PAMs) of α7 nicotinic acetylcholine receptors (nAChR) bind to a site in the transmembrane domains of α7 and diminish desensitizing effects of agonists to produce strong activation when co-applied. GAT107 ((+)-4BP-TQS) has been identified as an ago-PAM, that, unlike the PAMs PNU-120596 and TQS, produces strong activation without the co-application of an agonist. Data indicate that GAT107 produces direct allosteric activation by binding to both the transmembrane site shared by PNU-120596 and TQS and a unique extracellular allosteric activation site with unique activation profiles. GAT107 strongly activates mutant forms of the α7 receptor such as C190A that are incapable of orthosteric activation by ACh, even when ACh is co-applied with a PAM. TMP-TQS (*cis-trans*-4-(2,3,5,6-tetramethylphenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-sulfonamide) functions as an allosteric antagonist that blocks GAT107 allosteric activation of both wild-type α7 and α7C190A. In silico modeling predicted the binding of 2NDEP (1,1-diethyl-4(naphthalene-2-yl)piperazin-1-ium) to the putative allosteric activation site in the extracellular domain of the receptor, and we confirmed 2NDEP to be an allosteric agonist, able to activate both wild-type α7 and α7C190A in a TMP-TQS-sensitive manner (Gulsevin et al., 2019). A family of tri-substituted 2-aminopyrimidines, first identified as high affinity ligands of the AChBP, produce PNU-120596-dependent calcium signals in α7-transfected HEK cells (Kaczanowska et al., 2019). We evaluated the orthosteric and allosteric activities of these structurally complex heterocyclic compounds on both wild-type α7 and α7C190A. To varying degrees, theses agents activated currents when applied alone to *Xenopus* oocytes expressing α7 but not other nAChR subtypes. Following activation, we observed an associated persistent PAM-sensitive desensitization of α7 receptors. Compounds also effectively activated C190A mutants in a PNU-120596-dependent and TMP-TQS-sensitive manner. Taken together, these data indicate that these tri-substituted 2-aminopyrimidines function at both the orthosteric and allosteric activation sites of α7 nAChR.

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Poster

644. Nicotinic Acetylcholine Receptors: Structure and Regulation

Location: Hall A

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Program #/Poster #: 644.14/B38

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH Grant GM103801
NIH Grant GM48677

Title: Expression of α3β2β4 nicotinic acetylcholine receptors by rat adrenal chromaffin cells determined using novel conopeptide antagonists

Authors: *A. J. HONE[1,3,4], L. RUEDA-RUZAFA[5,3], T. J. GORDON[1], J. GAJEWIAK[1], S. CHRISTENSEN[1], T. DYHRING[6], A. ALBILLOS[3], J. MCINTOSH[2,7];
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Abstract: Postsynaptic nicotinic acetylcholine receptors (nAChRs) expressed by chromaffin cells of the adrenal medulla are directly involved in the stimulus-secretion coupling response and the release of catecholamines into the bloodstream. However, despite decades of use as a model for studying exocytosis, few studies have been conducted using subtype-selective ligands to pharmacologically identify the nAChRs expressed by these cells. Quantitative polymerase chain-reaction analysis of rat adrenal medulla revealed a relative abundance of mRNAs for α3, α7, β2 and β4 subunits and a lower abundance of mRNAs for α4 and α5 subunits. A novel conopeptide antagonist, PeIA-5469, that targets α3β2, and the α3β4-selective α-conotoxin TxID were used in combination with whole-cell patch-clamp electrophysiology to probe for the presence of receptors formed from the identified subunit mRNAs. Our results demonstrate that rat adrenal medulla contain two populations of chromaffin cells that express either α3β4* alone (~60%), or α3β4* together with the α3β2β4* subtype (~40%) (asterisk denotes the potential presence of other subunits). Conclusions were derived from results demonstrating that acetylcholine-gated currents could be inhibited by 97 ± 1 % (n=18) using TxID. In a subset of these cell, PeIA-5469 inhibited the acetylcholine-gated currents by 28 ± 8 % (n=7). In the remaining 11 cells, the acetylcholine-gated currents in the presence of PeIA-5469 were 102 ± 4 % of control amplitudes. Additional experiments using the α4β2 positive allosteric modulator NS206 were conducted to probe for the presence of receptors formed from α4 and β2 subunits. In the presence of TxID, there was no increase in acetylcholine-gated current amplitudes when the cells were exposed to NS206 (-48 ± -25 pA vs -18 ± -8 pA, respectively, n=17). The results of these studies demonstrate that rat adrenal chromaffin cells express two main populations of nAChRs, namely α3β4* and α3β2β4*.

Disclosures: A.J. Hone: None. **L. Rueda-Ruzafa:** None. **T.J. Gordon:** None. **J. Gajewiak:** None. **S. Christensen:** None. **T. Dyhring:** None. **A. Albillos:** None. **J. McIntosh:** None.

Poster

644. Nicotinic Acetylcholine Receptors: Structure and Regulation

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 644.15/B39

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH award R01 DA042749
NIH award R01 GM103801

Title: Lead α-conotoxins for development of novel, highly selective, α3β2*-nicotinic acetylcholine receptor antagonists

Authors: *B. EATON[1], E. JAISWAL[1], R. J. LUKAS[1], T. GORDON[2], A. J. HONE[3], J. MCINTOSH[3,5,4], P. WHITEAKER[1];
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Abstract: The medial habenula-interpeduncular (MH-IPN) tract nuclei play an important role in nicotine reward, withdrawal, and satiety. The MH and IPN express significant levels of α3β4*-, α3β2*-, and α6β2*-nAChR. Investigations of nicotine's effects within the MH and IPN have predominantly focused on α3β4*-nAChR. However, the highest densities of α3β2*-nAChR within the CNS are found in the MH-IPN tract. Therefore, it seems likely that α3β2*-nAChR play an important role in nicotine addiction phenotypes and may be effective targets for novel smoking cessation aides. Preliminary experiments have shown that infusion of the IPN with the α-conotoxin, α-CtxMII, disrupts aspects of nicotine withdrawal. Unfortunately, α-CtxMII inhibits both α3β2*- and α6β2*-nAChR, and there is currently no ligand that can be used to selectively target α3β2*-nAChR. Using directed mutagenesis of α-Ctxs MII and PeIA, we have previously demonstrated that affinity for α3β2*-nAChR can be reduced without significantly decreasing affinity for α6β2*-nAChR. Here we report our results after screening a library of >400 α-conotoxins and analogs to identify leads with selectivity for human α3β2*- over α6β2*-nAChR. Functional antagonism by each candidate was assessed in turn with $^{86}Rb^{+}$ efflux in SH-EP1 cells engineered to express α6/3β2β3-nAChR and then TEVC electrophysiology in *Xenopus laevis* oocytes made to express α3β2-nAChR. We have identified seven leads that have EC_{50} values in the low to mid nM range at α3β2*-nAChR, while exhibiting little or no activity at α6/3β2β3-nAChR at a concentration of 100 nM. These peptides also show little activity at the common α3β4- and α4β2-nAChR subtypes. No discrimination was seen between $(\alpha3\beta2)_2\beta2$- and $(\alpha3\beta2)_2\alpha3$-nAChR isoforms for any of the seven α3β2*-nAChR selective leads. We are now applying a positional scanning mutagenesis approach to these lead peptides with the aim of developing a panel of highly α3β2-nAChR selective derivatives, including ones bearing fluorescent or radioactive labels. These will be used to characterize the distinct contributions of α3β2*-nAChR function, with particular focus on the MH-IPN tract in which prominent α3β2*-nAChR expression overlaps with that of multiple other nAChR subtypes, including closely-related α3β4*- and α6β2*-nAChR.

Disclosures: B. Eaton: None. **E. Jaiswal:** None. **R.J. Lukas:** None. **T. Gordon:** None. **A.J. Hone:** None. **P. Whiteaker:** None. **J. McIntosh:** None.

Poster

644. Nicotinic Acetylcholine Receptors: Structure and Regulation

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 644.16/B40

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH award R01 DA042749
NIH award R01 GM103801

Title: Novel α-conopeptide derivatives of peia maintain α3β2 vs. α6β2 nicotinic receptor selectivity across species

Authors: *E. JAISWAL[1], B. EATON[1], P. WHITEAKER[1], J. MCINTOSH[2], A. HONE[2];
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Abstract: Smoking is the leading and preventable cause of death in the United States, driven by dependence on nicotine, the major addictive compound found in all tobacco products. The medial habenula (MH)-interpeduncular nucleus (IPN) tract is an important contributor to nicotine addiction phenotypes, and expresses the highest density of nicotinic acetylcholine receptors (nAChR) containing α3 and β2 subunits (α3β2*-nAChR; *denotes the possible presence of further subunits) in the central nervous system. However, the closely-related α3β4*- and α6β2*-nAChR subtypes are also prominently expressed in the same pathway. In order to determine the particular roles of α3β2*-nAChR in nicotine addiction phenotypes, highly selective compounds are required. We have developed a panel of 14 lead derivatives of α-Ctx PeIA that are potent (high-pM to low-nM) and selective (up to ≈1000x) for α3β2*-nAChR over other subtypes (including α6β2*-nAChR) heterologously expressed using rat subunits. However it has been observed that, at least in some cases, the exceptional selectivity of refined α-Ctx derivatives can be lost when they are applied to nAChR assembled from subunits of a different vertebrate species. Using two-electrode voltage-clamp recordings of nAChR expressed in *X. laevis* oocytes, we determined that absolute potencies at human α3β2*- and α6/α3β2β3*- nAChR were similar to those in rat and human. However, a modest trend towards reduced potency for human nAChR relative to rat α3β2*-nAChR was seen, especially in the cases of PeIA-5469 and PeIA -5460 (for which human α3β2*- over α6/3β2β3*- selectivity was reduced by 16- and 17-fold, respectively). However, the most-selective derivatives still retain ≈100-fold selectivity and low-nM affinity for human α3β2-nAChR. This will be sufficient to probe the properties and roles of α3β2*-nAChR in both human and rodent models.

Disclosures: E. Jaiswal: None. **B. Eaton:** None. **P. Whiteaker:** None. **J. McIntosh:** None. **A. Hone:** None.

Poster

644. Nicotinic Acetylcholine Receptors: Structure and Regulation

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 644.17/B41

Topic: B.02. Ligand-Gated Ion Channels

Title: Importance of fluidic control in high-throughput studies of acetylcholine and GABA receptors

Authors: *A. YEHIA, C. IONESCU-ZANETTI;
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Abstract: Extensive understanding of agonist/modulator/receptor interactions in ligand-gated ion channel assays is dependent upon advanced abilities in solution control and precise fluidic manipulation. These capabilities have traditionally resided in the domain of slow but reliable single cell patch clamp techniques due to technologically limiting factors plaguing most automated patch clamp (APC) systems. Even with the implementation of microfluidics, precise timing in fluidic exchange while consistently applying continuous solution flow has been elusive to most high throughput APC systems, limiting the scope of most drug research in that domain. By eliminating the need for external liquid handlers for in-assay solution exchange, we utilize a unique APC capable of in-plate continuous perfusion and precise parallel application of compounds while clamping and recording from ensembles of cells in whole-cell patch clamp formation. Here we demonstrate the effects of precise fluidics on high throughput research in nACh receptor agonist response and desensitization. We also show the effects on consistency of GABA receptor current responses. While imperfect agonist washout presents a challenge for traditional APC systems, this data set shows the superior performance of this microfluidic approach, forming a great foundation for serial application of modulators in high throughput APC environments.

Disclosures: A. Yehia: None. **C. Ionescu-Zanetti:** None.

Poster

645. GABA(A) and Glycine Receptor Pharmacology

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 645.01/B42

Topic: B.02. Ligand-Gated Ion Channels

Support: MEXT/JSPS KAKENHI Grant Number JP 16H05133 16K15318

Title: The underlying mechanism of propofol-induced intracellular calcium elevation

Authors: *N. SAKAI[1], **T. URABE**[2], S. MOTOIKE[3], K. HARADA[1], I. HIDE[1], S. TANAKA[1]; [1]Grad Sch. of Biomed & Hlth. Sci, Hiroshima Univ., HIroshima-shi, Japan; [2]Dept. of Anesthesiol. and Critical Care, Grad. Sch. of Biomed. and Hlth. Sciences, Hiroshima Univ., Hiroshima-shi, Japan; [3]Dept. of Dent. Anesthesiology, Grad. Sch. of Biomed. & Hlth. Sciences, Hiroshima Univ., Hiroshima-shi, Japan

Abstract: Propofol, most frequently used as general anesthetic, is thought to exert its anesthetic actions via $GABA_A$ receptors. Propofol also has additional beneficial actions such as myocardial and neuronal protection, whereas adverse actions such as angialgia and propofol infusion syndrome (PRIS). However, the precise mechanisms of these propofol actions remain unclear.In this study, we examined the propofol-induced elevation of intracellular calcium using SHSY-5Y neuroblastoma cells, COS-7 cells, HEK293 cells, and HUVEC loaded by calcium indicator Fluo-4 in order to identify the underlying mechanism. Propofol (higher than 50μM) induced intracellular calcium elevation in a dose-dependent manner in SHSY-5Y cells as well as COS-7 cells, HEK293 cells, and HUVEC. These phenomena were not influenced by the elimination of extracellular calcium. And, the calcium elevation was abolished when intracellular or intra-endoplasmic reticulum (ER) calcium was depleted by BAPTA-AM or thapsigargin, respectively, suggesting that the calcium was mobilized from ER. Studies using various inhibitors including U-73122, Xestospongin C, and dantrolene revealed that the propofol-induced calcium elevation was not mediated through G-protein coupled receptors, IP3 receptors, or ryanodine receptors.We captured the live imaging of ER, Mitochondria, and Golgi apparatus after the propofol application using ER-tracker, Mito Tracker™ResCMXRos, and CellLight™Golgi-GFP BacMam2.0, respectively. Accompanying the calcium elevation, the structures of these intracellular organelles were altered. Especially, ER and Mitochondria was fragmented and aggregated, which might not be restored as long as we observed. This morphological change of ER structure could be observed even after intracellular calcium was depleted by BAPTA-AM. These results suggest that propofol directly act on these organelles, thereby mobilizing calcium.In case of clinical usage, the maximum plasma concentration of propofol is approximately 30-40μM. Although the concentration of propofol used in this experiment was larger than that of clinical use, it is possible that the concentration could reach more than 40μM at the site where propofol was injected into the blood vessel or in case of high-dosed and prolonged usage of propofol. Therefore, these propofol-induced phenomena might be involved in its various adverse effects including angialgia and PRIS.

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Poster

645. GABA(A) and Glycine Receptor Pharmacology

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 645.02/B43

Topic: B.02. Ligand-Gated Ion Channels

Support: Stanford School of Medicine SPARK program
Stanford Dept of Anesthesia FIDL program

Title: Development of a next generation of GABAergic compounds for anesthesia and epilepsy

Authors: *M. F. DAVIES[1], A. JAHANGIR[2], M. SHAMLOO[4], R. K. LAM[2], H. S. MCCARREN[5], B. S. BARKER[6], E. J. BERTACCINI[3];
[1]Anesthesia, Stanford Univ. Sch. Med., Stanford, CA; [2]Neurosurg., [3]Anesthesia, Stanford Univ. Sch. of Med., Stanford, CA; [4]Neurosurg., Stanford Univ., Stanford, CA; [5]Neurosci., US Army Med. Res. Inst. of Chem. Def., Aberdeen Proving Ground, MD; [6]Neurosci., USAMRICD, Aberdeen Proving Ground, MD

Abstract: All currently used intravenous anesthetic agents are associated with an entire spectrum of undesirable side effects, most notably cardiovascular instabilities. These side effects are poorly tolerated in many patients without our intervention, but especially in very young children who possess immature physiologic compensatory mechanisms, as well as in the elderly with confounding comorbidities and otherwise exhausted compensatory mechanisms. In light of this, we have pursued the development of new lead compounds to produce the next generation of safer anesthetic agents. Our methodologies of *in silico* screening and prediction of compounds which bind to our validated model of the gamma amino butyric acid receptor ($GABA_AR$) have now identified a novel class of lead compounds which demonstrate overt anesthetic activity. The most potent of the series is KSEB 14-01 which anesthetizes both tadpoles (EC_{50}= 0.28 μM; n=5) and male Sprague Dawley rats (ED_{50} = 0.78 μM, n=5) with a potency greater than that of propofol, the current intravenous anesthetic standard. KSEB 14-01 increases Cl ion flux in CHO cells transfected with α1β2γ2 receptor subunits (EC_{50} = 1.7 μM) (FLIPR Tetrus, Eurofins San Diego CA). These structures are devoid of the chemical moieties known to produce adrenal suppression, the dreaded side of effect of the other commonly used anesthetic, etomidate. *Of even greater importance is the fact that our new class of compounds shows minimal to no suppression of blood pressure and respiration or changes in blood gas concentration of CO_2, O_2, and O_2 saturation or in blood pH at anesthetic concentrations, in stark contrast to the deleterious effects of propofol on these parameters.* These compounds are derived from novel chemical structures not previously associated with or known to produce significant anesthetic effect. We have now refined our lead to enhance its solubility while maintaining the desirable characteristics of anesthesia without significant hemodynamic or respiratory suppression. This

class of compound will have ready application as an anesthetic in any patient with the potential for such physiologic instabilities and, through its $GABA_AR$ mechanism, provide a stable means of acute and possibly chronic seizure suppression.

Disclosures: **M.F. Davies:** A. Employment/Salary (full or part-time):; Stanford School of Medicine. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Stanford SPARK. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stanford University. **A. Jahangir:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Bert Pharma Inc. **M. Shamloo:** None. **R.K. Lam:** None. **H.S. Mccarren:** None. **B.S. Barker:** None. **E.J. Bertaccini:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Bert Pharma Inc..

Poster

645. GABA(A) and Glycine Receptor Pharmacology

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 645.03/B44

Topic: B.02. Ligand-Gated Ion Channels

Support: Finnish Foundation for Alcohol Studies
University of Turku Graduate School (Drug Research Doctoral Programme)

Title: Alcohol enhances hops modulation of $GABA_A$ receptors

Authors: *A. Y. BENKHEROUF, S. L. SOINI, M. UUSI-OUKARI;
Integrative Physiol. and Pharmacol., Univ. of Turku - Inst. of Biomedicine, Turku, Finland

Abstract: Hops are major component of beer that is added during brewing. In addition to its wide range of bioactivity, it exhibits neuroactive properties as a sedative and sleeping aid. These effects are mediated by an increase in the function of γ-aminobutyric acid type A ($GABA_A$) receptors, the major sites of fast synaptic inhibition in the central nervous system (CNS). Recent evidence revealed prenylflavonoids in hops acting as potent positive modulators on native and recombinant $GABA_A$ receptors. These findings raised the question whether ethanol brings further potentiation in the GABAergic modulation of hops compounds in beer.
In radioligand binding assays, we assessed the synergy of selected hops compounds with respect to their pharmacological activity in the absence and presence of ethanol. [^{3}H]ethynylbicycloorthobenzoate (EBOB), a potent radiolabelled noncompetitive blocker, was used on native $GABA_A$ receptors expressed in male Sprague-Dawley rat brain membranes. Combinations of 6-prenylnaringenin (6PN) and/or humulone with isoxanthohumol (IXN) or 8-prenylnaringenin (8PN) led to an additive potentiation in GABA-induced [^{3}H]EBOB

displacement that was equal to the sum of the displacement by individual compounds. Despite the fact that ethanol alone showed no effect on GABA-induced [^{3}H]EBOB displacement, it induced a significant reduction in the residual radioligand binding in the presence of 1 µM hops prenylflavonoid or humulone. Furthermore, the inclusion of ethanol produced a leftward shift in the IXN-induced [^{3}H]EBOB displacement curve. Ethanol reduced the IC_{50} of IXN modulation from 16.7 µM to 13.2 µM in forebrain and from 18.0 µM to 15.9 µM in cerebellum. Similarly, in the presence of low IXN (1 µM), ethanol decreased the IC_{50} of GABA-induced displacement of [^{3}H]EBOB binding from 3.2 µM to 2.9 µM in forebrain and from 2.3 µM to 1.8 µM in cerebellum.
Our results displayed an evident additive effect in the allosteric modulation of $GABA_A$ receptors by hops compounds and demonstrated ethanol synergy as a second-order modulator in [^{3}H]EBOB assay suggesting a probable enhancement in the intoxicating effects of ethanol in hops enriched beer.

Disclosures: A.Y. Benkherouf: None. **S.L. Soini:** None. **M. Uusi-Oukari:** None.

Poster

645. GABA(A) and Glycine Receptor Pharmacology

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 645.04/B45

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH Grant AA021213

Title: Structural pharmacology of native brain GABA-A receptors

Authors: *R. W. OLSEN[1], A. K. LINDEMEYER[1], M. WALLNER[1], X. R. LI[2], K. W. HUYNH[2], Z. H. ZHOU[2];
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Abstract: GABA-A receptors (GABAR) are the major mediators of inhibitory neurotransmission and targets for many therapeutic agents for seizures, anxiety, sleep, learning, cognition, and drug use disorders. Recent technological advances in single-particle electron cryomicroscopy (cryoEM) data collection and processing have produced high resolution protein structures including recombinant GABAR. This powerful technique can test hypotheses about direct ethanol (EtOH) enhancement of extrasynaptic δ subunit-containing GABAR. We purified δ-GABAR from pig cerebellum using an antibody to δ subunit (gift of W Sieghart and P Scholze, Vienna), and synaptic γ2-GABAR from cortex using a benzodiazepine Ro7-1986 (Roche, Basel) affinity column (Stauber et al.,1987), obtaining sufficient purity for cryoEM. We described binding sites for EtOH antagonist Ro15-4513 (~10 nM) on δ-GABAR, likely at the

extracellular domain α+/β- interface, competitively inhibited by EtOH (IC_{50}~20 mM) and defined by the α6(R100Q) polymorphism found in EtOH-hypersensitive rats (Wallner et al.,2014). These EtOH sites differ from GABAR anesthetic sites in the transmembrane domain (Mihic et al.,1997, EtOH IC_{50}~100 mM). Using pig cerebellum membranes (2.5 pmol/mg protein of α1-GABAR, 1.0 pmol/mg of α6-GABAR, including 50%=0.5 pmol/mg of δ-GABAR), 50% of the detergent-solubilized [^{3}H]Ro15-4513 binding was bound to anti-δ immunobeads, eluted by pH 3.6, followed (as in Liu et al.,2018) by size-exclusion chromatography and electron microscopy (2D for negative staining to identify single particles with receptor size and shape, 3D reconstruction and refinement for cryoEM images, and modeling. Analyzing *native brain* GABAR proteins minimizes problems associated with recombinantly expressed GABAR, which may lack endogenous assembly, trafficking, and clustering proteins, auxiliary subunits, lipids, and post-translational modifications, and may assemble into non-native architecture and subunit arrangements. CryoEM structures have confirmed ligand binding sites, agonist gating of ion channel, modulation by PAMs, and the Monod-Wyman-Changeux allosteric model. The importance of cryoEM to explain complex cellular and brain functions, diseases, and structure-based drug design cannot be overstated.

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Poster

645. GABA(A) and Glycine Receptor Pharmacology

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 645.05/B46

Topic: B.02. Ligand-Gated Ion Channels

Support: FONDECYT 1170252
FONDECYT 3170108

Title: Modulation of recombinant and cortical $GABA_A$ receptors by the alkaloid gelsemine

Authors: *A. M. MARILEO, J. A. GAVILAN, C. O. LARA, C. F. BURGOS, V. P. SAN MARTIN, A. SAZO, J. FUENTEALBA, L. GUZMÁN, P. A. CASTRO, L. G. AGUAYO, G. MORAGA-CID, G. E. YÉVENES.;
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Abstract: Gelsemine is one of the main alkaloids produced by the *Gelsemium genus* of plants. Behavioral studies have shown that gelsemine exerts analgesic and anxiolytic effects in rodents. Despite these evidences, the pharmacological targets underlying the behavioral effects of gelsemine are still unclear. Several evidences have suggested that the analgesic and anxiolytic actions of gelsemine are related with the functional modulation of inhibitory glycine receptors.

However, it is currently unknown whether gelsemine is able to modulate the activity of inhibitory $GABA_A$ receptors. The present work aims to characterize the functional modulation of $GABA_A$ receptors by gelsemine using electrophysiology, calcium imaging and bioinformatics. Using whole-cell recordings of $GABA_A$ receptors expressed in HEK293 cells, we determined that benzodiazepine-sensitive $GABA_A$ receptors (i.e. $\alpha1\beta2\gamma2$, $\alpha2\beta3\gamma2$, $\alpha3\beta3\gamma2$ and $\alpha5\beta2\gamma2$) were inhibited by gelsemine. On the other hand, benzodiazepine-resistant $GABA_A$ receptors (i.e. $\alpha1\beta2\gamma2$ H101R mutant and $\alpha1\beta2$ receptors) were also inhibited by gelsemine. Further electrophysiological studies performed on cultured mouse cortical neurons showed that whole-cell current through native $GABA_A$ receptors were inhibited by the alkaloid. The acute application of gelsemine to these neurons produced a significant reduction of the frequency, but not of the amplitude, of the GABAergic mIPSCs. Similar experiments showed that the frequency of glutamatergic mEPSCs was also decreased by the alkaloid. Coincidentally, calcium imaging studies indicated that gelsemine decreased the frequency of spontaneous cytosolic calcium transients. Our results show that gelsemine modulate the activity of recombinant and native $GABA_A$ receptors, possibly through a direct interaction of the alkaloid with the ion channel. In addition, our results showed that gelsemine negatively modulates excitatory and inhibitory synaptic activity of cultured cortical neurons. Altogether, these results suggest that the analgesic and anxiolytic actions of gelsemine, at least in part, appears to be not related with the potentiation of benzodiazepine-sensitive $GABA_A$ receptors.

Disclosures: **A.M. Marileo:** None. **J.A. Gavilan:** None. **C.O. Lara:** None. **C.F. Burgos:** None. **V.P. San Martin:** None. **A. Sazo:** None. **J. Fuentealba:** None. **L. Guzmán:** None. **P.A. Castro:** None. **L.G. Aguayo:** None. **G. Moraga-Cid:** None. **G.E. Yévenes.:** None.

Poster

645. GABA(A) and Glycine Receptor Pharmacology

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 645.06/B47

Topic: B.02. Ligand-Gated Ion Channels

Support: FONDECYT 1170252
FONDECYT 1160851
FONDECYT 3170108

Title: Functional modulation of the glycine receptor alpha3 subunit by tropeines

Authors: *V. P. SAN MARTÍN, C. F. BURGOS, A. M. MARILEO, C. O. LARA, A. E. SAZO, J. FUENTEALBA, L. GUZMÁN, P. A. CASTRO, L. AGUAYO, G. MORAGA-CID, G. YÉVENES;
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Abstract: Glycine receptors (GlyRs) are chloride-permeable pentameric ligand-gated ion channels. The inhibitory activity of GlyRs is fundamental for physiological processes, such as motor control and respiration. In addition, several pathological states, such as hyperekplexia, epilepsy, and chronic pain, are associated with abnormal glycinergic inhibition. Several studies have shown than positive allosteric modulators targeting the GlyR α3 subunit (α3GlyR) displayed beneficial effects in chronic pain models. Interestingly, previous electrophysiological studies have shown that tropeines, a family of synthetic antagonists of 5-HT3Rs, potentiate the activity of other GlyR isoforms in the nanomolar range. However, despite its importance as a pharmacological target in chronic pain, it is currently unknown whether the α3GlyR function is modulated by tropeines. The present work intends to initiate the characterization of the potential modulation of α3GlyR by tropeines using electrophysiological techniques and molecular docking simulations. Our electrophysiological experiments show that tropisetron, a prototypical tropeine, exerted concentration-dependent inhibitory effects on α3GlyRs at the low micromolar range. In addition, three other tropeines (granisetron, ondansetron, and dolasetron) showed similar effects. Single-channel recordings show that tropisetron inhibition is associated with a decrease in the open probability of the ion channel. Using the α3GlyR crystal structure as template, molecular docking assays suggest that tropeines preferentially bind to an agonist-free, closed state of the ion channel. The tropeine binding occurs in a discrete pocket around the vicinity of the orthosteric site within the extracellular domain of α3GlyR. Our results describe the pharmacological modulation of tropeines on α3GlyRs. These findings may contribute to the development of GlyR-selective tropeine derivatives for basic and/or clinical applications.

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Poster

645. GABA(A) and Glycine Receptor Pharmacology

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 645.07/B48

Topic: B.02. Ligand-Gated Ion Channels

Title: A novel highly alpha5-subunit selective benzodiazepine

Authors: *P. SCHOLZE, X. SIMEONE, F. KONIUSZEWSKI, M. MÜLLEGGER, A. SMETKA, F. STEUDLE, R. PUTHENKALAM, M. ERNST;
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Abstract: The most frequent $GABA_A$-receptor subtype is composed of two alpha two beta and one gamma2-subunit. Benzodiazepine, which are commonly used in the treatment of sleep disorders, anxiety, epileptic seizures and many other conditions, bind selectively at the alpha-

gamma-interface of those receptors. Nearly all of the clinically relevant drugs target all $GABA_A$receptor subtypes with equal affinity. The nature of the alpha subunit seems to be critical for the clinical effect elicited by the compound. Therefore drug development research is focusing on identifying subtype selective drugs such as, among others, drugs selective for alpha5-containing $GABA_A$receptors. Although those receptors are rare (<5% of total) and their distribution is limited to few brain areas like hippocampus, they are believed to be promising future drug targets to potentially treat cognitive and/or mood disorders. One of the compounds already identified is SH-053-2′F-R-CH3, which is moderately selective for alpha5-subunit containing $GABA_A$ receptors. Here we present data on a novel imidazobenzodiazepine-compound. Using radioligand displacement assays on transfected HEK 293 cells and two-electrode voltage clamp electrophysiology in *Xenopus laevis* oocytes, we demonstrated that an acid group as substituent leads to large improvements of functional and binding selectivity for alpha5beta3gamma2 over other $GABA_A$receptors (e.g. >60fold compared to alpha1beta3gamma2). In order to provide a structural hypothesis for the extraordinary potency preference of the novel ligand we performed a computational study utilizing homology models and computational docking. Based on these results, point mutated subunits were generated and analyzed. Both atom level structural studies and mutational analysis confirm that loop C of the GABAA-receptor alpha-subunit is the dominant molecular determinant of drug selectivity. With this novel alpha5-subunit-selective drug we propose to have discovered a future promising drug candidate.

Disclosures: P. Scholze: None. **X. Simeone:** None. **F. Koniuszewski:** None. **M. Müllegger:** None. **A. Smetka:** None. **F. Steudle:** None. **M. Ernst:** None. **R. Puthenkalam:** None.

Poster

645. GABA(A) and Glycine Receptor Pharmacology

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 645.08/B49

Topic: B.02. Ligand-Gated Ion Channels

Title: Human and dog $\alpha_4\beta_3\delta$ $GABA_A$ receptors display differential sensitivity to GABA and positive allosteric modulators

Authors: *A. L. ALTHAUS[1], K. KAMBARA[2], S. BERTRAND[2], D. C. BERTRAND[2], M. A. ACKLEY[1];
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Abstract: The type A γ-aminobutyric acid ($GABA_A$) receptors are a large heterogeneous class of pentameric chloride channels comprised of two α, two β, and one γ, δ, ρ, θ, or ε subunits (Sigel E and Steinmann ME 2012). Thought to be the most important inhibitory receptors in the brain, $GABA_A$ receptors are targets for clinically active drugs used to treat a variety of psychiatric and

neurological disorders. To date, 19 genes encoding for $GABA_A$ receptors have been identified in vertebrates and these receptors are very well conserved throughout the animal kingdom, with some precursors already present in bacteria (Thompson 2012).
Xenopus oocytes are a powerful in vitro system in which to study specific $GABA_A$ receptor configurations. To examine potential species differences between human and dog $GABA_A$ receptors, we utilized *Xenopus* oocytes recombinantly expressing species-specific $GABA_A$ receptors representative of either the synaptic ($\alpha1\beta2\gamma2$) or exytrasynaptic ($\alpha4\beta3\delta$) type. Both dog and human $\alpha1\beta2\gamma2$ receptors exhibited similar sensitivity to GABA, while dog $\alpha4\beta3\delta$ receptors exhibited a 10-fold reduction in GABA sensitivity relative to human. In addition, dog $\alpha4\beta3\delta$ receptors were less sensitive to the δ specific allosteric modulator DS2 compared to human $\alpha4\beta3\delta$ receptors.
Sequence alignment between the human and dog subunits reveal a high degree of conservation for the $\beta3$ subunit, small but interesting differences in the $\alpha4$ subunit, and relatively more variation in the δ subunit. Ongoing work is aimed at identifying which parts of the receptor underlie the observed species differences in pharmacological sensitivity. Understanding species differences in $GABA_A$ receptor activity, particularly with respect to pharmacological sensitivity of novel therapeutics, is critical for interpreting the translational validity of preclinical data.

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Thompson AJ, Alqazzaz M, Ulens C, Lummis SCR. The pharmacological profile of ELIC, a prokaryotic GABA-gated receptor. *Neuropharm* 63: 761-67, 2012

Disclosures: A.L. Althaus: A. Employment/Salary (full or part-time):; Sage Therapeutics. **K. Kambara:** 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.; Sage Therapeutics. **S. Bertrand:** 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.; Sage Therapeutics. **D.C. Bertrand:** 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.; Sage Therapeutics. **M.A. Ackley:** A. Employment/Salary (full or part-time):; Sage Therapeutics.

Poster

645. GABA(A) and Glycine Receptor Pharmacology

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 645.09/B50

Topic: B.04. Ion Channels

Support: Ontario Graduate Scholarship
Frederick Banting and Charles Best Canada Graduate Scholarship
CIHR Foundation Grant

Title: Characterizing negative allosteric modulators of α5GABA$_A$ receptors in primary hippocampal neurons

Authors: *M. A. MANZO[1], W. W. LI[1], D.-S. WANG[1], B. A. ORSER[1,2,3];
[2]Anesthesia, [1]Univ. of Toronto, Toronto, ON, Canada; [3]Sunnybrook Hlth. Sci. Ctr., Toronto, ON, Canada

Abstract: Excess function of α5 subunit-containing GABA$_A$ receptors (α5GABA$_A$Rs) has been implicated in several neurological disorders including Alzheimer's Disease, perioperative neurocognitive disorder, depression and motor deficits after stroke. Negative allosteric modulators that preferentially inhibit α5GABA$_A$Rs (α5-NAMs) have been developed to treat these disorders. α5-NAMs lack many of the adverse neurological effects associated with non-selective GABA$_A$R antagonists; indeed, several α5-NAMs have already been investigated in clinical trials. To date, α5-NAMs have primarily been studied in GABA$_A$Rs recombinantly expressed in non-neuronal cells. The data show that α5-NAMs also act on other GABA$_A$R subtypes with lower efficacy and selectivity. Surprisingly, no studies have directly compared the effects of α5-NAMs on native GABA$_A$Rs. This information would assist in the development and selection of more effective compounds for clinical trials. Thus, the goal of the current study is to characterize and compare the effects of α5-NAMs on the amplitude of a tonic current primarily generated by α5GABA$_A$Rs in primary neurons. Five α5-NAMs including α5IA, MRK-016, L-655,708, Ono and basmisanil, were each studied at 3 concentrations. Tonic current was recorded using whole-cell voltage clamp technique in cultured hippocampal neurons isolated from fetal mice. Results showed that α5IA inhibited the tonic current by 30 ± 7% at 1 nM, 47 ± 5% at 10 nM, and 56 ± 8% at 100 nM (mean ± SEM, $n = 9$, $p < 0.05$ compared with 1 nM). MRK-016 (1, 10, 100 nM), L-655,708 (2, 20, 200 nM) and Ono (1, 10, 100 nM) showed similar levels of inhibition at all concentrations ($n = 8$-10, $p > 0.05$ for each drug). In contrast, basmisanil enhanced the tonic current by 9 ± 11% (10 nM) and 6 ± 22% (100 nM); and inhibited the current at 1 μM (56 ± 9%, $n = 8$, $p < 0.01$ compared with lower concentrations). Next, a comparison of all α5-NAMs at concentrations with the highest efficacy demonstrated that they all similarly inhibited tonic current (40 ± 6% to 56 ± 9%, $p = 0.3$). In conclusion, all α5-NAMs at the most efficacious concentrations are equally effective. Only α5IA inhibits the tonic current in a concentration-dependent manner. Uniquely, basmisanil enhances the tonic current at low concentrations, and inhibits it at the highest concentration. These results suggest that factors other than efficacy, such as toxicity, should be considered when selecting an α5-NAM for clinical trials.

Disclosures: M.A. Manzo: None. **W.W. Li:** None. **D. Wang:** None. **B.A. Orser:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Dr. Orser is an inventor of Canadian Patent 2,852,978 and United States Patent 9,517,265 and a pending patent (United States Patent: 62/268,137).

Poster

645. GABA(A) and Glycine Receptor Pharmacology

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 645.10/B51

Topic: B.02. Ligand-Gated Ion Channels

Title: Comparison of Z-drugs on the three gamma subunits of $GABA_A$ receptors

Authors: *G. A. RICHTER, P. K. AHRING, V. W. Y. LIAO, N. ABSALOM, P. VAN NIEUWENHUIJZEN, M. CHEBIB;
The Univ. of Sydney, Camperdown, Australia

Abstract: Background and Aim: It is well established that benzodiazepines bind to $GABA_A$ receptors at the interface between α_x-γ_2 subunits. While the majority of $GABA_A$ receptors contain γ_2 subunits, a small portion in distinct brain regions contain a γ_1 or γ_3. Little is known about the physiological importance of these subunits, and no drug has been found which selectively modulates them over γ_2. To investigate this, we are using a mutant mouse knock-in γ_2F77I model which has drastically attenuated zolpidem, but not diazepam binding in the α_x-γ_2 pocket. We are testing the nonbenzodiazepine 'z-drugs' zolpidem (Ambien), eszopiclone (Lunesta), and zaleplon (Sonata). In this model, 'classic benzodiazepine' binding is largely unaffected, so we use diazepam as a control. Methods: 1. Using c-Fos immunohistochemistry we investigated the response to zolpidem (10 mg/kg), diazepam (5 mg/kg), zaleplon (3 mg/kg), and vehicle in male γ_2F77I mice and wildtype littermate controls (n=8). Locomotor activity over 90 minutes was tracked in an open field test. 2. To determine if benzodiazepine binding-site affinity changes after damage to the brain, 12-13-week-old male mice were given a photothrombotic lesion targeting the M1 motor cortex. Three weeks later, an *in-vitro* autoradiography competition experiment against [^{3}H]-flumazenil was run in mutant and wildtype mice three weeks post-stroke with (n=5). 3. To determine receptor response to these drugs, $GABA_A$ receptors containing one of the three types of γ subunits, or the γ_2F77I mutant, were expressed in *Xenopus laevis* oocytes and two electrode voltage clamp recordings were taken. Results: We found that in γ_2F77I mice zolpidem did not significantly reduce locomotor activity and overall c-Fos expression was lower in these mice compared to wildtype. No differences were found with diazepam. Autoradiography revealed that in mutant mice, zaleplon was more effective than zolpidem at competing off [^{3}H]-flumazenil suggesting that zaleplon could be binding to non γ_2 $GABA_A$ receptors. Electrophysiology data demonstrates that zaleplon also has modulatory effects on γ_3 vs. γ_2F77I or γ_1. Conclusions: These results suggest that zaleplon may be exhibiting some of its effects via γ_3 $GABA_A$ receptors.

Disclosures: G.A. Richter: None. **P.K. Ahring:** None. **V.W.Y. Liao:** None. **N. Absalom:** None. **P. Van Nieuwenhuijzen:** None. **M. Chebib:** None.

Poster

645. GABA(A) and Glycine Receptor Pharmacology

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 645.11/B52

Topic: B.02. Ligand-Gated Ion Channels

Title: A role for entropic forces in tuning a ligand gated ion receptor function

Authors: *K. KAMBARA[1], P. M. SELZER[2], S. NOACK[2], Y. MORENO[3], J. HARRINGTON[3], D. BERTRAND[1];
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Abstract: Entropic forces play an important role in the conformational changes occurring in proteins and can modulate the allosteric transitions. A good example was recently provided by the role of the carboxy terminus at the human UDP-α-d-glucose-6-dehydrogenase (UGDH) in which the entropic force produced by an intrinsically disordered sequence causes a shift towards high affinity for an allosteric inhibitor (1). These observations raised an important question that may be broadly applicable to even more complex proteins such as ligand gated ion channels (LGIC).
To examine the putative role of entropic forces on the function of LGIC's the use of homomeric receptors, such as that formed by the γ-aminobutyric acid (GABA) chloride permeable channel, represents an ideal model. Recombinant receptors from the tick *Ixodes scapularis* were expressed in *Xenopus* oocytes and recordings were performed using two electrode voltage clamp. Extension of the carboxy terminus by adding fourteen amino acids that are predicted to adopt an intrinsically disordered state caused no detectable alteration of the receptor expression. However, a hundred-fold decrease in the effective concentration of GABA was observed. This suggests that increasing the length of the carboxy terminus reduced the energy barrier for receptor activation. In agreement with the hypothesis of the role of the entropic forces on allosteric transitions, reversing the sequence of the carboxy terminal end also caused an increase in the apparent affinity of the receptors for GABA. Further increase of the length of the carboxy terminal by duplication of the initial fourteen amino acid caused the same increase in apparent affinity for GABA without altering the response time course.
These observations confirm the relevance of the entropic forces and suggest that binding of a peptide or a molecule on a receptor can alter the energy landscape of receptors. Such modification by, for example associated proteins, could play a determinant role in normal physiological conditions as well as in pathologies such as Alzheimer's disease with the example of the beta amyloid Aβ interaction with the α7 neuronal nicotinic acetylcholine receptors (2,3).

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Poster

645. GABA(A) and Glycine Receptor Pharmacology

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 645.12/B53

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH Grant AA006399
NIH Grant AA020980
Waggoner Center for Alcohol and Addiction Research

Title: Photomodulation of alpha1beta3gamma2 $GABA_A$ receptors expressed in Xenopus laevis oocytes using a tethered propofol photoswitch

Authors: *C. M. BORGHESE[1], E. J. BERTACCINI[2], J. R. TRUDELL[2], R. A. HARRIS[1]; [1]Univ. of Texas at Austin, Austin, TX; [2]Dept. of Anesthesia, Stanford Univ., Stanford, CA

Abstract: Photoswitches are freely diffusible molecules with two photo-dependent isomeric forms, each with different actions on their biological targets. Tethered photoswitches, in addition, have chemical groups that can be covalently bound to a biological target, either to a native or engineered residue. This tethering leads to high local concentration (the residue cannot diffuse away) and spatial restriction within the biological target. Either kind of photoswitches can be agonists, inverse agonists, antagonists, blockers or modulators.
Previous studies have used a diffusible propofol photoswitch (Stein 2012) and a tethered propofol photoswitch with a very long spacer between the tethering cysteine (located in the extracellular domain) and the propofol moiety (Yue 2012). Our aim was to identify and characterize the propofol binding sites in $GABA_A$ α1β3γ2 using a tethered photoswitch (MAP4), with short spacers between the tether (methane thiosulfonate), the azobenzene, and the ligand (propofol) groups, which would allow a more precise identification of the residues involved in the propofol binding. We focused on the β+α- interface of the transmembrane domains (TMs). First, we replaced all cysteines present in the TMs, and one in the b extracellular domain, with alanines (Cys-to-Ala receptor), without affecting the basic function or modulation of the receptor when expressed in *Xenopus laevis* oocytes. Then we used molecular modeling to identify

possible tethering sites in β3TM3 and α1TM1, and introduced cysteines in the candidate positions.
Most of the cysteine mutants, after incubation with MAP4, showed little to no modulation, similar to the Cys-to-Ala receptor. But after incubating α1β3(M283C)γ2 with MAP4 and upon illumination with lights of specific wavelengths, we observed modulation of GABA responses, which decreased as GABA concentration increased. This indicated that MAP4 covalently bound to β3(M283C) and the propofol moiety docked into and out of the binding site, depending on the light-induced isomerization of the azobenzene group. The location of the mutations that produced photomodulation suggested that the propofol binding site is located near the extracellular side of the β+ α- interface.

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Poster

645. GABA(A) and Glycine Receptor Pharmacology

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 645.13/B54

Topic: B.02. Ligand-Gated Ion Channels

Support: ERA SynBIO grant MODULIGHTOR PCIN-2015-163-C02-01
AGAUR/Generalitat de Catalunya CERCA Programme, 2017-SGR-1442
MINECO project CTQ2016-80066R
Russian Science Foundation Grant 18-15-00313

Title: Azobenzen/nitrazepam-based light-controllable modulators of inhibitory brain receptors

Authors: *G. MALEEVA[1], D. WUTZ[2], K. RUSTLER[2], A. GOMILA[1], A. NIN-HILL[3], E. PETUKHOVA[4], M. ALFONSO-PRIETO[5,6], P. SCHOLZE[7], F. PEIRETTI[8], C. ROVIRA[3,9], B. KONIG[2], P. GOROSTIZA[10,9,11], P. BREGESTOVSKI[12,4,13];
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Abstract: Inhibitory neurotransmission in the brain is mediated mainly by two ligand gated receptors - $GABA_A$Rs and GlyRs. Disequilibrium in their function leads to many sever neurological disorders, such as epilepsy, hyperekplexia, anxiety, depression, schizophrenia and sleep disorders. Thus, development of effective modulators that would regulate the activity of these receptors with minimized side effects is of great importance. Photopharmacology is a unique tool for these purposes allowing precise spatial and temporal light-driven control of pharmacophores´ activity, and consequently of their target proteins. Here we present a series of azobenzene-based derivatives of benzodiazepine that successfully photocontrol activity of GABA and GlyRs. Compounds obtained by azologization of 7-aminonitrazepam with nitrosobenzenesulfonamide and nitrosopyridine (UR-DW285 and UR-DW290 respectively) demonstrated reversible photochromism and were selected for *in vitro* testing at inhibitory receptors. GABA and GlyRs were heterologously expressed in cultured CHO cells, their activity was monitored using whole-cell configuration of patch-clamp technique. At visible light UR-DW285 inhibited activity of $GABA_A$, GABA-rho2 and alpha2 GlyRs, while upon UV (365nm) irradiation their activity was restored. Using series of point mutations and molecular modelling approach we were able to demonstrate that UR-DW285 is a photo-switchable blocker of the ion channel pore of GABA and GlyRs. UR-DW290 displayed minor activity at GABARs, but it allowed photosensitive modulation of GlyRs of various subunit composition. In *trans* configuration UR-DW290 slightly inhibited glycine-induced currents, while in *cis*, generated by UV illumination, inhibitory effect was significantly strengthened. Zebrafish testing demonstrated high efficiency of UR-DW290 for the photo-control of their inhibitory system *in vivo*. In summary, we have developed a group of azobenzene/nitrazepam based compounds that modulate activity of two main inhibitory brain receptors in light-dependent manner. In contrast to nitrazepam, they did not potentiate GABAR currents but induced subunit-specific inhibition of both $GABA_A$Rs and GlyRs.

Disclosures: **G. Maleeva:** None. **D. Wutz:** None. **K. Rustler:** None. **A. Gomila:** None. **A. Nin-Hill:** None. **E. Petukhova:** None. **M. Alfonso-Prieto:** None. **P. Scholze:** None. **F. Peiretti:** None. **C. Rovira:** None. **B. Konig:** None. **P. Gorostiza:** None. **P. Bregestovski:** None.

Poster

645. GABA(A) and Glycine Receptor Pharmacology

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

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Topic: B.02. Ligand-Gated Ion Channels

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National Institutes of Health, USA (R01 MH096463)
Ministry of Science and Technology, Taiwan (MOST 105-2325-B002-004)
Ministry of Science and Technology, Taiwan (MOST 107-2321-B-010)

Title: The alpha-6 subunit-containing $GABA_A$ receptor is a novel therapeutic target for schizophrenia and migraine

Authors: *L.-C. CHIOU[1,2,4], H.-J. LEE[1], M.-T. LEE[1,2], H.-R. TZENG[1], P.-C. FAN[3], H. KUBOTA[5], A. MOURI[5], D. E. KNUTSON[6], J. COOK[6], M. ERNST[7], W. SIEGHART[7], T. NABESHIMA[5];
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Abstract: The α6 subunit-containing $GABA_A$ receptors (α6$GABA_A$Rs) are expressed in cerebellar granule cells centrally and in trigeminal ganglia (TG) peripherally. Due to the lack of selective ligands for α6$GABA_A$Rs, their pathophysiological role(s) were largely unknown. We have identified a series of pyrazoloquinolinones to be α6$GABA_A$R-selective positive allosteric modulators (PAM),[1] and demonstrated the efficacy of Compound 6 in suppressing migraine via TG α6$GABA_A$Rs peripherally,[2] trigeminal neuropathy[3] and sensorimotor-gating deficit centrally via cerebellar α6$GABA_A$Rs[4] in rodents. DK-I-56-I is a deuterated derivative of Compound 6 with enhanced pharmacokinetic profiles.[1] Here, we compared central and peripheral effects of DK-I-56-I and Compound 6 in various rodent models of neuropsychiatric disorders. The central effects evaluated include the attenuation on methamphetamine and phencyclidine (PCP)-induced deficit in prepulse inhibition (PPI), as well as on chronic PCP-induced social withdrawal and impairment of novel object recognition. DK-I-56-I (3-10 mg/kg, *i.p.*) rescued PPI disruptions induced by methamphetamine and PCP. Furthermore, *i.p.* DK-I-56-I at 3 mg/kg also reversed the social withdrawal and memory impairment in mice receiving 14-day PCP treatment. The central effect of DK-I-56-1 is comparable with Compound 6. The antimigraine activity of DK-I-56-I was examined histopathologically in intracisteral (*ic.*) capsaicin-induced trigeminovascular system (TGVS) activation in rats and behaviorally in repeated nitroglycerin (NTG)-induced grimaces in mice. DK-I-56-I (3-10 mg/kg, *i.v.*), similar to Compound 6, significantly inhibited the brain stem activation, TG CGRP elevation, and dural CGRP depletion in *ic.* capsaicin-treated rats. Mice treated with NTG once every two days for 5 times displayed significant headache-like behaviors, including orbital tightening, nose & cheek bulge, and ear & whisker position changes, which were measured as the mouse grimace scale (MGS). We evaluated preventative and abortive effects of DK-I-56-I on the MGS on day 9 (the 5th session). In contrast to Compound 6 that only showed abortive effect in the NTG-induced migraine model, DK-I-56-I (3 mg/kg, *i.p.*) displayed both preventative and abortive effects, probably due to its enhanced bioavailability. These results suggest that both central and peripheral α6$GABA_A$Rs are novel therapeutic targets

for schizophrenia and migraine, respectively, and α6GABA$_A$R-selective PAMs are a potential therapy. [1]Knutson et al (2018) J Med Chem 61:2422. [2]Fan et al (2018) Neuropharmacology 140:1. [3]Vasović et al (2019) Eur J Pain 23:973. [4]Chiou et al (2018) Br J Pharmacol 175:2414.

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Poster

645. GABA(A) and Glycine Receptor Pharmacology

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 645.15/B56

Topic: B.02. Ligand-Gated Ion Channels

Support: E!10687 GASH02

Title: Preclinical and clinical studies with GT-002, a novel GABA$_A$ receptor ligand with putative antipsychotic and pro-cognitive effects

Authors: *M. R. WITT, C. RYAN, S. REHNMARK, M. NIELSEN;
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Abstract: GT-002 is a novel compound of the triazoloquinazoline class which binds with high affinity to the benzodiazepine site of the gammma-aminobutyric acid (GABA$_A$) receptor complex in the mammalian brain. The compound shows potent antipsychotic effects in rodent *in-vivo* models comparable to those of clozapine. Furthermore, GT-002 shows pro-cognitive effects in the Novel Object Recognition (NOR) test and increases social interaction in rat models. GT-002 has been tested in 28-day GLP tox study in dogs without adverse effects. In summary, GT-002 has a profile that is distinct from other GABA$_A$ receptor modulators such as Diazepam.

Disclosures: M.R. Witt: A. Employment/Salary (full or part-time):; Gabather AB. **C. Ryan:** A. Employment/Salary (full or part-time):; Gabather AB. **S. Rehnmark:** A. Employment/Salary (full or part-time):; Gabather AB. **M. Nielsen:** A. Employment/Salary (full or part-time):; GabatherAB.

Poster

645. GABA(A) and Glycine Receptor Pharmacology

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 645.16/B57

Topic: B.02. Ligand-Gated Ion Channels

Title: Development and characterisation of a panel of 19 $GABA_A$ receptor cell lines to facilitate the identification of subtype specific GABA compounds

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Abstract: The majority of inhibitory neurotransmission in the brain is mediated by the binding of γ-aminobutyric acid (GABA) to the $GABA_A$ receptor subtype. These pentameric receptors are assembled from a variety of subunit combinations, the majority of which are composed of two α subunits, two β subunits, and either a γ or δ subunit. The varying subunit combinations determine the biophysical and pharmacological properties of the receptor such as the GABA affinity and modulatory compound sensitivity. Dysregulation of GABAergic neurotransmission is associated with a number of diseases and psychiatric disorders which make these receptors attractive targets for drug discovery programs, especially as there is a need for greater subtype selectivity in order to improve drug efficacy, safety and tolerability. Developments in HTS technologies have allowed for rapid testing of large numbers of compounds against ion channel targets, however until now, the lack of an expansive panel of $GABA_A$ cell lines has limited the identification and characterisation of subtype-specific $GABA_A$ compounds.
Using the inducible HEK parental cell line, we have developed 19 $GABA_A$ recombinant cell lines consisting of α1–6 in combination with β1-3+γ2L, as well as the α4β3δ receptor. Automated patch-clamp validation of the cell lines allowed testing of at least of 6 subtypes in a single experiment, resulting in rapid accumulation of pharmacological data. Responses to the agonist, GABA were reproducible over several applications, with the α6 containing subunits conferring the highest sensitivity to GABA. Further validation with known positive allosteric modulators Diazepam, which displayed modulation (EC_{50} of 10-60nM) of α1, α2, α3 and α5 containing subtypes only, and Allopregnanolone, which displayed activity at all 19 $GABA_A$ subtypes (EC_{50} of 10-50nM) was in line with literature data.
Using one of these robust cell lines ($GABA_A$ α3β2γ2) we screened 2000 compounds in a fluorescence assay which generated 11 positive allosteric modulator hits. These hits were confirmed by automated patch-clamp, with EC_{50} values ranging from 0.6-4μM. A number of these hit compounds also produced a leftward shift in GABA sensitivity. Selectivity studies against 9 recombinant $GABA_A$ cell lines revealed one compound with higher selectivity for α2

and α3 subtypes in comparison to α1 subtypes and minimal or no activity against the α4-6 containing subtypes. We have shown that screening hit compounds against a panel of GABA cell lines can be accomplished quickly and efficiently. The selectivity assay will allow for determination of improved subtype specificity in lead compounds obtained from GABA drug discovery programs.

Disclosures: L. Hutchison: None. **P. Madau:** None. **L. McCracken:** None. **A. Dickson:** None. **C. Kadi:** None. **H.J. Tracey:** None. **D.E. Smith:** None. **C. Brown:** None. **L. Gerrard:** None. **P. Conway:** None. **D. Dalrymple:** None. **I. Mcphee:** None. **D. Pau:** None.

Poster

645. GABA(A) and Glycine Receptor Pharmacology

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 645.17/B58

Topic: B.02. Ligand-Gated Ion Channels

Support: Neurobiology of Aging Training Grant Associate Fellowship T32 AG 020494
NIGMS-NIH Initiative to Maximize Student Diversity Fellowship R25 GM 125587

Title: Mapping the binding site mediating carisoprodol's direct activation of $GABA_A$ receptors

Authors: *M. C. CLAUDIO[1], H. HAYATSHAHI[2], N. M. MISHRA[2], G. H. DILLON[3], K. A. EMMITTE[2], J. LIU[2], R. HUANG[3];
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Abstract: Carisoprodol (CSP) is a centrally-acting prescription muscle relaxant that can directly activate and allosterically modulate the $GABA_A$ receptor. $GABA_A$ receptors are the target of many different clinically prescribed compounds because of the role they play in regulating the central nervous system. Our previous studies have shown that CSP differentially potentiates $GABA_A$ receptor subtypes via allosteric modulation and direct activation. It has been reported that a single amino acid residue, L415, located at the top of the fourth transmembrane domain (TM4) in the α1- subunit of the $GABA_A$ receptor is critical to CSP's direct gating effect. Whether the residue is involved in CSP binding remains unsolved. The purpose of the present study is to explore the binding site mediating CSP's direct action with *in-silico* docking, site-directed mutagenesis and whole-cell electrophysiology. Initial *in-silico* docking of CSP at the $GABA_A$ receptor suggested that the CSP binding pocket may be formed by residues from the TM4, pre-TM1 and cys-loop regions of the α-subunits. In whole-cell electrophysiology studies performed on HEK-293 cells either stably or transiently expressing different $GABA_A$ receptor subtypes, specific modifications of CSP's molecular structure produced greater direct action on

$GABA_A$ receptors. Furthermore, the ability of CSP and its analogs to open the channels aligned with *in-silico* docking at the interest region in the $GABA_A$ receptors. The role of the residues predicted as a CSP binding site in *in-silico* docking analysis are being verified with mutagenesis and patch clamp studies. It is expected that the results will not only enhance our understanding of CSP pharmacology but also the structure-function relationship at $GABA_A$ receptors.

Disclosures: M.C. Claudio: None. **H. Hayatshahi:** None. **N.M. Mishra:** None. **G.H. Dillon:** None. **K.A. Emmitte:** None. **J. Liu:** None. **R. Huang:** None.

Poster

645. GABA(A) and Glycine Receptor Pharmacology

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 645.18/B59

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH Grant F31 NS101804-02
NIH Grant R21 NS099991-01

Title: Effects of the diazepam binding inhibitor on GABA-mediated currents

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Abstract: Benzodiazepines (BZDs) are a major class of drugs used to modulate GABA-mediated signaling in the brain. Since their synthesis in the 1950s, these drugs have been widely used for their sedative, anxiolytic and anticonvulsant effects, which are elicited by binding to the extracellular domain of the GABA-A receptor (GABAR). A competitive binding experiment in 1983 using rat brain homogenate to displace radiolabeled BZD binding to GABARs identified a putative endogenous BZD, the diazepam binding inhibitor (DBI) (Guidotti et al., PNAS 1983). Recent work suggests that DBI is able to alter GABA-mediated signaling in mouse brain (Alfonso et al., Cell Stem Cell 2012; Dumitru et al., Neuron 2017; Christian et al., Neuron 2013; Courtney and Christian, Neuroscience 2018), yet our understanding of exactly how DBI interacts with GABARs is limited.
In order to evaluate the direct effects of DBI on GABARs, we purified human DBI and expressed $\alpha_5\beta_3\gamma_{2L}$ GABARs in human embryonic kidney (HEK) 293-T cells. We performed both whole-cell and outside-out patch clamp electrophysiology using rapid ligand exchange. We measured GABA-elicited current responses in the presence and absence of DBI, and monitored changes in peak current amplitude and the rate of deactivation. Preliminary results indicate that outside-out patches exposed to DBI have a moderate slowing in their rate of deactivation,

indicating DBI is acting as a mild positive modulator. However, initial experiments using whole-cell recording show DBI causes an almost complete suppression of GABA-elicited current. We are performing additional experiments to understand whether these differences in DBI effects on outside-out patches versus whole cells are due to differences in receptor composition, subunit inclusion or other factors associated with whole-cell biology.
Additionally, we have performed preliminary radioligand binding experiments which show purified DBI is able to displace radio-labelled flunitrazepam from binding $\alpha_1\beta_2\gamma_{2L}$ GABARs expressed in membranes purified from HEK cells. This suggests that DBI able to bind GABARs at the BZD site. Taken together, the electrophysiology and binding data provide evidence that DBI is able to directly interact with the GABAR and modulate its function.

Disclosures: J.S. Borchardt: None. **R.A. Pearce:** None. **C.M. Czajkowski:** None. **N. Giezendanner:** None.

Poster

645. GABA(A) and Glycine Receptor Pharmacology

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 645.19/B60

Topic: B.02. Ligand-Gated Ion Channels

Support: 16SDG26590000 to CRB
UT Health Start-up to CRB
NIH T32 HI04776 to EL

Title: Allopregnanolone potentiates and prolongs phasic inhibition of dorsal vagal motor neurons via the protein kinase C pathway

Authors: *E. LITTLEJOHN, L. ESPINOZA, C. BOYCHUK;
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Abstract: Neurons in the dorsal motor nucleus of the vagus (DMV) comprise the preganglionic parasympathetic motor output to much of the subdiaphragmatic viscera and critically contribute to autonomic regulation of homeostasis. DMV neuron function is tightly regulated by gamma-aminobutyric (GABA) type A receptors. However, GABAA receptors have another endogenous ligand allopregnanolone (Allo). Allo is a centrally and peripherally produced neuroactive steroid metabolite which readily crosses the blood brain barrier is a potent allosteric modulator of $GABA_A$ receptor inhibition. Although no studies to date have investigated the potential for Allo to induce changes in GABAergic signaling to DMV neurons, Allo signaling may represent a novel pathway to augment the gut-brain axis signaling. **We hypothesize that acute Allo exposure will increase inhibition of DMV neurons**. To test this hypothesis we isolated brain stem slices from adult male mice and used whole-cell patch-clamp electrophysiology to examine

the effects of Allo (100nM) or vehicle on $GABA_A$ receptor mediated postsynaptic inhibition. To test our hypothesis, we incubated brainstem slices in Allo or vehicle containing artificial cerebral spinal fluid (ACSF) for 30min. We then analyzed GABAergic currents (phasic and tonic) in DMV neurons during drug washout at 30, 60, and 120 minutes (min) following the secession of Allo incubation. IPSC frequency and decay time were increased within 60 min of Allo washout. There was no significant modification of tonic GABAergic currents at any time point. Since IPSC modulation was present long after Allo removal, we examined non-allosteric effects of Allo on DMV inhibition. We applied PKC inhibitor (Bisindolylmaleimide II, 500nM) during Allo and Veh incubation as well as during washout to elucidate the role of posttranslational modification by protein kinase C (PKC) in mediating the inhibitory effects of Allo. In the presence of PKC inhibitor, the effects of Allo on PSC frequency were abolished and the effects on decay time were reduced by 70%. Additionally, we found that Allo begins augmenting GABAergic inhibition in DMV neurons immediately after exposure. Using a within-subject design, we recorded IPSCs before (control condition) and after a 10min Allo superfusion. Our data suggests that both frequency and decay time of IPSCs are increased within 10min of Allo application. It further suggests that this brief exposure to Allo potentiates $GABA_A$ receptor mediated inhibition in DMV neurons long (>120 min) after Allo exposure. Allo may play an important role in dynamically modulating vagal inhibition in models of disease.

Disclosures: E. Littlejohn: None. **L. Espinoza:** None. **C. Boychuk:** None.

Poster

646. Metabotropic Receptors for Other Transmitters and Peptides

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 646.01/B61

Topic: B.03. G-Protein Coupled Receptors

Support: NIH Grant R01-HD089147

Title: Comparison of the pharmacological signatures of arginine vasopressin and oxytocin analogs at marmoset, macaque, and human vasopressin 1a and oxytocin receptors

Authors: *M. L. PIERCE[1], J. A. FRENCH[2], T. F. MURRAY[1];
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Abstract: Arginine vasopressin (AVP) and oxytocin (OT) are neuropeptides that bind to G-protein coupled receptors and influence social behavior. Consensus mammalian AVP and OT (Leu^8-OT) sequences are highly conserved. However, in New World monkeys (NWM), six distinct OT ligand variants have been discovered. Notably, in marmosets, an amino acid change in the 8th position of the peptide (Pro^8-OT) exhibits unique structural and functional properties.

In addition to sequence homology between AVP and OT, there is ~85% structural homology between the OT receptor (OTR) and vasopressin 1a receptor (V1aR) resulting in significant cross-reactivity between the ligands and receptors. Chinese hamster ovary (CHO) cells expressing marmoset, macaque, or human OTR (mOTR, qOTR, and hOTR) or V1aR (mV1aR, qV1aR, and hV1aR) were used to assess AVP, Leu^8-OT and Pro^8-OT pharmacological signatures. To assess activation of Gq, functional assays were performed using Fluo-3 to measure ligand-induced Ca^{2+} mobilization. At qOTR and hOTR (endogenous ligand Leu^8-OT), AVP was much less potent than Leu^8- or Pro^8-OT at elevating intracellular calcium; whereas at mOTR (endogenous ligand Pro^8-OT), there was no significant difference in AVP and OT potency. In all three V1aR-expressing cell lines, AVP was more potent than the OT ligands. To assess ligand-induced hyperpolarization, FLIPR Membrane Potential (FMP) assays were performed. At mOTR and hOTR, Leu^8-OT was more potent than Pro^8-OT or AVP. In qOTR, AVP was less potent than both OT analogs. In all three V1aR lines, AVP was more potent than the OT analogs. The distinctive U-shaped concentration-response curve displayed by AVP may reflect enhanced desensitization of the mV1aR and hV1aR, which is not observed with qV1aR. Evaluation of Ca^{2+}-activated K^+ channels using the inhibitors apamin, paxilline, and TRAM-34 demonstrated that both intermediate and large conductance Ca^{2+}-activated K^+ channels contributed to membrane hyperpolarization, with different pharmacological profiles identified for distinct ligand-receptor combinations. Integrative studies of behavior, genetics and ligand-receptor interaction are crucial for translating signaling activation at the cellular level to effects of AVP and OT ligands on social behavior.

Disclosures: **M.L. Pierce:** None. **J.A. French:** None. **T.F. Murray:** None.

Poster

646. Metabotropic Receptors for Other Transmitters and Peptides

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 646.02/B62

Topic: B.03. G-Protein Coupled Receptors

Support: Polish National Science Centre Grant to MK (2015/17/B/NZ4/02016)

Title: Somatostatin receptors on inhibitory SST, VIP and PV interneurons in the barrel cortex

Authors: *A. LUKOMSKA, G. DOBRZANSKI, M. LIGUZ-LECZNAR, M. KOSSUT; Lab. of Neuroplasticity, Nencki Inst. of Exptl. Biol. PAS, Warsaw, Poland

Abstract: A considerable diversity of inhibitory interneurons is a distinct characteristic of the mammalian neocortex. A unique form of inhibition is provided by inhibitory neurons that specifically suppress the firing of other inhibitory neurons leading to disinhibition, which can support plasticity, learning, memory. In the neocortex disinhibition is performed primarily by

interneurons containing somatostatin (SST-INs) and vasoactive intestinal peptide (VIP-INs), targeting parvalbumin-containing (PV-INs) interneurons. Our data for learning-dependent plasticity of the mice barrel cortex showed involvement of SST-Ins in the development of learning induced plastic change of vibrissae representation. In the brain SST is not only a marker of interneuron subtype but also an important neuropeptide that participates in numerous biochemical and signaling pathways *via* somatostatin receptors (SSTRs1-5). SST acts as a neuromodulator and neurotransmitter possibly by co-release with GABA, targeting not only principal cells, but also interneurons. However, the SSTRs distribution among cortical layers and their localization on particular types of interneurons has not been investigated in detail.We examined localization of different SSTR subtypes on the barrel cortex inhibitory interneurons containing PV, SST and VIP. Immunofluorescent staining using antibodies against SSTR1-5 was performed on brain sections from transgenic mice whose specific interneuron subtypes showed red fluorescence (PV-Ai14, SST-Ai14, VIP-Ai14).We found that SSTRs expression on PV, SST and VIP interneurons varies depending on the cortical layer. According to the specific pattern of the localization of the SSTRs in the barrel cortex, we classified them into two types. The first type was characterized by a high receptor (SSRT1 and SSTR2) concentration in the barrel walls, while the second type was characterized by a homogeneous receptor (SSTR3, SSTR4 and SSTR5) distribution in the barrel hollows. We demonstrated that PV cells do not express SSTR2, in contrast to other SSTRs. Other interneurons expressed all SSTRs. SST-INs, which were not found to make chemical synapses among themselves, expressed all five SSTR subtypes, suggesting their extrasynaptic localization.

Disclosures: **A. Lukomska:** None. **G. Dobrzanski:** None. **M. Liguz-Lecznar:** None. **M. Kossut:** None.

Poster

646. Metabotropic Receptors for Other Transmitters and Peptides

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 646.03/B63

Topic: B.03. G-Protein Coupled Receptors

Support: Fundacion LaCaixa
FCT (POCI-01-0145-FEDER-031274)
Centro 2020 (CENTRO-01-0246-FEDER-000010)

Title: A2A adenosine receptors blockade reverts synaptic and memory in aged rats

Authors: *R. A. CUNHA[1], C. SOUZA[2], J. GUTIERREZ[3], H. B. SILVA[2], P. M. CANAS[2]; [1]CNC -Center For Neurosci. and Cell Biol., Coimbra, Portugal; [2]CNC-Center for Neurosci. and Cell Biol., Coimbra, Portugal; [3]CNC-Center for Neurosci. and Cell Biol., CNC-Center for Neuroscience and Cell Biology, Portugal

Abstract: Adenosine is a signaling molecule released in an activity-dependent manner directly or upon catabolism of ATP by ecto-nucleotidases. The extracellular levels of adenosine and ATP, both danger signals in the brain, rise even more in noxious brain condition and the over-activation of adenosine A_{2A}receptors (A_{2A}R) is paramount to trigger neuronal damage (J Neurochem 2016; 139:1019-55). Since neurodegenerative diseases are prevalent upon aging, we now posted that A_{2A}R over-activation might be a critical factor responsible the age-associated increase risk of brain disorders. Objective: We now tested if A_{2A}R blockade reverts synaptic and memory impairment in aged rats. Methods: We first compared memory performance in young adult (3 months-old) and aged (20-22 months-old) rats. Most of the aged rats displayed a poorer memory performance compared to young adult rats. Half of the aged impaired and half of the young rats were treated for 3 weeks with the selective A_{2A}R antagonist SCH58261 (0.1 mg/kg/daily, ip). Results: SCH58261-treated aged rats recovered performance in memory tests to the level of young rats, in which SCH58261 had no effects. Memory-impaired aged rats also displayed lower hippocampal synaptic plasticity together with a lower density of vesicular glutamate transporter type 1 (vGluT1), an increased density of A_{2A}R and of ecto-5'-nucleotidase and increased ATP release from hippocampal synaptosomes. All these changes were reverted by treatment with SCH58261 in aged rats. Conclusions: These findings show that A_{2A}R over-function is critically required for the development of age-associated memory deficits, likely involving synaptic dysfunction. This prompts considering A_{2A}R as a biomarker of poorer quality brain ageing. Supported by Fundacion LaCaixa, FCT (POCI-01-0145-FEDER-031274) and Centro 2020 (CENTRO-01-0246-FEDER-000010).

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Poster

646. Metabotropic Receptors for Other Transmitters and Peptides

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 646.04/B64

Topic: B.03. G-Protein Coupled Receptors

Support: ANR-13-BSV1-0001
Conseil Régional d'Alsace (pharmadol)
Communauté Urbaine de Strasbourg (Pharmadol)
ICFRC (Pharmadol)
OSEO (Pharmadol)
Direction Générale des Entreprises (Pharmadol)
LABEX ANR-10-LABX-0034

Title: The neuropeptide FF1 receptor/rfamide-related peptide 3 system modulates nociception, opioid analgesia, inflammatory pain and luteinizing hormone release in rodents

Authors: *F. SIMONIN[1], **R. QUILLET**[1], S. SCHNEIDER[1], V. UTARD[1], A. DRIEU LA ROCHELLE[1], M. GERUM[1], K. ELHABAZI[1], J. B. HENNINGSEN[2], P. GIZZI[1], V. KUGLER[1], T. SORG-GUSS[3], V. M. SIMONNEAUX[4], B. ILIEN[1], F. BIHEL[1];
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Abstract: RFamide-relatide peptide 3 (RFRP3) and Neuropeptide FF (NPFF), belong to the family of so-called RFamide peptides. In mammals, they are involved in the modulation of several functions including metabolism, reproduction and nociception. They target two different G protein-coupled receptor subtypes called Neuropeptide FF1 receptor (NPFF1R alias GPR147 or GnIH receptor) and Neuropeptide FF2 receptor (NPFF2R or GPR74), respectively. However, the respective role of these two receptors is unclear, and the study of their function *in vivo* is severely limited by the lack of highly selective antagonists. In this work, we describe the identification of small compounds that display high affinity and selectivity for NPFF1R as well as potent antagonist activity *in vitro*. We then showed that one of them, RF3286, efficiently and selectively blocks RFRP3-induced hyperalgesia in mouse and luteinizing hormone release in hamster, indicating that this compound is a useful pharmacological tool to study the *in vivo* functions of NPFF1R and its endogenous ligand RFRP3. Pharmacological blockade of NPFF1R with RF3286 prevented the development of pain hypersensitivity and analgesic tolerance induced by chronic administration of morphine revealing that NPFF1R/RFRP3 system is critically involved in neuroadaptation associated with administration of opiates. These results were further confirmed in NPFF1R knockout animals. Moreover, we observed the expression of NPFF1R and RFRP3 transcripts by fluorescent *in situ* hybridization in the dorsal horn of spinal cord, indicating that this receptor/peptide system can modulate nociception in part by spinal mechanism. We further observed that cells expressing NPFF1R transcripts were also MOP positives (50%) and DOP positives (20%), suggesting a direct modulatory role of NPFF1R on the action of opioid. Finally, we observed an increase of NPFF1R positive cells in dorsal horn of spinal cord of CFA-treated animals compared to saline controls suggesting a potential role of this system in inflammatory pain. In agreement with these data, we further showed that pharmacological blockade of NPFF1R with RF3286 can efficiently reverse hyperalgesia induced by CFA injection. Altogether, our data allowed us to identify NPFF1R/RFRP3 as a pronociceptive anti-opioid system and further suggest that antagonists of this receptor might represent interesting therapeutic tools to limit the development of opioid-induced hyperalgesia and analgesic tolerance associated with chronic opioid administration as well as hyperalgesia induced by inflammatory pain.

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Poster

646. Metabotropic Receptors for Other Transmitters and Peptides

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 646.05/B65

Topic: B.03. G-Protein Coupled Receptors

Support: KAKENHI 19K06739

Title: Identification of the key molecules involved in GPCR-mediated primary cilium shortening

Authors: Y. KOBAYASHI[1], S. TOMOSHIGE[1], D. MIKI[1], T. MIYAMOTO[2], ***Y. SAITO**[1]; [1]Hiroshima Univ., Higashi-Hiroshima, Japan; [2]Res. Inst. for Radiation Biol. and Med., Hiroshima Univ., Hiroshima, Japan

Abstract: The primary cilium is a protrusion supported by a microtubule axoneme that extends from the basal body. It is a sensory organelle that responds to environmental stimuli and communicates the signal to the cell's interior function. Primary cilium coordinates multiple cellular signaling pathways through ion channels and conventional G-protein-coupled receptors (GPCRs) harbored in the cilium membrane. During postnatal development, the neuronal cilium membrane becomes equipped with a limited set of GPCR such as melanin-concentrating hormone (MCH) receptor 1 (MCHR1), which has the important connection with fundamental systems influencing feeding, mood and sleep. Cilium length has been predicted to be a critical parameter that has implications for cilia function in most neuron. Recently, we have found a new biological phenomenon, that is the MCH-induced cilia length shortening via ciliary MCHR1 in rat hippocampal slice culture, human induced pluripotent stem cells, and human telomerase-immortalized retinal pigmented epithelial (RPE1) cells. By using RPE1 cells, we further showed the MCH-MCHR1-Gi/o-Akt pathway causes a series of signal cascade connecting dynamics to cytoplasmic tubulin depolymerization and actin polymerization. However, the major downstream targets from Akt activation toward cilia shortening remain unclear. In this study, we investigated changes in the transcriptome profile in MCHR1-expressing RPE1 cells with RNA-seq technology. There were more than 500 genes, which were significantly changed more than two-fold in response to MCH treatment. After performing qPCR to validate the results of RNA-seq, several candidates in the list showed great potential for further study as reflected by the fold change in mRNA expression along time-course. Finally, functional analysis by using siRNA knockdown and CRISPR-ObLiGaRe knockout revealed several molecules as the significant regulator for MCHR1-mediated cilia shortening. One of these molecules has been reported to be associated with schizophrenia, bipolar depression, and major depressive disorder. Thus, our

findings will offer the new insights into the relationship between GPCR-mediated neuronal cilia length control and pathophysiology of mental illness.

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Poster

646. Metabotropic Receptors for Other Transmitters and Peptides

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 646.06/B66

Topic: B.03. G-Protein Coupled Receptors

Title: Lysophosphatidic acid activates satellite glia cells and Schwann cells

Authors: *C. I. CIOTU[1], L. GEBHARDT[3,4], T. WEISS[2], A. KREMER[4], M. J. FISCHER[1]; [1]Ctr. for Physiol. and Pharmacol., [2]Dept. of Surgery, Med. Univ. of Vienna, Vienna, Austria; [3]Inst. of Physiol. and Pathophysiology, [4]Dept. of Med. 1, Friedrich-Alexander-University of Erlangen-Nürnberg, Erlangen, Germany

Abstract: Lysophosphatidic acid (LPA) is a bioactive lipid acting on G-Protein coupled receptors (LPAR1-6), leading to calcium influx. LPA has been identified as a powerful pruritogen; in rodent models, it induces scratching behavior upon intradermal injection. Autotaxin, the main extracellular enzyme that catalyzes LPA synthesis is found elevated in patients suffering from cholestatic itch and can serve as a marker for intrahepatic cholestasis of pregnancy. Here we show that LPA activates satellite glial cells as opposed to having direct action on neurons. In addition, we record similar effects in Schwann cells, which are of glial lineage like the satellite glial cells, and characterize these effects from a functional standpoint. Cell activation was assessed using calcium microfluorimetry in dorsal root ganglia and Schwann cell primary cultures and immunohistochemistry served to validate the receptor distribution on the different cell types. In a dorsal root ganglia primary cell culture, acute exposure to LPA was followed by calcium influx in satellite glial cells, yet only few neurons exhibited this phenomenon. Moreover, responses to LPA were inversely correlated with those for agonists of transient receptor potential channels, including TRPV1. Direct TRPV1 activation by LPA was marginal and no differences were observed in the respective TRPV1 knockout mice. LPA induces calcium transients in Schwann cells, mainly from intracellular stores, which can be abolished by selective inhibition for the LPA1 receptor. Upon repeated LPA application in continuous superfusion conditions, desensitization can be observed. Antibody staining for LPA1 receptors revealed a highly localized distribution, hypothesized to fit growth areas of the cell. Schwann cells and satellite glial cells respond to lysophosphatidic acid, pointing to signaling pathways with importance for neuronal responsiveness and sensory responses such as itch and pain.

Disclosures: **C.I. Ciotu:** None. **L. Gebhardt:** None. **T. Weiss:** None. **A. Kremer:** None. **M.J. Fischer:** None.

Poster

646. Metabotropic Receptors for Other Transmitters and Peptides

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 646.07/B67

Topic: B.03. G-Protein Coupled Receptors

Support: NSERC of Canada 05407-2014
Fonds de Récherche du Québec- Santé

Title: G-protein-coupled estrogen receptor 1 (GPER1)-mediated enhancement of excitatory synaptic transmission in layer II of the entorhinal cortex

Authors: ***A. A. BATALLÁN BURROWES**, A. SUNDARAKRISHAN, C. A. CHAPMAN; Concordia Univ., Montreal, QC, Canada

Abstract: Estrogens are thought to contribute to cognitive function via rapid synaptic changes associated with activation of α, β, and GPER1 estrogen receptor (ER) sub-types. GPER1 is the predominantly expressed ER in the hippocampal formation, followed by β, and α receptors. Hippocampal application of 17-β estradiol (E2) enhances excitatory synaptic transmission and improves working memory performance. Activation of ERs can inhibit GABAergic neurons, modulate excitatory NMDA and AMPA currents, and reversibly increases CA1 pyramidal neuron dendritic spine density. The entorhinal cortex is the major source of cortical sensory and associational input to the hippocampal formation. However, it is unclear how estrogen may impact synaptic transmission in the entorhinal cortex. The present study assessed the effects of the acute application of E2 on excitatory glutamatergic synaptic transmission in layer II of the rat entorhinal cortex in vitro. On PD63, rats were ovariectomized and implanted with a subdermal E2 capsule to maintain constant low levels of circulating E2. Electrophysiological recordings were collected between PD70 and PD91. Acute horizontal brain slices were obtained and evoked field excitatory postsynaptic potentials (fEPSP) were recorded in layer II following stimulation of layer I afferents. After baseline recordings, 20 min application of E2 (100 nM) yielded an approximately 10% increase in fEPSP amplitude that reversed during the 30 min washout period. Application of the ERα agonist PPT (100 nM) did not significantly change synaptic responses compared to baseline. Conversely, application of the GPER1 agonist G1 (100 nM) induced a reversible increase in fEPSP amplitudes similar to that induced by E2. This indicates that the rapid enhancement of excitatory synaptic transmission induced by estrogen in the entorhinal cortex is likely mediated by activation of GPER1 receptors. This enhancement may support estrogen's contribution to cognitive function in the hippocampal region.

Disclosures: **A.A. Batallán Burrowes:** None. **A. Sundarakrishan:** None. **C.A. Chapman:** None.

Poster

646. Metabotropic Receptors for Other Transmitters and Peptides

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 646.08/B68

Topic: B.03. G-Protein Coupled Receptors

Support: FONDECYT grant N° 1191274

Title: Interaction between dopamine and type 2 corticotropin releasing factor receptors modulates the basolateral amygdalar transmission to the medial prefrontal cortex

Authors: H. E. YARUR, J. A. ZEGERS, I. VEGA-QUIROGA, *K. GYSLING;
Dept. of Cell. and Mol. Biol., Pontificia Univ. Catolica de Chile, Santiago, Chile

Abstract: The prefrontal cortex (PFC) is a brain area involved in working memory, attention and goal directed behavior. Stressful events could modify the animal behavior, affecting the performance of working and/or emotional memories. One of the brain areas which projects heavily to the ventral region of the PFC and that have been implicated in the emotional information of the stimuli is the basolateral amygdala (BLA) (LeDoux, 2000). Acute stressful stimuli can block the induction of plasticity between the BLA and the PFC (Maroun and Richter-Levin, 2003). Corticotrophin releasing factor (CRF) is a central regulator of endocrine and behavioral responses to stressors. The evidence shows that dopamine (DA) receptors (D1R and D2R) modulate transmission between BLA-PFC (Floresco and Tse, 2007). Furthermore, CRF and DA act synergistically to regulate the transmission of the BLA to PFC (Orozco-Cabal et al, 2008). Thus, we decided to further study whether type-2 CRF (CRF2) and DA receptors regulate synaptic transmission between BLA and PFC. To this end, we performed *in vivo* microdialysis experiments in the presence or absence of pharmacological antagonists for CRF and DA receptors. Our results show that antisauvagine 30, CRF2 antagonist, increased PFC glutamate extracellular levels and decreased DA extracellular levels induced by BLA stimulation. The combination of D1R and CRF2 antagonists blunted the increase of PFC glutamate levels induced by BLA stimulation. However, the combination of D2R and CRF2 antagonists disrupted the effect of the CRF2 antagonist alone over PFC glutamate levels induced by BLA stimulation. Synaptic expression of CRF2 and dopamine receptors was analyzed in PFC synaptosomes devoid of post-synaptic elements. CRF2 was mainly colocalized with D1R in PFC synaptosomes. Furthermore, agonist dependent-ERK signaling of CRF2 and D1R in was suppressed by the co-incubation of PFC synaptosomes with both agonists. Our results suggest that CRF2 exerts control over PFC glutamate and dopamine extracellular levels induced by BLA

stimulation. In addition, our results suggest a complex interaction between dopamine receptors and CRF2 modulating the BLA-PFC synapsis.

Disclosures: H.E. Yarur: None. **J.A. Zegers:** None. **I. Vega-Quiroga:** None. **K. Gysling:** None.

Poster

646. Metabotropic Receptors for Other Transmitters and Peptides

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 646.09/B69

Topic: B.03. G-Protein Coupled Receptors

Support: AA26117
AA26551
AA17531
AA7565
AA22449
AA25117
UL1TR001420

Title: Loss of trace amine-associated receptor 2 function results in impairments in hippocampus-dependent behavior and hippocampal synaptic function

Authors: *A. G. ALMONTE[1], A. DEAL[2], J. K. KONSTANTOPOULOS[2], J. L. WEINER[1], E. A. BUDYGIN[2];
[1]Physiol. and Pharmacol., [2]Neurobio. and Anat., Wake Forest Sch. of Med., Winston-Salem, NC

Abstract: Trace amine-associated receptor 2 (TAAR2) is a member of a family of G-protein coupled receptors that are activated by a class of biogenic amines called trace amines, which are present at nanomolar concentrations in the brain and periphery. While previous work suggests that TAAR2 is expressed in the olfactory system and may function as a chemosensory receptor, little is known about TAAR2 expression and function in other brain areas. Here, we have begun a behavioral and neurophysiological characterization of a TAAR2 knockout mouse line in which the TAAR2 gene is deleted and replaced with a lacZ reporter. We show reporter expression in various brain regions, in particular the hippocampus. We find that TAAR2 KO mice have impaired performance in the novel object recognition and object location memory tasks, which are two hippocampus-dependent behavioral tests. Extracellular field potential recordings at hippocampal Schaffer collateral-CA1 synapses reveal differential effects of TAAR2 deletion along the dorsoventral axis. In the dorsal hippocampus, TAAR2 KO mice show normal baseline synaptic transmission, but impaired induction of long-term potentiation (LTP). In the ventral hippocampus, however, TAAR2 KO mice display decreased baseline synaptic transmission and

normal LTP induction. Notably, our observations of deficits in the novel object recognition and object location memory tasks and in LTP induction in dorsal hippocampal slices are consistent with the known roles of the dorsal hippocampus in encoding this type of declarative memory. Together, these behavioral and neurophysiological phenotypes suggest novel roles for TAAR2 function in modulating behavioral output, synaptic function, and the induction of synaptic plasticity.

Disclosures: A.G. Almonte: None. **A. Deal:** None. **J.K. Konstantopoulos:** None. **J.L. Weiner:** None. **E.A. Budygin:** None.

Poster

646. Metabotropic Receptors for Other Transmitters and Peptides

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 646.10/B70

Topic: B.03. G-Protein Coupled Receptors

Support: FONDECYT grant N° 1191274
CONICYT PhD fellowship to JAZ

Title: Role of type-2 corticotrophin-releasing factor receptors in nucleus accumbens neurotransmitter levels after basolateral amygdala stimulation

Authors: J. A. ZEGERS, *H. E. YARUR, C. P. BASTIAS, K. GYSLING;
Dept. of Cell. and Mol. Biol., Pontificia Univ. Catolica De Chile, Santiago, Chile

Abstract: Basolateral amygdala (BLA) is a brain nucleus that innervates the nucleus accumbens (Nac) and prefrontal cortex (PFC) (McDonald, 1991). The relation between BLA and Nac has been implicated on the control of motivated behavior (Stuber et. al., 2011). Furthermore, BLA has been implicated in fear, anxiety and stress (Simon et. al., 2014; Janak and Tye, 2015). The stress response is centered in the corticotropin releasing factor (CRF) system (Bale and Vale, 2004). There are two major receptors for CRF in the brain, type-1 and type-2 corticotrophin-releasing factor receptors (CRF-R1 and CRF-R2). Several studies have shown a significant role of CRF-R1 in the stress response; however, the role of Nac CRF-R2 in the stress response is poorly understood. We studied the anatomy and role of CRF-R2 in the relation between BLA and Nac. First, to detect if CRF-R2 is localized in BLA synaptic terminals innervating Nac, we injected biotinylated dextran amine (BDA) in the BLA of adult male Sprague-Dawley rats. Then, we performed immunofluorescence on Nac synaptosomes, devoid of post-synaptic elements. Second, we studied the role of CRF-R2 in Nac neurotransmitter levels after BLA stimulation by double *in vivo* microdialysis in NAc and BLA of adult rats. We observed colocalization of CRF-R2 and BDA in Nac synaptosomes. In addition, using local infusion of antisauvaganine 30 (CRH-R2 antagonist) in the NAc, we observed an increase in Nac dopamine and glutamate

extracellular levels after BLA stimulation. Our results show that CRF-R2 is present in BLA nerve terminals innervating Nac. They also suggest that there is an inhibitory tone mediated by CRF-R2 that control Nac dopamine and glutamate extracellular levels depending on BLA stimulation.

Disclosures: J.A. Zegers: None. **H.E. Yarur:** None. **C.P. Bastias:** None. **K. Gysling:** None.

Poster

646. Metabotropic Receptors for Other Transmitters and Peptides

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 646.11/B71

Topic: B.03. G-Protein Coupled Receptors

Support: Intramural Funds of NIDA

Title: Structural and pharmacological characterization of the μ-opioid-galanin Gal_1 receptor heterodimer

Authors: *P. A. DE OLIVEIRA[1], N. CASAJUANA-MARTÍN[2], H. ZHU[3], C. NING-SHENG[1], E. MORENO[4], A. BONIFAZI[1], A. GONZÁLEZ[2], V. CASADÓ-ANGUERA[4], S. PITTENGER[3], A. NEWMAN[1], V. CASADÓ[4], M. HALL[3], L. PARDO[2], S. FERRE[1];
[1]Natl. Inst. on Drug Abuse, IRP, Baltimore, MD; [2]Autonomous Univ. of Barcelona, Barcelona, Spain; [3]Natl. Ctr. for Advancing Translational Sci., Rockville, MD; [4]Univ. of Barcelona, Barcelona, Spain

Abstract: We have recently shown that μ-opioid receptors (MOR) form functional heteromers with galanin Gal_1 receptors (Gal1R) in the ventral tegmental area (VTA) and that these MOR-Ga1R heteromers determine the dopaminergic effects of opioids.[1,2] Among the pharmacological properties of the MOR-Gal1R heteromers, we found that Gal1R ligands significantly counteract MOR signaling (negative crosstalk) and a specific insensitivity to methadone, as compared to other opioids, such as morphine and fentanyl.[2] This pharmacodynamic difference between methadone and the other opioids determined a weaker proficiency of methadone to activate the dopaminergic system and predicted a dissociation of the therapeutic versus euphoric effects of methadone.[2] We are now studying the molecular mechanisms responsible for these pharmacological properties of the MOR-Gal1R heteromer in mammalian transfected cells, using radioligand binding experiments, cell signaling assays, biophysical methods, including Bioluminescence Resonance Energy Transfer (BRET) and Bimolecular Complementation of BRET biosensors, and computational modeling. Results from co-transfection of MOR fused to complementary halves of a BRET biosensor and increasing amounts of Ga1R suggested the same intermolecular interface for MOR-MOR homomers and MOR-Gal1R heteromers. Experiments with synthetic peptides with the amino-acid sequence of the different

transmembrane (TM) domains of MOR and Gal1R confirmed the dimeric nature of the MOR-Gal1R heteromer and the specific TM domains involved in the heteromeric interface. This allowed the establishment of the quaternary structure of the MOR-Gal1R heteromer by computational modeling and its comparison with the MOR-MOR homomer. In silico experiments are now being performed to evaluate the molecular mechanisms responsible for the negative crosstalk of Gal1R and MOR ligands and the unique behavior of methadone within the MOR-Gal1R heteromer. The dimeric quaternary structure of the MOR-Gal1R heteromer implies the coupling with only one (heterotrimeric) molecule of G protein. Experiments with MOR and Gal1R fused to complementary halves of a BRET biosensor and the α subunit of different G protein subtypes fused to the other potentially interacting BRET biosensor are being performed to determine the preferred G protein and signaling of the MOR-Gal1R heteromer. This study should provide information that leads to new opioids with lower addictive liability or to compounds that can counteract the addictive effects of opioids, by targeting the MOR-Gal1R heteromer. [1]Moreno et al., J Neurosci, 2017;37:1176-1186 [2]Cai et al., J Clin Invest, 2019; doi: 10.1172/JCI126912

Disclosures: **P.A. De Oliveira:** None. **C. Ning-Sheng:** None. **A. Bonifazi:** None. **A. Newman:** None. **S. Ferre:** None. **L. Pardo:** None. **N. Casajuana-Martín:** None. **A. González:** None. **E. Moreno:** None. **V. Casadó-Anguera:** None. **V. Casadó:** None. **H. Zhu:** None. **S. Pittenger:** None. **M. Hall:** None.

Poster

646. Metabotropic Receptors for Other Transmitters and Peptides

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 646.12/B72

Topic: B.03. G-Protein Coupled Receptors

Title: Possibility to recover from anorexia: A disorganized synaptic network in the prefrontal cortex did not block the ability to restore hypophagia in adult stressed 5-HT4 knockout

Authors: M. EL OUAHLI[1], M. NAJIMI[2], F. CHIGR[2], ***V. COMPAN**[1];
[1]Nimes Univ., Nimes, France; [2]Beni Mellal Univ., Beni Mellal, Morocco

Abstract: Adult restoration of serotonin 4 receptor (5-HT_4R) expression in the medial prefrontal cortex (mPFC, HSV5-HT_4R-transduced mice) rescues hypophagia and specific molecular changes related to depression resistance in the dorsal raphe nucleus (DR) of stressed 5-HT_4R knockout (KO) mice, involving the glutamatergic descending pathway from the mPFC to the DR (Cell Report 2017). These neural events are then not implemented during earlier developmental stages, but adapt rapidly, with high flexibility, in response to uncontrollable stress. Is it because synapses, known as the functional unit of learning and memory, are less required for this behavioral response to stress? Here, we set out to observe the number of dendritic spines of

pyramidal cells in the mPFC under basal conditions in mice of both genotypes at 3 and 7 months after birth in the presence or absence of 5-HT_4Rs (GFP-M 5-HT_4R KO). The number of dendritic spines of pyramidal cells in the mPFC is similar between WT mice aged of 3 and 7 months, but 5-HT_4R KO mice displayed a reduced density of dendritic spines when aged of 7 months compared with WT animals at identical age under basal conditions. Half reduced mRNA levels of BDNF were correlated with the possible disorganized synaptic network in the mPFC in 5-HT_4R KO mice compared with WT animals. Further considering localization of 5-HT_4Rs on 60% of pyramidal glutamatergic neurons in the mPFC, the mRNA levels of intercellular adhesion molecule-5 (ICAM-5) were analyzed, as ICAM-5 appears to contribute to spine maturation in glutamatergic neurons. The mRNA levels of ICAM-5 were reduced in the mPFC in 5-HT_4R KO mice compared with WT animals. The present findings suggest that restoring hypophagia following stress during adulthood did not depend on an implemented cortical synaptic network.

Disclosures: **M. El Ouahli:** None. **M. Najimi:** None. **F. Chigr:** None. **V. Compan:** None.

Poster

646. Metabotropic Receptors for Other Transmitters and Peptides

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 646.13/B73

Topic: B.03. G-Protein Coupled Receptors

Support: KAKENHI 17K08555
KAKENHI 18K06865

Title: Mechanisms for pituitary adenylate cyclase-activating polypeptide-induced increase in excitability in adrenal medullary chromaffin cells

Authors: *M. INOUE, H. MATSUOKA, K. HARADA;
Cell and Systems Physiol., UOEH Sch. of Med., Kitakyushu, Japan

Abstract: Pituitary adenylate cyclase-activating polypeptide (PACAP) acts on adrenal medullary chromaffin (AMC) cells as a neurotransmitter of the preganglionic sympathetic nerve. We have elucidated that in guinea-pig AMC cells PACAP facilitates catecholamine secretion evoked by muscarinic receptor stimulation, PACAP itself induces a depolarizing inward current, and muscarine-induced depolarization is at least in part due to insertion of TRPC1/4 heteromeric channels into the cell membrane. The present experiments aimed first to investigate the ion channels involved in the PACAP-sensitive current in guinea-pig and mouse AMC cells and second to explore how PACAP enhances muscarinic receptor-mediated secretion. The whole-cell current was recorded at -50 or -60 mV in isolated AMC cells with the perforated patch clamp technique. Bath application of 3 nM PACAP and 1 μM muscarine produced inward currents in 6

and 8 of 9 guinea-pigs AMC cells, respectively. In contrast to guinea pigs, almost all the mouse AMC cells (14/15) developed inward currents in response to 3 nM PACAP, whereas only 30% of the mouse cells exhibited inward currents in response to 30 μM muscarine. Exposure to PACAP consistently resulted in enhancement of the muscarinic inward current. This enhancement of the muscarinic current did not depend upon the amplitude of PACAP-induced currents, and PACAP enhanced membrane insertion of TRPC1/4 channels in response to muscarine. In guinea-pig and mouse AM cells, 1 μM mucarine-induced currents were suppressed by quinine in a dose-dependent manner with an IC_{50} of 20 μM, whereas PACAP-induced inward currents were not noticeably suppressed by 100 μM quinine. The PACAP current was completely suppressed by the replacement of external Na^+ with N-methyl D-glucamine. Addition of 30 μM 9-phenanthrol, a specific TRPM4 channel, to the external solution resulted in the inhibition of PACAP currents by about 90%, and TRPM4-like immunoreactivity was detected at the cell periphery in guinea-pig and mouse AMC cells. The present results reveal that PACAP activates Na^+-permeable cation channels, which are not affected by quinine and suppressed by 9-phenanthrol. These properties of the ion channels are reminiscent of those of TRPM4. We conclude that PACAP activates Na^+-permeable cation channels in guinea-pig and mouse AMC cells and facilitates the membrane insertion of TRPC1/4 channels in response to muscarinic receptor stimulation.

Disclosures: **M. Inoue:** None. **H. Matsuoka:** None. **K. Harada:** None.

Poster

646. Metabotropic Receptors for Other Transmitters and Peptides

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 646.14/B74

Topic: B.03. G-Protein Coupled Receptors

Support: JSPS KAKENHI Grant 18K07392

Title: NECAB2 is a major calcium-binding protein of GPR3-positive neurons in various regions of the mouse brain

Authors: *F. IKAWA, S. TANAKA, K. HARADA, I. HIDE, N. SAKAI;
Dept. of Mol. and Pharmacol. Neurosci., Hiroshima Univ. Grad. Sch. of Biomed. and Hlth. Sci., Hiroshima, Japan

Abstract: The G-protein coupled receptor 3 (GPR3) is a member of the class A rhodopsin-type GPR family that is highly expressed in the brain. GPR3 comprises a subfamily with GPR6 and GPR12 and shows >50% identity at the amino acid level and a very close relationship with the lysophosphatidic acid family receptors, sphingosine-1-phosphate family receptors, and cannabinoid family receptors. We have recently clarified that GPR3 promoter activity increased

in the medial habenular nucleus, CA2 region of the hippocampus, thalamus, and pontine nucleus and was rather weak in the striatum and cerebellum using GPR3−/−; LacZ+/+ mice. However, subpopulations of GPR3 in neurons have not been fully elucidated. It was recently reported that diphenyleneiodonium chloride has agonistic potential for GPR3 to release calcium from ER in an IP3-dependent manner. In addition, EF-hand Ca-binding proteins (CaBPs) were used as valuable anatomical markers for morphologically and functionally distinct neuronal subpopulations. Among CaBPs, neuronal Ca^{2+}−binding proteins (NECABs) are attractive as markers because NECAB2 is reported to be specifically expressed in the CA2 area of the hippocampus where GPR3 is specifically distributed. The NECABs subfamily comprises three members (NECAB1-NECAB3), of which NECAB1/ NECAB2 are restricted to the nervous system. We investigated whether GPR3 co-localizes with NECAB1/ NECAB2 using immunohistochemistry and analyzing by confocal microscopy. Of note, GPR3-expressing neurons were exclusively positive for NECAB2 in areas highly expressing GPR3, including the medial habenular nucleus, CA2 region of the hippocampus, and thalamus. However, NECAB1 partially co-localizes with GPR3-positive neurons. NECAB2 reportedly interacts with the adenosine A2A receptor or metabotropic glutamate receptor 5, thereby contributing to receptor functions. These results suggest that the neuronal expression of GPR3 may be associated with NECAB2 and could modulate calcium signaling in specific neurons.

Disclosures: F. Ikawa: None. **S. Tanaka:** None. **K. Harada:** None. **I. Hide:** None. **N. Sakai:** None.

Poster

646. Metabotropic Receptors for Other Transmitters and Peptides

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 646.15/B75

Topic: B.03. G-Protein Coupled Receptors

Support: R37NS008174

Title: PI 4-kinase and PIP 5-kinase cooperate to replenish $PI(4,5)P_2$ after receptor-mediated depletion

Authors: *L. DE LA CRUZ[1], J. B. JENSEN[1], B. HILLE[2];
[1]Dept. of Physiol. and Biophysics, Univ. of Washington, Seattle, WA; [2]Physiol. & Biophysics, Univ. of Washington Dept. of Physiol. and Biophysics, SEATTLE, WA

Abstract: $PI(4,5)P_2$ is a key cofactor for many cellular processes in neurons. This phospholipid is synthesized from PI sequentially by PI 4-kinases and PIP 5-kinases, and it is depleted in plasma membrane (PM) by activation of muscarinic M_1R receptors. After M_1R activation, both PI4P and $PI(4,5)P_2$ are depleted, and $PI(4,5)P_2$ recovery takes ~125 s. However, if only the 5-

phosphate is removed from $PI(4,5)P_2$ (by activation of a voltage-sensing lipid phosphatase), recovery from PI4P takes only ~10 s. Using tsA201 cells transiently transfected with the enzymes PI4KIIIα or PIP5KIγ, we explored whether $PI(4,5)P_2$ recovery after M_1R activation could be accelerated by PI4K overexpression, and tested for cooperativity between PI4K and PIP5K. We evaluated $PI(4,5)P_2$ recovery after M_1R stimulation using KCNQ2/3 current. These ion channels require $PI(4,5)P_2$ and are rapid real-time indicators specific for PM $PI(4,5)P_2$. KCNQ2/3-current recovery showed a delay of 20-30 s before recovery began either in control or in PIP5KIγ-overexpressing cells, whereas recovery started immediately in PI4KIIIα+complementary proteins (CP) TTC7 and EFR3-overexpressing cells. The half-time of recovery was 81 s (control), 50 s (PI4K), and 70 s (PIP5K). Acceleration of recovery by PIP5K may reflect changes in PI4K localization. PI4KIIIα localized as a diffuse label in cytosol when expressed alone. However, co-overexpression of the 4-kinase with CP gave a PM localization in ~30% of cells, and additional co-overexpression of PIP5KIγ increased that to 50%. We performed mass spectrometry comparing phosphoinositides PI, PIP and PIP_2 in PI4KIIIα- or PIP5KIγ-overexpressing cells to control. There was no change in total PI levels but a 15-20% decline in PIP with PI4KIIIα or PIP5KIγ. At the same time, total PIP_2 increased 25% for PI4KIIIα and 35% for PIP5KIγ. With overexpression of PIP5K the overall conversion of PIP to PIP_2 was expected. However, with PI4KIIIα alone, an increase of PIP was expected rather than a decrease. The direct augmentation of PIP_2 observed in mass spec experiments and the increased localization of PI4KIIIα to the PM with the co-expression of PIP5KIγ suggest that the two enzymes might form a functional complex that resynthesizes $PI(4,5)P_2$ directly from PI (Supported by NIH/NINDS R37NS008174).

Disclosures: L. De La Cruz: None. **J.B. Jensen:** None. **B. Hille:** None.

Poster

646. Metabotropic Receptors for Other Transmitters and Peptides

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 646.16/B76

Topic: B.03. G-Protein Coupled Receptors

Support: NIMH ZIAMH002498

Title: Characterizing distinct subsets of hippocampal CA2 neurons through afferent and efferent circuit mapping and electrophysiological recording in vasopressin 1b-Cre transgenic mice

Authors: *N. I. CILZ, S. WILLIAMS, A. J. HOWLEY, E. SHEPARD, S. YOUNG;
Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: The dorsal CA2 area is an important component for circuits underlying social memory and aggression. The CA2 area is molecularly defined by several different region-specific genes,

including the vasopressin (Avp) 1b receptor (Avpr1b) (Young et al., 2006). Previously, we have shown that the Avp-Avpr1b system is important for both social aggression (Pagani et al., 2015) and memory (Smith et al., 2016). The underlying Avp-Avpr1b circuitry and cellular mechanisms, however, remain to be fully understood. To address these matters, we utilized a combination of techniques including viral-mediated circuit-tracing and *in vitro* electrophysiology in transgenic mice. To visualize the distribution of Avpr1b-expressing cells throughout the hippocampus, we crossed Avpr1b-Cre mice with a reporter line and found robust CA2 Avpr1b expression along the hippocampal dorsoventral axis. We utilized injections of Cre-dependent retro AAV and AAV vectors to map inputs and downstream targets, respectively, of the CA2 region at different dorsoventral locations. To better understand the relationship between Avp and Avpr1b expression, we used immunohistochemistry to stain for neurophysin 2 (the Avp carrier protein) fibers in Avpr1b-Cre reporter mice. Neurophysin 2 fibers were seen near Avpr1b-enriched hippocampal areas, supporting a modulatory action of Avp. To complement these findings, we attempted to map Avp inputs to the CA2 region using a Cre-dependent retro AAV in Avp-Cre mice. Finally, we made whole-cell recordings from Avpr1b-expressing cells in Avpr1b-Cre reporter mice to probe the cellular level of this circuit. We first characterized the electrophysiological properties of Avpr1b-expressing cells at different dorsoventral levels. We next probed for Avpr1b modulatory effects using exogenous application of an Avpr1b-selective agonist. We found that Avpr1b activation increases the excitability of Avpr1b-expressing cells. These findings expand on our previous studies by providing a more detailed understanding of the hippocampal Avpr1b-expressing circuit and Avp-Avpr1b signaling in the CA2 area.

Disclosures: **N.I. Cilz:** None. **S. Williams:** None. **A.J. Howley:** None. **E. Shepard:** None. **S. Young:** None.

Poster

646. Metabotropic Receptors for Other Transmitters and Peptides

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 646.17/B77

Topic: B.03. G-Protein Coupled Receptors

Support: NIDA Grant R01 DA041336

Title: Structure-activity relationships of psilocybin analogs at serotonin 5-HT_2 receptor subtypes

Authors: *A. K. KLEIN[1], J. D. MCCORVY[2], S. D. BRANDT[3], A. L. HALBERSTADT[1]; [1]Psychiatry, UCSD Med. Ctr., San Diego, CA; [2]Med. Col. of Wisconsin, Wauwatosa, WI; [3]Liverpool John Moores Univ., Liverpool, United Kingdom

Abstract: In recent years, there has been increasing scientific interest into the effects and pharmacology of serotonergic hallucinogens. In addition, many structural analogs of controlled

hallucinogens have appeared as new designer drugs. While a large amount of experimental work has been conducted to characterize the effects of the tryptamine hallucinogen psilocybin (4-phosphoryloxy-*N*,*N*-dimethyltryptamine), there has been little systematic investigation of the structure-activity relationships (SAR) of other 4-substituted tryptamine derivatives. The present investigation attempts to address the gap of information. SAR studies were conducted with 16 tryptamines containing a variety of *N*,*N*-dialkyl substituents (methyl, ethyl, propyl, isopropyl, or allyl) and either a 4-hydroxy or a 4-acetoxy group. The ability of these compounds to activate human 5-HT_2 subtypes (5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C}) was assessed using calcium mobilization assays. Head twitch response (HTR) studies were conducted in C57BL/6J mice to assess activation of the 5-HT_{2A} receptor (the site primarily responsible for hallucinogenesis) *in vivo*. The HTR was detected using a head-mounted neodymium magnet and a magnetometor coil; compounds were injected IP and head twitch counts were assessed over 30 min. The tryptamines acted as full or partial agonists at 5-HT_2 subtypes. Although the compounds displayed approximately equal potency at 5-HT_{2A} and 5-HT_{2B} sites, they typically had >10-fold lower potency at 5-HT_{2C} sites. In addition, *O*-acetylation reduced the 5-HT_{2A} agonist potency of 4-hydroxylated tryptamines by about an order of magnitude. All of the compounds induced head twitches in mice, consistent with an LSD-like behavioral profile. Most of the compounds had about the same potency as psilocybin (ED_{50} = 1.40 µmol/kg IP) in the HTR assay, indicating that the specific *N*,*N*-dialkyl substitution pattern is not a major determinant of behavioral potency in mice. Furthermore, in contrast to the *in vitro* data, *O*-acetylation of the 4-hydroxy group had little effect on HTR potency. These findings shed light on the SAR of *N*,*N*-dialkyltryptamines containing a 4-oxygenated substituent. The tryptamine derivatives have psilocybin-like pharmacological properties, supporting their classification as serotonergic hallucinogens. Psilocybin is rapidly *O*-dephosphorylated to psilocin (4-hydroxy-*N*,*N*-dimethyltryptamine) *in vivo* and is thought to act as a pro-drug; comparison of the *in vivo* and *in vitro* potencies of the 4-acetoxy-*N*,*N*-dialkyltryptamines indicates that these compounds may also serve as pro-drugs for their *O*-deacetylated derivatives.

Disclosures: **A.K. Klein:** None. **J.D. McCorvy:** None. **S.D. Brandt:** None. **A.L. Halberstadt:** None.

Poster

646. Metabotropic Receptors for Other Transmitters and Peptides

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 646.18/B78

Topic: B.03. G-Protein Coupled Receptors

Title: EEG correlates of the head twitch response induced by 5-HT_{2A} receptor agonist 25I-NBOH

Authors: *A. CONTRERAS, M. KHUMNARK, R. M. HINES, D. J. HINES;
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Abstract: Serotonin (5-HT) is an evolutionarily conserved neuromodulator known to regulate attention and perception, as well as stabilize mood. Of the 5-HT receptor types, the 5-HT2A receptor is highly enriched in the frontal cortex and thought to mediate attentional processes. The 5-HT2A receptor also appears to be central to the mechanism of action for classical hallucinogens, with behavior like the head twitch response (HTR) in rodents serving as an assay for 5-HT2A activation and potential hallucinogenic effects. While the HTR provides a behavioral profile of 5-HT2A activation, less is known about the circuit level changes induced by hallucinogenic compounds acting at the 5-HT2A receptor. To better understand these changes, we used a combination of behavioral assays and EEG to characterize the HTR response in mice after administration of the potent and highly selective 5-HT2A receptor agonist 25I-NBOH. In the open field, mice injected with 25I-NBOH exhibited a robust HTR and a disorganization of behavior which included frequent stops. Treated animals displayed the HTR as early as 3 minutes after drug administration, which confirms findings from previous studies characterizing the HTR using other 5-HT2A agonists. We also observed that as the 60-minute testing period progressed, the HTR became less frequent and animals had longer stops. We then performed a series of EEG studies to understand the patterns of activity that underlie the HTR. We found that a characteristic pattern composed of two distinctive waveforms (Phase I and Phase II) occurred after injection of 25I-NBOH. This pattern also correlates temporally with the HTR, with Phase I most commonly preceding the HTR and Phase II mapping directly onto the HTR. Data suggests that dual administration of nicotine and hallucinogenic compounds alters the HTR effects, and we found that mice given a pretreatment of nicotine before 25I-NBOH injection exhibit an attenuated HTR along with alterations in the waveform patterns observed in 25I-NBOH alone.
Our findings contribute to our understanding of 5-HT2A actions, with major implications for clarifying the role of serotonergic and cholinergic signaling in the cortex for novel therapies.

Disclosures: A. Contreras: None. **M. Khumnark:** None. **R.M. Hines:** None. **D.J. Hines:** None.

Poster

646. Metabotropic Receptors for Other Transmitters and Peptides

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 646.19/B79

Topic: B.03. G-Protein Coupled Receptors

Support: NSF Grant 1606882

Title: The effects of cannabinoid-type 1 receptor biased agonism on cellular signaling

Authors: *H. K. ANDERSEN, K. B. WALSH;
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Abstract: Biased agonists stabilize receptor conformations that preferentially stimulate cell signaling pathways. Cannabinoids have been found to have biased effects on the cannabinoid-type 1 (CB1) receptor when stimulating the inhibitory G protein (G_i) and β-arrestin pathways. Binding of cannabinoids to the CB1 receptor causes a dissociation of G_i into $G\beta\gamma_i$ and $G\alpha_i$ subunits, which mediate neuronal activity. An intriguing question remains whether cannabinoids differentially induce $G\beta\gamma_i$ and $G\alpha_i$ effects. In this study we examined CB1 receptor activation of the G protein-gated inward rectifier potassium (GIRK) channel (a $G\beta\gamma_i$ mediated effect) using a fluorescent assay developed in our lab. Since $G\alpha_i$ inhibits adenylyl cyclase, we used a cAMP ELISA to quantify cannabinoid-induced cAMP suppression. Data from both assays were measured using a pituitary cell line (AtT20) that endogenously express GIRK channels and was transduced with the human CB1 receptor (AtT20/CB1). Six cannabinoids including, WIN 55,212, AM1248, Anandamide, BAY 59-3074, CP 55,940 and Δ9-tetrahydrocannabinol (THC) were tested in the assays. All of the cannabinoids caused a strong suppression of forskolin/IBMX-stimulated cAMP production (ranging from 70 ± 5 % for Anandamide to 79 ± 4 % with WIN 55,212). In contrast, when normalized to GIRK channel activation caused by WIN 55,212 (100 %), the cannabinoids showed striking differences in their abilities to activate the GIRK channel (ranging from 136 ± 4 % for Anandamide to 13 ± 6 % with BAY 59-3074). In conclusion, our data suggest that cannabinoids may differentially stimulate the $G\beta\gamma_i$ subunit.

Disclosures: H.K. Andersen: None. **K.B. Walsh:** None.

Poster

646. Metabotropic Receptors for Other Transmitters and Peptides

Location: Hall A

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Topic: B.03. G-Protein Coupled Receptors

Support: Wellcome Trust Project Grant WT083199MF
Biotechnology and Biological Science Research Council Core Support Grant BBF0083091
core funding from the University of Kent School of Pharmacy (to Y.A.U)

Title: C-terminal phosphorylation of latrophilin-1 regulates the interaction between its fragments

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Abstract: Latrophilin-1 (LPHN1), is a presynaptic adhesion G protein-coupled receptor (aGPCR), present mainly in the brain. It binds several ligands, including α-latrotoxin (α-LTX) from black widow spider venom, which causes a massive mobilisation of stored calcium and release of neurotransmitters from nerve terminals. As a typical aGPCR, LPHN1 undergoes autoproteolysis within the "GPCR autoproteolysis-inducing" (GAIN) domain, which produces two fragments: the extracellular N-terminal fragment (NTF) and the heptahelical C-terminal fragment (CTF). The NTF and CTF of LPHN1 can exist as independent proteins in the plasma membrane. However, the binding of α-LTX or another ligand to NTF induces its association with the CTF and triggers G protein-mediated signalling. The functions of most GPCR are usually critically controlled by their C-terminal phosphorylation. However, CTF phosphorylation in LPHN1 has not been described yet and what role CTF phosphorylation could play in LPHN1 functions remains to be seen.
Post-translational modifications of the CTF in native and recombinant LPHN1 were analysed using glycohydrolases, alkaline phosphatase and protein phosphatase inhibitors. The differentially phosphorylated species of CTF were resolved by SDS electrophoresis without sample boiling, followed by western blot analysis. The interaction between the NTF and CTF was tested by affinity chromatography on α-LTX or wheat germ agglutinin (WGA) columns and by centrifugation in sucrose density gradients.
Our results demonstrate that a large percent of LPHN1 CTF in central nerve terminals is phosphorylated at several sites. Phosphorylated CTF co-purifies with the NTF on affinity columns and on sucrose density gradients. On the other hand, dephosphorylated CTF largely behaves as an independent protein. This indicates that the NTF of LPHN1 has a much higher affinity for the phosphorylated form of CTF. The binding of α-LTX to the complex of NTF with phosphorylated CTF leads to CTF dephosphorylation by presynaptic protein phosphatases and release of CTF from the NTF-CTF complex. Taken together, our results suggest that phosphorylation and dephosphorylation of LPHN1 depends on ligand binding, which regulates the interaction between its fragments and its function as a G protein-coupled receptor.

Disclosures: O. Benlaouer: None. **M. Atiqur Rahman:** None. **C. Manser:** None. **J. Silva:** None. **Y. Ushkaryov:** None.

Poster

646. Metabotropic Receptors for Other Transmitters and Peptides

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 646.21/B81

Topic: B.03. G-Protein Coupled Receptors

Support: Camden Health Research Initiative (CHRI)
Department of Biomedical Sciences, CMSRU

Title: Clinical study of the expression of cannabinoid receptors in temporal lobe epilepsy: Role of cannabinoid receptors in the regulation of α-synuclein expression in neuronal cells

Authors: *G. A. CARRASCO, S. VIMAWALA, J. KUSUSKY, N. PARIPATI, T. N. FERRARO, R. J. BUONO;
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Abstract: Temporal lobe epilepsy (TLE) is the most common form of refractory focal epilepsy and is usually regarded as a multifactorial polygenic disorder. Data from clinical studies suggest that cannabidiol and Δ^9-tetrahydrocannabinol may be effective in the prevention of seizures in some TLE patients. Here we used Western blots to study the protein expression of CB_1 and CB_2 cannabinoid receptors in human temporal lobe (Broadman area 39) from TLE and control patients. As recent studies describe α-synuclein deposits in some forms of epilepsy, the expression of this protein in human temporal lobe was also studied by Western blots. Further, we used Western blots and qRT-PCR to assess the effect of cannabinoid agonists on the expression of α-synuclein in rat prefrontal cortex (PFCx), and the regulation of its expression by selective cannabinoid agonists in a neuronal cell model, CLU213 cells.
Preliminary results revealed a significant ($p<0.05$) increase in both CB_1 and CB_2 protein levels in TLE patients (n=20) compared to controls (n=3) (45% and 30% increase for CB_1 and CB_2 receptors, respectively). The expression of 5-HT_{2A} receptors and GRK5 proteins was not significantly ($p>0.05$) different between the two groups. An approximately 25% increase ($p<0.05$) in α-synuclein protein expression in temporal cortex was found in TLE patients compared to controls.
In our preclinical studies, rats were injected with a non-selective CB_1/CB_2 receptor agonist, CP55940 (50 μg/kg, 7 days, ip). We found a significant ($p<0.05$) 20% reduction in α-synuclein mRNA levels in CP55940 treated-animals (n=6) compared to controls (n=6). Further studies conducted in CLU213 cells (n=6) showed that α-synuclein expression was significantly ($p<0.05$) reduced by either 1um or 1nM CP55940 incubation (45% an 35% inhibition, respectively). Preliminary data (n=3) using selective CB_1 (ACEA) or CB_2 (GP1a) cannabinoid receptor agonists suggests that activation of CB_2 receptors produces a stronger inhibition of α-synuclein mRNA expression than CB_1 receptors.
Overall, these studies support a rationale for the use of selective cannabinoid agonists in the reduction of brain α-synuclein and in the possible treatment of some forms of TLE.

Disclosures: G.A. Carrasco: None. **S. Vimawala:** None. **J. Kususky:** None. **N. Paripati:** None. **T.N. Ferraro:** None. **R.J. Buono:** None.

Poster

646. Metabotropic Receptors for Other Transmitters and Peptides

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 646.22/B82

Topic: B.03. G-Protein Coupled Receptors

Title: Glutamate receptors interactions and Alzheimer's disease

Authors: *M. V. VASEFI[1], K. MEEUWSEN[1], P. WARWICK[1], A. HAMILTON[2], S. FERGUSON[3];
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Abstract: Alzheimer's disease (AD) is the seventh leading cause of death in the United States, affecting 5.5 million Americans with the number expected to double by 2050. As such, AD is expected to be a major public health problem in the upcoming decades. AD exhibits a primary hallmark of early deposition of Amyloid-Beta (Aβ) oligomers, which play a major role in the neuropathology of the disease. Glutamate receptors function as cellular binding sights for Aβ oligomers, resulting in receptor clustering and synaptic dysfunction. Aβ oligomer has also been shown to interact with metabotropic glutamate receptor subtype 5 (mGluR5). The extracellular building of Aβ/mGluR5 changes the receptor signaling and trafficking in the cells. Interactions between mGluR5 and N-methyl-D-aspartate (NMDA) receptors have been described previously. mGluR5 is a positive modulator of NMDA receptors. Agonist manipulation of mGluR5 reverses several NMDA antagonist-induced responses. NMDA receptors are tetrameric channels composed of two NR1 and two NR2 or NR3 subunits. It is indicated that the NMDA receptor composition, specifically the NR2 subunit, that dictates whether NMDA receptor activation will promote cell death (NR2B) or cell survival (NR2A). This work focuses on the interaction of the Aβ/mGluR5 and NMDA receptor, with a focus on NR2B containing NMDA receptor, expanding the view beyond a single receptor or a signaling pathway in AD. The increased in surface expression of NR2B containing NMDA receptor was observed in the present of Aβ in the neurons however, mGluR5 antagonist, CTEP, blocked the effect. Upregulated NR2B containing NMDA receptor display changes in the trafficking which induced by the activity of the mGluR5 in the present of Aβ oligomers. The mechanisms by which the activity of the NMDA receptor is altered by the formation of Aβ/mGluR5 complex, result in an understanding of neuronal receptor trafficking and synaptic plasticity in AD.

Disclosures: M.V. Vasefi: None. **K. Meeuwsen:** None. **P. Warwick:** None. **A. Hamilton:** None. **S. Ferguson:** None.

Poster

646. Metabotropic Receptors for Other Transmitters and Peptides

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 646.23/B83

Topic: B.03. G-Protein Coupled Receptors

Support: NIH NIDA IRP

Title: Molecular mechanisms of superagonism elicited by synthetic cannabinoid actions on CB1 receptors

Authors: *H. YANO[1], A. F. HOFFMAN[2], C. R. LUPICA[2], M. H. BAUMANN[3], L. SHI[4]; [2]Electrophysiology Res. Section, [3]Designer Drug Res. Unit, [4]Computat. Chem. and Mol. Biophysics Unit, [1]Natl. Inst. on Drug Abuse IRP, Baltimore, MD

Abstract: Misuse of synthetic cannabinoids (SCs) continues to increase worldwide and is often associated with serious adverse effects including hallucinations, cardiovascular abnormalities, coma, or death. Many SCs are aminoalkylindole molecules that are distinct from the naturally occurring psychoactive phytocannabinoid, Δ^9-tetrahydrocannabinol (Δ^9-THC), found in cannabis. It is established that Δ^9-THC is a partial agonist at cannabinoid CB1 receptors, whereas SCs demonstrate much higher efficacy and potency at this site, and this likely relates to a much higher incidence of medically adverse effects. Moreover, some SCs exhibit a maximal efficacy at CB1 receptors that exceeds that seen with typical full agonists, and this has been termed "superagonism". Additionally, superagonism is usually associated with increased potency at CB1 receptors. At present, it is unknown whether these unique pharmacological characteristics at CB1 receptors directly relate to the adverse effects of some SCs, or whether their actions at non-CB1 sites may also be involved. In the current study, we examined molecular mechanisms of superagonism of SCs at CB1 receptors.
We first tested a series of SCs in our bioluminescence resonance energy transfer (BRET) assay in a CB1-Gi protein engagement configuration. Unlike other receptor function assays, this approach avoids caveats associated with signal amplification that can lead to false-positives for superagonism. Based on the structure-activity relationship for superagonism established by this BRET assay, we then performed molecular dynamics simulations of the CB1 receptor complexed with selected SCs to identify the molecular determinants of SC binding efficacy, and to characterize superagonism conformational states of the CB1 receptor-SC complex. Finally, to evaluate superagonism of selected SCs at CB1 receptors, we will perform electrophysiological experiments in hippocampal brain slices from both wildtype and CB1 knockout mice to determine effects of these SCs on glutamate release inhibition mediated by CB1 receptors, and to evaluate potential off-site effects of these drugs. In summary, our findings delineate molecular

mechanisms of superagonism at CB1 receptors and further our understanding of the mechanisms through which SCs may cause serious adverse health effects.

Disclosures: **H. Yano:** None. **A.F. Hoffman:** None. **C.R. Lupica:** None. **M.H. Baumann:** None. **L. Shi:** None.

Poster

646. Metabotropic Receptors for Other Transmitters and Peptides

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 646.24/B84

Topic: B.03. G-Protein Coupled Receptors

Support: UNAM
CONACyT

Title: Distinct phosphorylation sites/clusters in the carboxyl terminus regulate alpha1D-adrenergic receptor subcellular localization and signaling

Authors: ***G. CARMONA ROSAS**[1], D. HERNANDEZ ESPINOSA[2], R. ALCANTARA HERNANDEZ[2], M. ALFONZO MENDEZ[3], J. GARCIA SAINZ[2];
[1]Univ. of Chicago, Chicago, IL; [2]UNAM, Mexico, Mexico; [3]NIH, Baltimore, MD

Abstract: The human α1D-adrenergic receptor is a seven transmembrane-domain protein that mediates many of the physiological actions of adrenaline and noradrenaline and participates in the development of hypertension and benign prostatic hyperplasia.
We recently reported that different phosphorylation patterns control α1D-adrenergic receptor desensitization. However, to our knowledge, there is no data regarding the role(s) of this receptor's specific phosphorylation residues in its subcellular localization and signaling. In order to address this issue, we mutated the identified phosphorylated residues located on the third intracellular loop and carboxyl tail. In this way, we experimentally confirmed α1D-AR phosphorylation sites and identified, in the carboxyl tail, two groups of residues in close proximity to each other, as well as two individual residues in the proximal (T442) and distal (S543) regions. Our results indicate that phosphorylation of the distal cluster (T507, S515, S516 and S518) favors α1D-AR localization at the plasma membrane, i. e., substitution of these residues for non-phosphorylatable amino acids results in the intracellular localization of the receptors, whereas phospho-mimetic substitution allows plasma
membrane localization. Moreover, we found that T442 phosphorylation is necessary.
for agonist- and phorbol ester-induced receptor colocalization with β-arrestins.
Additionally, we observed that substitution of intracellular loop 3 phosphorylation sites for non-phosphorylatable amino acids resulted in sustained ERK1/2 activation; additional mutations in the phosphorylated residues in the carboxyl tail did not alter this pattern. In contrast,

mobilization of intracellular calcium and receptor internalization appear to be controlled by the phosphorylation of both third-intracellular-loop and carboxyl terminus-domain residues. In summary, our data indicate that a) both the phosphorylation sites present in the third intracellular loop and in the carboxyl terminus participate in triggering calcium signaling and in turning-off α1D-AR-induced ERK activation; b) phosphorylation of the distal cluster appears to play a role in receptor's plasma membrane localization; and c) T442 appears to play a critical role in receptor phosphorylation and receptor-β-arrestin colocalization.

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Poster

646. Metabotropic Receptors for Other Transmitters and Peptides

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 646.25/B85

Topic: B.03. G-Protein Coupled Receptors

Support: NIH Grant R01-DA032895

Title: Characterization of an intranuclear β1-adrenergic receptor signaling pathway in astrocytes

Authors: *K. C. BENTON, D. S. WHEELER, M. B. ANSARI, B. KURTOGLU, A. DOOHAN, S. KHURSHEED, R. KNORR, J. MAGLASANG, D. C. LOBNER, P. J. GASSER; Biomed. Sci., Marquette Univ., Milwaukee, WI

Abstract: The classical model of adrenergic signaling involves activation of G-protein-coupled receptors localized to the plasma membrane. A growing body of evidence suggests that adrenergic receptor signaling can also be initiated at intracellular membranes. We have recently identified β1-adrenergic receptors (β1-AR) localized to the nuclear envelope in cultured cortical astrocytes and have obtained evidence that ligand-induced activation of these nuclear receptors initiates G-protein mediated signaling in the nuclear compartment. These data have led to the hypothesis that, in addition to its plasma membrane receptor-mediated actions, norepinephrine (NE) can exert actions directly at the nucleus. Access of NE to nuclear membrane-localized receptors would require transport of the ligand across both plasma and outer nuclear membranes. Previous studies demonstrated that organic cation transporter 3 (OCT3), a high-capacity transporter for NE and other monoamines, is localized to both plasma membranes and outer nuclear membranes in astrocytes and neurons. The present studies examine the expression and localization of other monoamine transporters in cultured cortical astrocytes to fully describe potential mechanisms by which NE may access nuclear β1-AR. Reverse transcriptase PCR revealed the expression of mRNA for the uptake$_1$ transporters for NE (NET), dopamine (DAT), and serotonin (SERT), as well as the uptake$_2$ transporters PMAT (plasma membrane monoamine

transporter), OCT1, OCT2, and OCT3 in cortical astrocytes. Subcellular fractionation followed by western blot analysis was used to examine nuclear and plasma membrane distribution of these transporters. Immunoreactivity for NET, OCT2, OCT3, and PMAT was observed in both plasma membrane and nuclear fractions in these studies. To examine the potential role of these transporters in gating activation of nuclear β1-AR, cultured astrocytes were transfected with cytoplasmic- or nuclear-localized FRET sensors for cAMP based upon Epac (Exchange protein activated by cAMP). Treatment of astrocytes with NE led to increases in cAMP in both cytosolic and nuclear compartments. Ongoing experiments will further investigate the role of plasma and nuclear localized monoamine transporters in cytosolic and nuclear NE-induced cAMP responses.

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Poster

646. Metabotropic Receptors for Other Transmitters and Peptides

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Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 646.26/B86

Topic: B.03. G-Protein Coupled Receptors

Support: NSF Grant HRD-1238723

Title: Phosphorylation of STAT3 by human serotonin 2C receptor in IDI and INI isoforms

Authors: Z. MILETIC LANAGHAN, M. MAISHA, M. CURTIS, L. FEARS, M. IVY, *H. M. FENTRESS;
Tennessee State Univ., Nashville, TN

Abstract: Serotonin (5-HT) is an indolamine neurotransmitter involved in a variety of functions including regulation of mood, appetite, sleep, learning, memory, and neuronal excitability. 5-HT elicits its effects by binding to at least 14 different receptor subtypes. One of the receptors, the 5-HT_{2C} receptor, has been studied and used as a target for atypical antipsychotic medication. 5-HT_{2C} subtype receptor exists as a 7-transmembrane spanning G protein-coupled receptor (GPCR) found in the central nervous system, and is the only GPCR known to undergo RNA editing, creating at least14 known isoforms in the human brain which affect its ability to couple with G proteins and other signaling proteins. The structurally similar 5-HT_{2A} receptor has been shown to activate the G protein independent JAK/STAT pathway. The purpose of this study was to explore if and how the human 5-HT_{2C} receptor also activates the JAK/STAT pathway by studying different isoforms of the receptor and comparing acute versus chronic treatments. Human Embryonic Kidney (HEK) 293 cells were transfected with human 5-HT_{2C} receptors in both the IDI and INI isoforms to produce stable cell lines. 5-$HT_{2C\text{-}IDI}$ receptor transfected cells

were treated with vehicle (control), 5-HT, olanzapine (neutral antagonist), or SB206553 (inverse agonist) for 30 minutes (acute) and 1 hour (chronic). 5-$HT_{2C\text{-}INI}$ receptor transfected cells were treated with control, 5-HT, and olanzapine for 30 minutes. Treated cells were lysed, proteins were separated by SDS-PAGE, and levels of phosphorylated JAK2, phosphorylated STAT3, and unphosphorylated STAT3 were analyzed using western blots. In cells treated for 30 minutes with vehicle, phosphorylation of STAT3 was observed in cells transfected with the 5-HT_{2C} receptor but not in untransfected cells indicating constitutive phosphorylation of STAT3 by the 5-HT_{2C} receptor. Upon treatment with serotonin, phosphorylated levels of STAT3 were increased in cells expressing the 5-HT_{2C} receptor in both isoforms while STAT3 phosphorylation was completely blocked with cells treated with olanzapine or SB206553 for 30 minutes, suggesting that these two compounds were inverse agonists. However, in the 1 hour treatment, olanzapine did not block constitutive phosphorylation which is expected if it is a neutral antagonist. This suggests that olanzapine may have a delayed effect. Phosphorylated levels of JAK2 were unaffected across all treatments in 5-$HT_{2C\text{-}IDI}$ receptors. These findings indicate that 5-HT_{2C} receptors are activating STAT3 independently of JAK2 and olanzapine behaves differently depending on the length of treatment. Acting on STAT3 may be the mechanism for how antipsychotics work.

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Poster

646. Metabotropic Receptors for Other Transmitters and Peptides

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Topic: B.03. G-Protein Coupled Receptors

Support: NIH Grant R01 N5078792
NIH Grant R01 AG055357

Title: Differential modulation of L-type channel activity by G-protein coupled receptors

Authors: *K. N. MAN[1], J. W. HELL[2];
[1]Pharmacol., Univ. of California, Davis, Davis, CA; [2]Dept. of Pharmacol., UC Davis, Davis, CA

Abstract: L-type calcium channels Cav1.2 and Cav1.3 play pivotal roles in neuronal functions, including control of neuronal excitability, vesicular neurotransmitter release and initiation of gene transcription. In particular, Cav1.2 is required for certain forms of long-term potentiation in the hippocampus and for an intact spatial memory. Mutations in Cav1.2 underlies Timothy syndrome, which presents with arrythmia and autism spectrum disorder. Studying regulation of L-type channel function by neuromodulators will provide insights into mechanisms for memory formation and inform the development of therapeutics on the restoration of channel function.

Here we show that dopamine D1-like receptor regulates L-type channel activity in hippocampal neurons in a local manner. The D1-like receptor agonist SKF81297 potentiates L-type activity when included in the patch pipette but not when in the external solution during cell-attached single-channel recording in rat and mouse hippocampal neurons isolated from the CA1 region. The effect is specifically mediated by D1-like D1 and/or D5 receptor, as it can be blocked by D1-like blocker SCH23390. In contrast, α_1-adrenergic receptor (α_1-AR) agonist phenylephrine potentiates L-type activity when included in the external solution, but not when included in the patch pipette. Stimulation by muscarinic receptor agonist muscarine and/or mGluR Group I receptor agonist DHPG by inclusion in the external solution had no effect. Inhibition of PKA activity abrogates the effect of D1-like receptor activation on the increase in L-type activity. Preliminary data show that D1-like receptor stimulation increases phosphorylation of serine at position 1928 on the α_1 subunit of Cav1.2. D1-like potentiation of L-type activity is abrogated in mice expressing a mutant Cav1.2 defective of S1928 phosphorylation (S1928A knockin mutant). These results show that D1-like receptors are localized in close proximity to L-type channels to the region delimited by the patch pipette. D1-like receptor potentiates L-type calcium channel activity in hippocampal neurons, possibly through a canonical PKA-dependent mechanism. Phosphorylation of Cav1.2 S1928 is required for L-type activity upregulation. How localized signaling to channels by D1-like receptor occurs and the physiological significance of the regulation remains to be established.

Disclosures: K.N. Man: None. **J.W. Hell:** None.

Poster

646. Metabotropic Receptors for Other Transmitters and Peptides

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 646.28/B88

Topic: A.08. Development of Motor/ Sensory/ and Limbic Systems

Title: The effect of Resveratrol on ocular regeneration on Dugesia dorotocephala

Authors: *N. FERRARO, A. CICCOTTO;
St. Joseph By the Sea HS, Staten Island, NY

Abstract: *Dugesia dorotocephala* are flat, soft-bodied worms with regenerative abilities. Planaria can regenerate any part of the body including the central nervous system and can reproduce sexually as well as asexually. They have a triploblastic body plan and an abundance of adult stem cells. Also known as Neoblasts, they are naturally occurring pluripotent adult stem cells. Resveratrol is a phytoalexin that is commonly found in grape skins and has been found to counteract the oxidation of low-density lipoproteins with ethanol (ETOH) which acts as an increase of circulating high-density lipoproteins that can help for cardiovascular protection. Resveratrol is also known to act as an antioxidant by preventing the oxidation of polyunsaturated

fatty acids which can reduce the risk of heart disease. **β**;;;-Arrestins 1 and 2 belong to a family of adapter proteins associated with rod and cone cells of the eye. Arrestin plays a role in desensitization of G-protein coupled receptors or 7TMR (7 transmembrane receptors) in the **β**;;;$_2$AR pathway and Rhodopsin photosensing pathway. Arrestin proteins function as adapter proteins as well as participate in desensitization of 7TMRs. Binding of β;;-arrestin to the phosphorylated receptor desensitizes the receptor by inhibiting the interaction between the 7TMR and G-protein marking the receptor for sequestration into an endosome. In the current study, planaria were decapitated and arrestin was used as a biomarker for ocular regeneration upon treatment with resveratrol.

Disclosures: **N. Ferraro:** None. **A. Ciccotto:** None.

Poster

646. Metabotropic Receptors for Other Transmitters and Peptides

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 646.29/B89

Topic: G.08. Drugs of Abuse and Addiction

Support: R44 GM125390

Title: Using receptor kinetics to quantitatively measure agonist bias at G-protein coupled receptors

Authors: S. MARTINKA[1], S. HOARE[2], K. HARLEN[1], A. QUINN[1], P. TEWSON[1], ***T. E. HUGHES**[1];
[1]Montana Mol., Bozeman, MT; [2]Pharmechanics, Owego, NY

Abstract: Biased agonism is a crucial concept in the search for drugs that produce analgesia without addiction. G-protein coupled receptors can signal through two different pathways: the G-proteins for which they were named, and β-arrestin. These two different pathways can mediate very different cellular responses, and some agonists at a particular receptor can be biased towards the activation of one of the pathways, a phenomenon known as biased agonism. This bias is typically measured by comparing two different end-point assays for G-protein and β-arrestin signaling. Such a comparison is difficult, and different results can be produced by measuring at different time points [1]. We recently created a green fluorescent β-arrestin sensor that can be used to follow the signaling over time in living cells. This kinetic measurement can be compared to G-protein signaling measured with sensors to Ca^{2+}, cAMP, or DAG. To determine whether the kinetics of the responses of these pathways could be used to determine bias, we measured the responses of the Angiotensin II receptor over time (~ 15 min.) to a panel of known biased agonists (at saturating concentrations). Treating the receptor as an enzyme, and fitting the responses enabled us to extract the initial rate of the reaction (kTau) for the activation

of the β-arrestin or G-protein signaling [2]. The ratio of kTau produced a precise, reproducible measure of bias that was consistent with the literature. We are currently testing whether this approach will be useful in the search for biased agonists at receptors that are involved in pain and addiction.

1.Klein Herenbrink, C. et al. The role of kinetic context in apparent biased agonism at GPCRs. Nat. Commun. 7, 10842 (2016). 2.Hoare, S. R. J., Pierre, N., Moya, A. G. & Larson, B. Kinetic operational models of agonism for G-protein-coupled receptors. J. Theor. Biol. 446, 168-204 (2018).

Disclosures: **T.E. Hughes:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Montana Molecular. **S. Hoare:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Pharmechanics. **S. Martinka:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Montana Molecular. **P. Tewson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Montana Molecular. **A. Quinn:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Montana Molecular. **K. Harlen:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Montana Molecular.

Poster

646. Metabotropic Receptors for Other Transmitters and Peptides

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 646.30/B90

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant GM124623

Title: Engineered zinc binding in the orthosteric binding site of beta$_2$-adrenergic receptor and trace amine-associated receptor 1 (TAAR1)

Authors: T. RUEDLIN[1], A. ZEGLEN[2], C. KARL[2], *Y. NORIMATSU[1];
[1]Physiol., A.T. Still Univ., Kirksville, MO; [2]Truman State Univ., Kirksville, MO

Abstract: Trace amine-associated receptor 1 (TAAR1) is a G protein-coupled receptor and a promising drug target for schizophrenia, major depression, and drug addiction. TAAR1 is expressed in the major monoaminergic pathways, including the ventral tegmental area, substantia nigra, locus coeruleus, raphe nucleus, caudate nucleus, putamen, nucleus accumbens and amygdala, and activated by a wide range of trace amines and monoamines. G protein dependent

signaling (increased cyclic AMP and stimulation of G protein-gated inward rectifying potassium channels) and beta-arrestin 2-dependent signaling are observed with receptor activation. In order to understand the activation mechanism of TAAR1, we created homology models of the active and inactive states based on X-ray crystal structures of beta2-adrenergic receptor (b2AR) and ran molecular dynamics simulations. A group led by Thue W. Schwartz previously showed that a single amino acid substitution, N312C enables zinc to activate b2AR. We tested this engineered zinc binding site in b2AR and also a corresponding mutation in TAAR1 in the *Xenopus* oocyte heterologous expression system using the two-electrode voltage clamp technique.

Disclosures: **T. Ruedlin:** None. **A. Zeglen:** None. **C. Karl:** None. **Y. Norimatsu:** None.

Poster

647. Synaptic Transmission: Modulation and Mechanisms III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 647.01/B91

Topic: B.06. Synaptic Transmission

Support: G. Ribble fellowship from Dept. of Biology, Univ. of KY (UB, ES, AO, CM)
Kentucky Science and Engineering Foundation (KSEF-3712-RDE-019) at the Kentucky Science and Technology Corporation (RLC, CM)

Title: Pharmacological identification of cholinergic receptor subtypes in modulation of neural circuits in *Drosophila melanogaster*

Authors: *U. BHUTTO[1], E. SOMASUNDARAM[2], C. MALLOY[3], R. L. COOPER[4];
[1]Biol., [2]Univ. of Kentucky, Lexington, KY; [3]Mol. Neurophysiol. and Biophysics, Natl. Inst. of Hlth. Office of Intramural, Bethesda, MD; [4]Dept Biol, Univ. of Kentucky Dept. of Biol., Lexington, KY

Abstract: Acetylcholine (ACh) is an abundant neurotransmitter and neuromodulator in many species. In Drosophila melanogaster ACh is the neurotransmitter used in peripheral sensory neurons and is a primary excitatory neurotransmitter and neuromodulator within the central nervous system (CNS). The receptors that facilitate cholinergic transmission are divided into two broad subtypes: the ionotropic nicotinic acetylcholine receptors (nAChRs) and the metabotropic muscarinic acetylcholine receptors (mAChRs). This receptor classification is shared in both mammals and insects; however, both the pharmacological and functional characterization of these receptors within the Drosophila nervous system has lagged behind its mammalian model counterparts. In order to identify the impact of ACh receptor subtypes in regulating the performance of neural circuits within the larval CNS, we used a behavioral and electrophysiological approach to assess cholinergic modulation of locomotion sensory-CNS-motor circuit excitability. We exposed intact and semi-intact 3rd instar larvae to ACh receptor

agonists and antagonists to observe their roles in behavior and regulation of neural circuit excitability and to investigate AChR pharmacological properties in vivo. We combined this with targeted AChR RNAi-mediated knockdown to identify specific receptor subtypes facilitating ACh modulation of circuit efficacy. We identify a contribution by both mAChRs and nAChRs in regulation of locomotive speed and reveal that they play a role in modulation of the excitability of a sensory-CNS-motor circuit. We further reveal a conspicuous role for mAChR-A and mAChR-C in motor neurons, directly, in modulation of their input-output efficacy in response to evoked sensory-CNS input, which is also manifested in alterations in locomotive speed.

Disclosures: U. Bhutto: None. **E. Somasundaram:** None. **C. Malloy:** None. **R.L. Cooper:** None.

Poster

647. Synaptic Transmission: Modulation and Mechanisms III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 647.02/B92

Topic: B.06. Synaptic Transmission

Support: NIEHS T32 Training Grant ES015457
DGSOM transition grant
MH114017

Title: Ziram, a pesticide associated with Parkinson's disease, increases excitability in aminergic and glutamatergic neurons through inhibition of the eag potassium channel

Authors: *J. HARRIGAN[1], D. F. BRAMBILA[4], F. E. SCHWEIZER[4,2], D. E. KRANTZ[5,3]; [1]Mol. Toxicology, UCLA, Los Angeles, CA; [2]Brain Res. Inst., UCLA, Los Angleles, CA; [3]Brain Res. Inst., UCLA, Los Angeles, CA; [4]Neurobio., [5]Psychiatry and Biobehavioral Sci., UCLA, David Geffen Sch. of Med., Los Angeles, CA

Abstract: Exposure to environmental toxins, including the fungicide ziram, has been linked to an increased risk of PD. We tested the neurophysiological effects of acute ziram exposure at the *Drosophila* larval neuromuscular junction (NMJ; see also poster by Brambila et al). Using calcium indicators, we find that ziram increases excitability in aminergic neuronal processes at the NMJ. Ziram also evokes calcium signals in cell bodies of the ventral nerve code, but only when the processes are intact, suggesting that ziram acts on aminergic process. Using electrophysiological recordings of post-synaptic activity at the NMJ we find that ziram enhances excitability of glutamatergic neurons. Potassium channels are one of the regulators of neuronal excitability, we tested whether potassium channel mutants would phenocopy the excitability increase of ziram. Mutant flies that lack the *ether-a-go-go* (*eag*) but not those that lack the Shaker potassium channel phenocopy ziram's excitability effects. We hypothesize that the

increase in neuronal excitability by ziram could represent an early pathological process that may contribute to the increased risk of developing PD.

Disclosures: J. Harrigan: None. **D.F. Brambila:** None. **F.E. Schweizer:** None. **D.E. Krantz:** None.

Poster

647. Synaptic Transmission: Modulation and Mechanisms III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 647.03/B93

Topic: B.06. Synaptic Transmission

Support: EY028212

Title: Molecular and circuit mechanisms underlying sustained anti-depression effects of subanesthetic ketamine

Authors: *X. QIAO[1], S. GRIECO[2], X. XU[3];
[1]Univ. of California Irvine, Irvine, CA; [2]Anat. and Neurobio., UCI, Newport Beach, CA; [3]Anat. and Neurobio., Univ. California, Irvine, Irvine, CA

Abstract: Subanesthetic-dose ketamine is shown to have sustained antidepressant effects, which offers a potential for developing effective antidepressants. However, it is crucial to better understand the mechanisms underlying ketamine's antidepressant action. Preclinical studies indicate that ketamine's antidepressant mechanisms involve mammalian target of rapamycin pathway activation and subsequent synaptogenesis in the prefrontal cortex. As neuregulin-1 (NRG1)/ErbB4 signaling in parvalbumin (PV) interneurons regulates cortical plasticity, we hypothesize that ketamine's antidepressant action depends on modulation of cortical plasticity through NRG1/ErbB4 signaling in PV interneurons. We find that NRG1 signaling is implicated in acute and sustained ketamine's antidepressant effects by using forced swim test (FST). Pretreating mice with exogenous NRG1 suppresses FST effects of ketamine treatment at 30 minutes or 24 hours post ketamine injection; PV ErbB4 KO mice do not show antidepressant-like FST behavior with ketamine treatment. We identify that in vivo single-dose ketamine treatment results in sustained down-regulation of NRG1 expression in PV interneurons in mouse prefrontal cortex at 24, 48 and 72 hours post treatment. Translating ribosome affinity purification was employed to measure cell-specific mRNAs under different conditions. In contrast, there is no significant change of NRG1 expression in excitatory neurons following ketamine treatment. To examine if subanesthetic ketamine increases cortical excitability by reducing synaptic inhibition to excitatory pyramidal neurons, we recorded electrically-evoked inhibitory postsynaptic currents (IPSCs) in pyramidal neurons in prefrontal cortical layer 2/3. Low-dose ketamine treatment induces sustained decrease in IPSCs in pyramidal neurons at 24, 48 and 72

hours after ketamine injection. Exogenous NRG1 application restores reduced inhibitory inputs onto pyramidal neurons. We further mapped excitatory inputs (EPSCs) onto PV interneurons in prefrontal cortical layer 2/3 using laser scanning photostimulation (LSPS) in brain slices. We find that excitatory inputs onto PV interneurons are reduced in ketamine-treated mice at 24 hours after injection and that exogenous NRG1 application restores the reduced excitatory inputs onto PV neurons. Our results demonstrate that subanesthetic ketamine treatment induces sustained cortical disinhibition by downregulating NRG1 signaling in PV interneurons. Our results reveal molecular and circuit mechanisms of sustained antidepressant action of ketamine and provide insights in developing new effective treatments for depression.

Disclosures: X. Qiao: None. **S. Grieco:** None. **X. Xu:** None.

Poster

647. Synaptic Transmission: Modulation and Mechanisms III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 647.04/B94

Topic: B.06. Synaptic Transmission

Title: Potential novel treatments for the nicotinic effects of nerve agent poisoning

Authors: C. L. WHITMORE, A. C. GREEN, *J. E. H. TATTERSALL;
Toxicology, Trauma and Med. Group, Dstl, Salisbury, United Kingdom

Abstract: Nerve agents inhibit the enzyme acetylcholinesterase (AChE), resulting in an accumulation of acetylcholine (ACh) at cholinergic synapses, including the neuromuscular junction. This ACh accumulation at both muscarinic (mAChR) and nicotinic (nAChR) receptors leads to the toxic effects of nerve agent poisoning, including increased secretions, miosis, changes in heart rate, muscular paralysis, seizures and respiratory depression. Current nerve agent treatments contain a muscarinic antagonist (usually atropine) to reduce the effect of excess ACh at mAChR, an oxime to restore AChE activity and a benzodiazepine to reduce or prevent seizures. In this combination, the oxime is the only component targeting overstimulation of the nAChR, albeit indirectly. The reliance on oxime enzyme reactivators is a fundamental weakness in this approach, since no single oxime demonstrates adequate reactivating activity against all the known nerve agents. Nicotinic antagonists have been largely neglected in nerve agent poisoning, mainly due to the difficulty of administering an effective dose which avoids toxic effects of the antagonist [1]. We have previously shown that administration of MB327, a non-competitive nAChR antagonist, restored function in nerve agent-poisoned muscle preparations *ex vivo* and protected guinea-pigs against nerve agent exposure as part of a therapeutic drug combination [1]. These results demonstrate the benefit of effective nAChR treatment, but the toxicity of MB327 is still a problem for practical use. Here, the results of two different approaches to reducing overstimulation at the neuromuscular junction are described, the use of nAChR modulators and

production, *in situ*, of the false transmitters acetylmonoethylcholine and acetyldiethylcholine by administration of monoethyl- and diethylcholine, respectively. Using an automated patch clamp system, we investigated the effect of neuronal nAChR modulators at human muscle type nAChRs ($\alpha_1\beta_1\delta\ \gamma/\varepsilon$) in CN21 cells *in vitro*. We also characterised the action of the false transmitters at human muscle type nAChRs and two mAChR subtypes. Finally, we have demonstrated that production of the false transmitters improved muscle function in the guinea-pig phrenic nerve/hemi-diaphragm preparation after nerve agent exposure. This work suggests that both nAChR modulators and production of false transmitters offer promising avenues towards new broad-spectrum therapeutics which can reduce the effects of excess ACh at the neuromuscular junction and provide the same benefit regardless of the nerve agent used.
Reference *1.Tattersall JEH. Curr. Opinion Physiol. 2018, 4:49-56.*

Disclosures: C.L. Whitmore: None. **A.C. Green:** None. **J.E.H. Tattersall:** None.

Poster

647. Synaptic Transmission: Modulation and Mechanisms III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 647.05/B95

Topic: B.06. Synaptic Transmission

Support: BUAP-VIEP-2018-100317188
PRODEP-511-6/18-6067

Title: Acetylcholine activates NMethylDAspartate receptormediated currents in absence of glycine in medium spiny neurons of rat

Authors: *J. L. FLORES-HERNANDEZ, O. TORRES-RAMIREZ, L. ARROYO-RIOS, A. LUNA-LEAL, B. SORIA_PEREZ, D. VAZQUEZ-CANDANEDO, G. LOPEZ-LOPEZ, E. MANJARREZ-LOPEZ;
Benemerita Univ. Autonoma De Puebla, Institute of Physiology, Mexico

Abstract: The function of the striatal is critically involved in the movement, learning, habit formation, and reward-related behavior. The most of population striatal neurons are GABAergic and they are represented by medium spiny projection neurons. The striatum also contains a small percentage of interneurons which provide this area with one of the highest acetylcholine (ACh) levels in the brain. The main target of cholinergic inputs is represented by spiny neurons which also receive cortical glutamatergic fibers. Recent studies report a decrease in the NMDAR-mediated currents (INMDA) by ACh. This effect is independent of the mechanism classics (muscarinic and nicotinic receptors). Moreover, the d-tubocurarine (nicotinic antagonist) reduces INMDA. These data suggest us the possibility of direct interaction between neurotransmitter

acetylcholine and molecules related to the NMDA receptor (NMDAR). NMDAR are heterotetrameric assemblies of two GluN1 subunits and other GluN2 (A-D). The functional diversity and signaling properties of GluN1/GluN2 NMDARs have been extensively characterized during the last 40 years, providing a wealth of information on the molecular basis of excitatory neurotransmission. Thus, it´s assumed that glycine is a co-agonist of the NMDA receptor and plays an essential role in the activation of this. However, our studies show INMDA in absence of glycine in medium spiny neurons (MSN´s). In the present study, by using an acutely dissociated MSN´s preparation with patch clamp technique in whole cell configuration, we found that the application of ACh (picomolar concentrations) as well of other drugs acting on muscarinic or nicotinic receptors induces an acute and reversible potentiation of INMDA (81% of control) in absence of glycine. This effect was persistent to the presence of the muscarinic antagonist atropine (10μM) and nicotinic antagonist d-tubocurarine (1μM). Furthermore, when ACh and glycine were co-applicated, the INMDA is reduced compared to glycine applicated alone. A detailed analysis of the effects of ACh could suggest that this neurotransmitter interfered with glycine-dependent NMDAR-activity. The application of the 5,7 dichloro kynurenic acid (a potent and selective competitive antagonist of the glycine site on NMDA receptors) in presence of glycine reduced the INMDA but with co-application of ACh, this effect was minor (46 ± 2% and 31 ± 4%, respectively). We conclude that INMDA can be potentiated directly by cholinergic drugs, possibly by direct interaction within one or more subunits of the NMDAR.

Disclosures: J.L. Flores-Hernandez: None. **O. Torres-Ramirez:** None. **L. Arroyo-Rios:** None. **A. Luna-Leal:** None. **B. Soria_Perez:** None. **D. Vazquez-Candanedo:** None. **G. Lopez-Lopez:** None. **E. Manjarrez-Lopez:** None.

Poster

647. Synaptic Transmission: Modulation and Mechanisms III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 647.06/B96

Topic: B.06. Synaptic Transmission

Support: NIH Grant R01 N5078792
NIH Grant R01 AG055357

Title: Regulation of membrane insertion of the AMPA-type glutamate receptor via β2 adrenergic receptor signaling

Authors: *B. LEE, E. A. HAMMES, J. W. HELL;
Pharmacol., Univ. of California, Davis, Davis, CA

Abstract: AMPAR-type glutamate receptors (AMPARs) mediate most of the fast excitatory synaptic transmission in the brain. AMPARs are composed of four subunits (GluA1-4) and GluA1/A2 and GluA2/A3 are prevalent in the brain (W. Lu et al., 2009). Their abundance at postsynaptic sites determines synaptic strength. Surface expression and phosphorylation of AMPARs increase during the long term potentiation (LTP) of synaptic transmission. AMPARs are inserted to the membrane in a retromer dependent manner. β2 Adrenergic Receptor (β2AR) forms supramolecular signaling complexes with AMPARs and regulates phosphorylation of AMPARs through Gs protein, adenylyl cyclase (AC), and PKA signaling, which are also associated with the AMPARs (Joiner et al., 2010). Phosphorylation of S845 by PKA augments AMPAR surface expression and postsynaptic targeting. Norepinephrine (NE) is the endogenous ligand of β2AR and is crucial for arousal and learning in novel and emotionally-charged situations inducing LTPs in hippocampus. The voltage-gated calcium channel (VGCC) $Ca_V1.2$ mediates calcium influx, which governs neuronal excitability, LTP, and learning. Importantly, it stabilizes surface insertion of AMPARs, which otherwise undergoes only short-lived insertions (10-30 sec) (Hiester et al., 2017). We investigated how trafficking of AMPARs to surface is mediated by stimulation of β2AR by NE. Hippocampal neuron culture from rats were treated with NE and stained with antibodies against surface GluA1 and total PSD95, which define postsynaptic sites. Colocalization of sGluA1 and PSD95 puncta was quantified. In parallel, mouse brain slices were incubated with NE to examine the change in phosphorylation of AMPAR GluA1 subunit at S845. After immunoprecipitation of GluA1 from brain slice lysates, phosphorylation of GluA1 was analyzed by immunoblotting. Interaction of AMPARs with their accessary proteins and retromer proteins was investigated by co-immunoprecipitation from brain slice lysates with or without NE treatment. The results of immunostaining with hippocampal neuron culture show that stimulation of β2AR by NE enhances insertion of AMPARs into the plasma membrane. The effect of NE on surface insertion of GluA1 is blocked by L-type calcium channel inhibitor. Also, phosphorylation of S845 was increased by NE. These results represent that stimulation of β2AR by NE promotes trafficking of AMPARs to the cell surface in an L-type channel dependent manner. Electrophysiological analysis suggests that this mechanism is important for certain forms of LTP.

Disclosures: B. Lee: None. **E.A. Hammes:** None. **J.W. Hell:** None.

Poster

647. Synaptic Transmission: Modulation and Mechanisms III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 647.07/B97

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

Support: UIC Startup funding

Title: Developmental NMDA receptor dysregulation in the infantile neuronal ceroid lipofuscinosis mouse model

Authors: *K. P. KOSTER[1], W. FRANCESCONI[2], F. BERTON[2], A. YOSHII[1];
[1]Dept. of Anat. & Cell Biol., Univ. of Illinois at Chicago, Chicago, IL; [2]Dept. of Cell. and Mol. Pharmacol., Rosalind Franklin Univ. of Med. and Scien, North Chicago, IL

Abstract: Mechanisms driving adult-onset neurodegenerative diseases remain enigmatic. Studying monogenic disorders that share features with common neurodegenerative diseases may highlight chief pathogenic mechanisms to better inform therapeutic strategies. Infantile neuronal ceroid lipofuscinosis (CLN1) is a devastating pediatric neurodegenerative disorder sharing pathological characteristics with Alzheimer's and related diseases. CLN1 is caused by mutations in *CLN1*, which encodes the depalmitoylating enzyme palmitoyl-protein thioesterase 1 (PPT1). Palmitoylation entails the post-translational addition of lipid (palmitate) to proteins, which can be depalmitoylated by PPT1. Protein palmitoylation dynamically regulates the localization and function of many synaptic proteins, including the N-methyl-D-aspartate receptor (NMDAR) subunits GluN2B, GluN2A, and the synaptic scaffold PSD-95. However, how loss of depalmitoylation by PPT1 leads to synaptic dysfunction and neuronal death in CLN1 is not understood. Here, we used the *Ppt1*$^{-/-}$ mouse model to decipher how lack of protein depalmitoylation drives synaptic dysfunction in CLN1, with potential implications across diseases. Synaptosomes prepared from cortices of wild-type (WT) and *Ppt1*$^{-/-}$ mice demonstrated decreased levels of GluN2A and PSD-95, which comprise NMDAR complexes at mature synapses. Total levels of GluN2B, which constitutes extrasynaptic NMDARs with prolonged decay kinetics, were unchanged. Correspondingly, NMDAR-mediated currents recorded from *Ppt1*$^{-/-}$ cortical neurons show decreased and enhanced contributions from GluN2A and GluN2B, respectively. In *Ppt1*$^{-/-}$ primary cortical neurons, calcium transients were diffuse, extrasynaptic, and sensitive to GluN2B-blockade, whereas WT cells exhibited compartmentalized calcium influx confined to spine heads. Potentially underlying these disruptions, Fyn kinase, which stabilizes GluN2B at the synaptic surface, and GluN2B are hyperpalmitoylated in *Ppt1*$^{-/-}$ neurons. Indeed, *Ppt1*$^{-/-}$ neurons demonstrated increased vulnerability to NMDA-induced excitotoxicity that, together with the hyperpalmitoylation of GluN2B and Fyn, was reversed by treatment with palmitoylation inhibitors. Thus, loss of PPT1 causes disrupted NMDAR function and susceptibility to excitotoxicity partly via hyperpalmitoylation of GluN2B and Fyn kinase, revealing these as novel mechanistic targets in CLN1. Notably, these proteins are already implicated in Alzheimer's disease and other neurodegenerative disorders, suggesting this may be a common mechanism underlying neurodegeneration with broad therapeutic potential.

Disclosures: K.P. Koster: None. **W. Francesconi:** None. **F. Berton:** None. **A. Yoshii:** None.

Poster

647. Synaptic Transmission: Modulation and Mechanisms III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 647.08/B98

Topic: B.06. Synaptic Transmission

Title: Cannabinoid-induced swimming-induced paralysis in the nematode *Caenorhabditis elegans*

Authors: *S. H. SHRADER, Y. G. TONG, J. H. FREEDMAN, Z. H. SONG;
Dept. of Pharmacol. and Toxicology, Univ. of Louisville Sch. of Med., Louisville, KY

Abstract: The neurotransmitter dopamine (DA) plays a central role in the regulation of learning, memory, emotion, cognition and locomotion. Aberrant dopaminergic signaling is associated with a variety of neurological and neuropsychiatric pathologies, including Parkinson's disease, schizophrenia, attention-deficit/hyperactivity disorder and bipolar disorder. Thus, pharmacological targeting of the DA system is considered to have numerous therapeutic potentials. Compounds able to alter the synthesis, uptake or signaling of DA may prove therapeutically useful. In the nematode *Caenorhabditis elegans*, extrasynaptic DA controls locomotion behavior. This study used loss of function mutants to test the hypothesis that phytocannabinoids in *C. elegans* may act as agonists at the D2-type DA receptor DOP-3, or inhibitors at dopamine transporter DAT-1, resulting in swimming-induced paralysis (SWIP). The SWIP behavioral assay was used to analyze the effects of two phytocannabinoids - cannabidiol (CBD) and cannabidivarin (CBDV), on the locomotion of wild-type nematodes and dopamine-signaling mutant strains. *C. elegans* strains were obtained from the Caenorhabditis Genetics Center and cultured on OP50-seeded NGM agar plates. SWIP behavioral assays were performed using the following strains: N2 Bristol wild-type, LX703 *dop-3(vs106)X*, RM2702 *dat-1(ok157)III* and CB1112 *cat-2(e1112)II*. Drugs were purchased from Cayman Chemicals and dissolved in ethanol to generate 0.1mM, 1mM and 10mM stock solutions. Ten to fifteen late L4 hermaphrodite larvae were placed in a well of 100microL distilled water containing 1microL of drug or vehicle. The numbers of nematodes swimming versus paralyzed were recorded after 10 minutes. For each treatment group per genotype, six wells were scored per experiment and experiments were repeated on five separate days (n=30). Both CBD and CBDV dose-dependently induced SWIP in N2 wild-type nematodes, but neither induced SWIP in *dop-3, dat-1 or* c*at-2* mutants. Our results suggest that these phytocannabinoids may act through the DOP-3 pathway to induce SWIP. Cannabinoids CBD and CBDV are able to induce the DA signaling in *C. elegans* and alter locomotor activity. These compounds may be potential drug candidates for the treatment of neurological and neuropsychiatric diseases characterized by dysregulation of dopamine signaling.

Disclosures: **S.H. Shrader:** None. **Y.G. Tong:** None. **J.H. Freedman:** None. **Z.H. Song:** None.

Poster

647. Synaptic Transmission: Modulation and Mechanisms III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 647.09/B99

Topic: B.06. Synaptic Transmission

Title: Social isolation combined with nicotine exposure alters the dopaminergic response to cocaine

Authors: *N. B. PAIGE, J. F. COMSTOCK, R. A. PENNELLA, S. A. TOWERS, J. P. MANUS, L. A. ROBINSON, D. B. LESTER;
Univ. of Memphis, Memphis, TN

Abstract: Factors relating to social interaction have been shown to alter patterns of psychostimulant use in preclinical and clinical models. In rodents, social isolation during adolescence is considered a stressor, leading to increased drug seeking and sensitization. In humans, nicotine is often one of the first drugs experimented with. The present study aimed to determine the effects of social isolation on nicotine salience using conditioned place preference (CPP) and the effects of social isolation and nicotine exposure on dopamine release in the nucleus accumbens (NAc). At 3 weeks of age, male C57BL/6J mice were either group housed or isolated for 3 weeks prior to nicotine CPP testing, in which mice were subcutaneously administered either nicotine (.35 mg/kg) or saline. Then, fixed potential amperometry was used to quantify dopamine release in anesthetized mice before and after administration of a drug challenge, the dopamine agonist and psychostimulant cocaine (10 mg/kg, i.p.). A three-way mixed ANOVA was used to determine the effect of housing and nicotine pretreatment on percent change in dopamine release over time. Regarding CPP results, there was a significant housing (group or isolated) x drug (nicotine or saline) x trial interaction on time spent in drug-paired chamber. Specifically, the isolated mice significantly preferred the nicotine-paired chamber more than mice in the other groups. Regarding dopamine recordings, there was a significant housing x drug exposure (nicotine or saline) x time (60 min recording period) interaction on percent change in dopamine release. Specifically, the isolated nicotine-exposed mice exhibited a significantly increased dopaminergic response to cocaine relative to the other groups 10 min post injection. Overall, these findings conclude that social isolation during adolescence increases nicotine salience, and nicotine administration in these isolated mice alters dopamine functioning in a direction that may enhance the reinforcing properties of cocaine. Identifying risk factors for drug abuse and understanding the neurochemical mechanisms associated with these risk factors is critical for prevention and treatment programs.

Disclosures: **N.B. Paige:** None. **J.F. Comstock:** None. **R.A. Pennella:** None. **S.A. Towers:** None. **J.P. Manus:** None. **L.A. Robinson:** None. **D.B. Lester:** None.

Poster

647. Synaptic Transmission: Modulation and Mechanisms III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 647.10/B100

Topic: B.06. Synaptic Transmission

Title: Alterations in addiction-related behaviors and dopamine functioning in C57BL/6J mice following social isolation and environmental enrichment

Authors: *J. F. COMSTOCK[1], S. A. TOWERS[1], N. B. PAIGE[1], A. M. BYRN[1], P. E. DICKSON[2], D. B. LESTER[1];
[1]Psychology, Univ. of Memphis, Memphis, TN; [2]The Jackson Lab., Bar Harbor, ME

Abstract: In rodents, environmental enrichment (EE) has been shown to provide a protective effect on addiction-related behaviors, such as novelty reactivity and drug-seeking. The current study examined the effect of EE on locomotor activity and mesolimbic dopamine functioning, with specific aims at distinguishing the effects of physical and social stimuli by including 3 housing conditions: EE (with physical objects such as running wheels and tunnels and cage mates), social enrichment (SE, with cage mates but no EE objects), and isolation (with no EE objects or cage mates). Mice were separated into these housing conditions at 3 weeks of age and remained for 10-12 weeks. In both males and females, isolated C57BL/6J mice displayed increased locomotor activity and rearing relative to EE mice, with SE mice falling in between. *In vivo* fixed potential amperometry was used to quantify dopamine release in the NAc elicited by electrical stimulation of the VTA in anesthetized mice before and after cocaine administration. The housing conditions did not alter baseline dopamine release or reuptake rates in either sex. However, the housing variable did alter dopaminergic responses to cocaine during the 1 hr recording session post injection. Dopamine release following cocaine peaked sooner (10 min instead of 20 min post injection) and escalated to a higher concentration in isolated mice relative to EE and SE mice. Given that no differences are observed between EE and SE mice, this protective effect may be driven by social stimuli rather than physical stimuli. However, a different pattern was observed in measurements of the synaptic half-life of dopamine following cocaine. Cocaine-induced increases in dopamine half-life peaked at 20 min in SE and isolated mice but not until 40-50 min in EE mice, when the responses of the other groups were declining back to baseline. This extended response to cocaine may then be attributed to the physical stimuli in the EE condition and could indicate a longer reinforced experience. But generally drugs have a higher abuse liability when dopamine efflux peaks and makes a rapid return to baseline, thereby promoting additional drug seeking. Thus, these data could provide neurochemical support for

behavioral studies showing EE mice are less likely to self-administer cocaine. Follow-up experiments are being done with DBA/2J mice, a strain that has been shown to be more affected by housing conditions relative to C57BL/6J mice in some behavioral assays.

Disclosures: J.F. Comstock: None. **S.A. Towers:** None. **N.B. Paige:** None. **A.M. Byrn:** None. **P.E. Dickson:** None. **D.B. Lester:** None.

Poster

647. Synaptic Transmission: Modulation and Mechanisms III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 647.11/B101

Topic: B.06. Synaptic Transmission

Title: Effects of subchronic oxytocin treatment on social behavior following social isolation in juvenile mice

Authors: K. BERRY[1], M. K. ESTES[2], N. B. PAIGE[2], M. MEADOWS[1], D. B. LESTER[2], ***T. D. ROGERS**[1];
[1]Middle Tennessee State Univ., Murfreesboro, TN; [2]The Univ. of Memphis, Memphis, TN

Abstract: Social isolation during adolescence has been shown to produce a variety of abnormal behaviors in mice. However, the neurochemical effects of social isolation during adolescence have not been fully described. Additionally, sex-specific changes in behavior following social isolation have yet to be fully explained. In the current study, male and female juvenile C57BL/6 mice were group-housed or housed in isolation for three weeks beginning at three weeks of age. Mice were then subchronically pretreated with either saline or oxytocin (1.0 mg/kg, i.p.). Subchronic pretreatment consisted of four i.p. injections separated by 48 hours which has been previously shown to effectively alter dopamine neurotransmission and prosocial behavior in mice. Mice were then tested in the three-chamber sociability test which is a commonly used method to test social approach behaviors and preference for social novelty. The test was conducted in a clear, plexiglass box with three chambers. The chambers are separated by clear dividers which have passages for the experimental mouse to move between the chambers. The center chamber remained empty while the side chambers each contained a wire pencil cup placed upside down. The test included three ten-minute phases. During the first phase, mice were allowed to habituate to the novel environment. In the second-phase, mice were presented with a social stimulus, a novel conspecific, in one of the pencil cups. The mouse was allowed to approach the novel social stimulus without the stimulus moving around in the chamber. During the third phase, a second mouse was introduced into the remaining pencil cup. The experimental mouse was allowed to choose to interact with either the now familiar social stimulus or the novel stimulus. Male mice displayed more social approach during phase two than females, and isolated mice displayed more social approach than group-housed mice. Isolation reduced social novelty

preference in males while increasing total social approach in both males and females during phase three. Oxytocin exaggerated social novelty preference in males and in group-housed females. The current research demonstrates the need to further investigate the behavioral, neurochemical, and sex-specific effects of early social isolation in mice.

Disclosures: T.D. Rogers: None. **K. Berry:** None. **M. Meadows:** None. **D.B. Lester:** None. **M.K. Estes:** None. **N.B. Paige:** None.

Poster

647. Synaptic Transmission: Modulation and Mechanisms III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 647.12/B102

Topic: B.06. Synaptic Transmission

Title: Systemic oxytocin treatment reverses the effect of social isolation on mesolimbic dopamine release

Authors: *M. K. ESTES[1], N. B. PAIGE[1], M. N. MILLS[1], T. D. ROGERS[2], D. B. LESTER[1]; [1]Psychology, Univ. of Memphis, Memphis, TN; [2]Psychology, Middle Tennessee State Univ., Murfreesboro, TN

Abstract: Oxytocin has been shown to reduce drug seeking in rodents and is being examined in clinical trials as a relapse-prevention treatment. The mesolimbic dopamine system, which consists of midbrain dopamine neurons that project to the nucleus accumbens (NAc), is known to play a vital role in drug abuse. We have recently shown that mice subchronically pretreated with oxytocin (1.0 mg/kg, i.p.) had a reduced dopaminergic response to a psychostimulant. The present study aimed to determine whether this oxytocin treatment could rescue abnormal dopamine functioning. Social isolation in rodents has been shown to increase psychostimulant self-administration and sensitization. In this study, male and female mice were either group-housed or isolated for 3 weeks following weaning, then subchronically pretreated with either oxytocin (1 mg/kg) or saline. Subchronic pretreatment consisted of 4 i.p. injections administered every 48 hours. Fixed potential amperometry was used to quantify VTA-stimulated dopamine release in the NAc of anesthetized mice before and after cocaine administration. Overall, females seemed to be more affected by social isolation than males on the variables measured. Specifically, saline-pretreated isolated females displayed increased baseline (pre-cocaine) dopamine release and an increased dopaminergic response to cocaine compared to other groups. Interestingly, these altered profiles of dopamine functioning were not observed in the isolated mice pretreated with oxytocin. These results demonstrate one aspect of the neurochemical impact of social isolation, particularly in females. The present findings further suggest that oxytocin pretreatment can reverse isolation-induced changes in the dopaminergic functioning, perhaps

providing insight on neurochemical mechanisms for behavioral studies showing oxytocin reduces drug seeking and other addiction-related behaviors.

Disclosures: **M.K. Estes:** None. **N.B. Paige:** None. **M.N. Mills:** None. **D.B. Lester:** None. **T.D. Rogers:** None.

Poster

647. Synaptic Transmission: Modulation and Mechanisms III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 647.13/C1

Topic: B.07. Synaptic Plasticity

Support: CONACYT-481709
SIP-IPN 2018 1021
IBRO, LARC, PROLAB, program.

Title: Effect of the levetiracetam on the synaptic plasticity in the dentate gyrus of the hippocampus of rats in the chronic phase of the temporal lobe epilepsy

Authors: *G. GONZÁLEZ-HERNÁNDEZ[1], I. J. CONTRERAS-GARCÍA[2], K. B. SÁNCHEZ-HUERTA[3], L. R. GALLARDO-GUDIÑO[4], J. G. MENDOZA-TORREBLANCA[3], C. M. QUEIROZ[5], S. R. ZAMUDIO-HERNÁNDEZ[1];
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Abstract: Temporal Lobe Epilepsy (TLE) is a chronic-degenerative neurological pathology, characterized by the appearance of seizures that causes changes in synaptic plasticity of intra-hippocampal circuits, causing learning and memory deficits. Recently, it was observed that the treatment with levetiracetam (LEV) during the period of epileptogenesis attenuated the cognitive deficits in a TLE model, But, it is unknown whether LEV, in addition to its anticonvulsant and neuroprotective effects, has any beneficial effect on the deficit of synaptic plasticity when is administered during the chronic phase of TLE. Thus, in this study the effect of LEV on the alterations of the synaptic plasticity of the hippocampal dentate gyrus (DG) of rats with TLE induced with lithium-pilocarpine was evaluated. Male Wistar rats were allocated in 4 groups: Control, Control-LEV, Epileptic and Epileptic-LEV. LEV (300 mg/kg/day) was administered along 7 days in the chronic phase of TLE. 3 days after the end of treatment, the rats were anesthetized and subjected to stereotaxic surgery where a concentric bipolar electrical stimulation electrode was implanted in the perforating pathway, and a concentric monopolar recording electrode was implanted in the hilus of the DG. An I/O curve protocol was applied,

with intensities from 50 to 1500 µA. An electrical stimulation protocol was also used for synaptic depression and facilitation by paired pulses in the perforating pathway, at inter-pulse intervals of 10, 20, 30, 70 and 250 ms with three intensity levels of 20, 50 and 100%. Finally, Long-Term Potentiation (LTP) was induced by triggering trains of 400 Hz using a stimulation intensity of 1500 µA. The evoked local field potentials were recorded and measured as EPSP slope and population spike (PS) amplitude. In the I/O curve protocol, Epileptic animals presented an increase in the amplitude of the PS with respect to Control and Control-LEV groups, interestingly; LEV in the Epileptic-LEV group reduced such increase in PS amplitude, but without reached control levels. In the depression and facilitation by paired pulses, a decrease in the facilitation and an increase in the depression in the Epileptic group were observed with respect to the controls; though, the epileptic group treated with LEV did not present a difference with respect to the Epileptic group. In LTP, it was observed that the Epileptic animals had a reduction of LTP with respect to the controls; however, the epileptic group treated with LEV did not reverse such alteration. It was concluded that LEV only reduced the excitability of the neuronal circuit but did not reverse the alterations on synaptic plasticity caused by ELT in its chronic phase.

Disclosures: G. González-Hernández: None. **I.J. Contreras-García:** None. **K.B. Sánchez-Huerta:** None. **L.R. Gallardo-Gudiño:** None. **J.G. Mendoza-Torreblanca:** None. **C.M. Queiroz:** None. **S.R. Zamudio-Hernández:** None.

Poster

647. Synaptic Transmission: Modulation and Mechanisms III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 647.14/C2

Topic: B.03. G-Protein Coupled Receptors

Support: ITF Grant MRP/101/17X
GRF Grant 11102417M
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Title: Cholecystokinin released from GABAergic neurons enhances inhibition function in the auditory cortex

Authors: *H. LING;
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Abstract: The neocortex mainly comprises pyramidal cells and non-pyramidal cells. Inhibition process is mainly mediated by some interneurons via the release of γ-Aminobutyric acid (GABA) from their terminals.GABAergic cholecystokinin (CCK) neurons are one of the major populations of interneurons in the auditory cortex (ACx). We injected the AAV-DIO-ChR2 with promoter (EF1α, elongation factor 1α), into ACx of Vgat-ires-cre mice, which restrictedly expressed Cre recombinase into GABAergic neurons. In the auditory cortex, a laser stimulation of the GABAergic CCK neurons induced an inhibitory response to an auditory stimulus that follow the laser stimulus. We hypothesized that high-frequency stimulation (HFS) of the GABAergic neurons induce the CCK release, which leads to enhance the inhibition of their own outputs to other cortical neurons. Also, we injected the pAAV-mU6-CAG-ChR2 with Cre-dependent U6-shRNA (CCK specific) cassette into Vgat-ires-cre mice to specifically knock down the expression of CCK in GABAergic neurons. The response to an auditory stimulus increased after laser stimulation with a lower CCK expression in GABAergic CCK neurons. We further hypothesized that a third receptor, CCK-C receptor, may exist in brain functioning in the inhibitory circuits on top of CCK-A and B receptors. Thus, we first utilized CCK-A/B receptor knock-out (CCK-AB-KO) mice in electrophysiology experiments. Auditory response was inhibited by a proceeded laser-stimulation of GABAergic neurons. The inhibition on the auditory responses was enhanced after high-frequency stimulation (80Hz, 100 pulses X 10, HFS). The same enhanced effect of inhibition was induced by CCK application that was followed by LFS. Neuronal responses in field potential to auditory stimulus was suppressed after HFS or CCK application in the auditory cortex. This enhanced inhibition disappeared after application of CCK antagonist: L365,260 before the HFS. In CCK-KO mouse, no significant change was observed the neuronal responses to either electrical stimulation or auditory stimulus. The results in the present study indicated that the inhibitory neuronal circuit in the neocortex could be enhanced by the high-frequency firing of GABAergic CCK neurons, through a possible new receptor, CCK-C receptor.

Disclosures: H. Ling: None.

Poster

647. Synaptic Transmission: Modulation and Mechanisms III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 647.15/C3

Topic: B.06. Synaptic Transmission

Support: W81XWH-15-1-0521 DOD Award

Title: Allopregnanolone: A biomarker candidate for mood disorders

Authors: *G. PINNA;
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Abstract: Major depressive disorder and posttraumatic stress disorder (PTSD) are complex, highly prevalent and debilitating psychiatric conditions characterized by poor life expectancy and destructive behaviors. Current diagnosis is based on subjective rather than objective measures leading to misdiagnose and ineffective treatments. Recent advances in the field using more reliable animal models, novel technologies and neurobiological methods have offered a number of promising biomarker candidates to diagnose depression and PTSD more accurately. These biomarkers also offer new means to treating patients more efficiently. During the past decade, several studies have consistently documented a downregulation of the GABAergic neurosteroid allopregnanolone and its equipotent isomer pregnanolone (PA) in serum, plasma, cerebrospinal fluid (CSF) and post-mortem brain from patients with major depression and PTSD. Remarkably, the FDA has recently approved allopregnanolone (i.e., brexanolone) as the first specific treatment for post-partum depression. This new treatment is characterized by a high response-rate, rapid-acting pharmacological effects and long-lasting behavioral improvements. Now, the question arises as to whether allopregnanolone can be developed as a reliable biomarker to predict susceptibility to mood disorders, reliably diagnose depression and PTSD, and whether neurosteroid-based therapeutics offer a reasonable advantage over commonly administered traditional antidepressants. While the potential role of neurosteroid biosynthesis and their function as biomarkers for mood disorders is fascinating, more work is still required to firmly establish their diagnostic role. Furthermore, the identification of a *biomarker axis* that takes into account the interplay and synergism of several biomarkers is suggested as a base of support to univocally identify and discriminate disorders with large comorbidity and symptoms overlap and to develop individualized treatments.
Supported by W81XWH-15-1-0521 DOD Award GP.

Disclosures: G. Pinna: None.

Poster

647. Synaptic Transmission: Modulation and Mechanisms III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 647.16/C4

Topic: B.06. Synaptic Transmission

Support: P50AA022538 NIAAA-NIH grant
VA Senior Research Career Scientist award
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Title: Altered $GABA_A$ receptor subunit expression and neurosteroid biosynthesis in subjects with alcohol use disorder

Authors: *E. GATTA[1], A. GUIDOTTI[1], D. ASPESI[2], D. R. GRAYSON[1], S. C. PANDEY[1,3], G. PINNA[2];

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Abstract: Alcohol use disorder (AUD) is a chronic relapsing disorder affecting 6% of the US adult population. Few studies have investigated the mechanisms whereby alcohol affects $GABA_A$ receptor ($GABA_AR$) subunit composition and alters GABAergic allosteric modulation elicited by neurosteroids. We recently showed reduced $GABA_AR$ δ subunit expression in the cerebellum of AUD subjects suggesting an impaired sensitivity of $GABA_AR$ to neurosteroids. The long-term effects of alcohol exposure on neurosteroid biosynthesis and its consequences on GABAergic neurotransmission in individuals with AUD remain underinvestigated. In a cohort of postmortem brains from 25 pairs of controls and AUD subjects (New South Wales Brain Tissue Resource Centre, University of Sydney, Australia), we determined the mRNA expression of several $GABA_AR$ subunits by RT-qPCR. Protein levels were determined by Western Blot and neurosteroids were quantified by gas chromatography-mass spectrometry (GC-MS). We observed reduced α_2 and δ subunit mRNA expression in prefrontal cortex, hippocampus, striatum and cerebellum of AUD subjects. Like the δ subunit, α_2 protein expression was decreased in the cerebellum of AUD subjects. These data suggest that both synaptic (α_2) and extrasynaptic (δ) $GABA_AR$ subtypes might be affected in AUD. Modulation of the extrasynaptic $GABA_AR$-mediated inhibition is enhanced by allopregnanolone (Allo) and its equipotent GABAergic isomer, pregnanolone (PA). Neurosteroid biosynthesis is initiated by cholesterol translocation into the inner mitochondrial membrane by the 18 kDa translocator protein (TSPO). Cholesterol is then converted by P450scc into pregnenolone, which is further metabolized into progesterone by 3β-hydroxysteroid dehydrogenase (3β-HSD). 5α-reductase Type 1 (5α-R1) and 3α-HSD then convert progesterone into Allo. Thus, we studied neurosteroid biosynthesis in the cerebellum and observed reduced TSPO, 5α-R1 and 3α-HSD mRNA expression in AUD, with no changes in 3β-HSD. As expected, this resulted in reduced levels of Allo and PA in the cerebellum. Whether changes in $GABA_AR$ subunit expression result from a direct effect of alcohol or whether this is secondary to alcohol affecting neurosteroid biosynthesis remains to be investigated. Given the role of Allo in regulating the fine-tuning of $GABA_AR$, our data suggest that alcohol-induced impairments in GABAergic neurotransmission might be profoundly impacted by reduced neurosteroidogenesis.
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Poster

648. Transcription and Translation in Plasticity I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 648.01/C5

Topic: B.07. Synaptic Plasticity

Support: Fondecyt grant 1191152

Title: Dynamical physical interaction between RCOR2 and SC35 in nuclear speckles. implications for regulating alternative splicing in neurons

Authors: F. A. GUZMÁN, C. RIVERA, D. ARANCIBIA, ***M. E. ANDRES**;
Cell. and Mol. Biol., Pontificia Univ. Catolica de Chile, Santiago, Chile

Abstract: RCOR2 (CoREST2) is a transcriptional corepressor that belongs to the CoREST family (RCOR1, RCOR2, and RCOR3), which interacts with the enzymes LSD1 (Lysine-specific demethylase-1) and HDAC1/2 (Histone deacetylase 1/2) to form complexes that determinate the neuronal phenotype. It has been shown that RCOR2 plays a key role in maintaining pluripotency in stem cells. RCOR2 knockout mice models have shown that this protein is essential for cortical development, balancing proliferation with differentiation process. Our lab has described that CoREST proteins have distinct biochemical properties that lead to different transcriptional repressive capacities. However, whether each CoREST protein has a specific function is unknown. In this work, we show that CoREST proteins occupy different compartments in cells including neurons. Surprisingly, we observed that RCOR2 forms nuclear protein cumulus resembling non-membranous organelles. Also, we present evidence that RCOR2 colocalizes with the typical nuclear speckle protein SC35, and deletion of the C-terminal end of RCOR2, which is a low complexity region rich in basic amino acids, abolished its localization in the nuclear speckles. RCOR2 interacts with SC35, and decreasing RCOR2 levels using siRNAs reduces SC35 levels too. Nuclear speckles are protein-RNA bodies specialized in splicing regulation and maturation of pre-mRNAs. Therefore, our data suggest that RCOR2 may have a role in controlling mRNA splicing and maturation.

Disclosures: F.A. Guzmán: None. **C. Rivera:** None. **D. Arancibia:** None. **M.E. Andres:** None.

Poster

648. Transcription and Translation in Plasticity I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 648.02/C6

Topic: B.07. Synaptic Plasticity

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NIH 5R01MH101491
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NSF (CBET)180 4220
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NSF GRFP
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Title: Self-cleaving CPEB3 ribozyme regulates pre-mRNA processing and modulates polyadenylation in the mouse hippocampus

Authors: *C. CHEN[1], L. TONG[1], M. NIKAN[4], C. W. COTMAN[1], E. SWAYZE[4], M. A. WOOD[2], A. LUPTAK[3];
[2]Neurobiol & Behavior, [3]Pharmaceut. Sci., [1]Univ. of California Irvine, Irvine, CA; [4]Neurosci. Drug Discovery, Ionis Pharmaceuticals, Carlsbad, CA

Abstract: Transcriptional regulation, *de novo* protein synthesis, and molecular and cellular cascades have been implicated in long-lasting forms of neuronal plasticity and memory processes. Cytoplasmic polyadenylation element binding protein 3 (CPEB3) is an RNA-binding protein that modulates dendritic polyadenylation-induced mRNA translation, which is essential for persistence of memory. Previous studies identified a human self-cleaving CPEB3 ribozyme through *in vitro* selection, and demonstrated the ribozyme contains a single nucleotide polymorphism (SNP) that has been correlated with the function of CPEB3 in episodic memory. However, very little is known about the role of CPEB3 ribozyme in the regulation of CPEB3 mRNA processing in neurons. In this study, we inhibited CPEB3 ribozyme *in vitro* and *in vivo* using novel antisense oligonucleotides (ASOs), which is a particularly effective tool to study the function of a ribozyme such as CPEB3. Using primary neuronal cultures, we demonstrated that CPEB3 ribozyme activity was inhibited in the presence of ASOs. Application of the lead ASO targeting the CPEB3 ribozyme resulted in an increase in CPEB3 mRNA and protein expression in neurons. The inhibition of the CPEB3 ribozyme followed by neuronal stimulation increased GluA1, PSD-95, and NMDAR2B protein expression, suggesting the role of CPEB3 ribozyme is activity-dependent. Furthermore, administration of ASOs into the mouse CA1 region of the hippocampus resulted in an inhibition of CPEB3 ribozyme activity, which in turn led to an increase in CPEB3 mRNA expression and GluA2 polyadenylation. Collectively, these results

suggested a possible mechanism by which the CPEB3 ribozyme regulates synaptic structure and function required for learning and memory.

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Poster

648. Transcription and Translation in Plasticity I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 648.03/C7

Topic: B.07. Synaptic Plasticity

Title: Isoform specific transcriptional regulation of lipophorin receptors generate functional diversity

Authors: J. YIN, ***E. SPILLMAN**, J. SHORT, C. SHENG, M. GIBBS, Q. YUAN; NINDS, NIH, Bethesda, MD

Abstract: Lipids are essential building blocks for cell membranes and organelles. They also have versatile roles in regulating cellular metabolism and signaling events. In the nervous system, lipid synthesis, uptake, and recycling involve complex neuron-glia interactions, which, although functionally important, remain poorly characterized. How do neurons acquire and utilize the lipid supply? And how are these processes monitored and regulated during development? These are outstanding questions we are trying to study using Drosophila as a model system. Ventral lateral neurons (LNvs) in the larval brain are projection neurons which receive synaptic inputs from the photoreceptors. Altering visual experience generates profound impacts on both structural and physiological properties of developing LNvs. Through a combination of cell-type-specific RNA-seq analyses and genetic studies, we identified isoform-specific expression of lipophorin receptors LpR1 and LpR2 in LNvs. Uncovering LpRs' roles in supporting dendrite morphogenesis and synaptic functions in the CNS. We also provided evidence for the activity-dependent transcriptional regulation of LpRs and offer a mechanism for augmenting the capacity of lipoprotein uptake in response to alterations of synaptic activity. To further understand the physiological significance of isoform-specific regulation of LpRs, we performed additional cell biological studies on short and long-isoforms of LpRs by examining their cellular distributions, involvement in the endocytic pathway and associations with lipoproteins. Our results show that isoform-specific transcriptional regulation generates LpRs with diverse structural and functional properties. In conjunction with previous studies, our findings provide in vivo evidence for neuronal lipoprotein receptors serving as targets of cell-type specific transcriptional regulation. This contributes to distinct modes of lipid uptake in different cell types, an important regulatory mechanism that serves unique functional requirements of neurons.

Disclosures: **J. Yin:** None. **E. Spillman:** None. **J. Short:** None. **C. Sheng:** None. **M. Gibbs:** None. **Q. Yuan:** None.

Poster

648. Transcription and Translation in Plasticity I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 648.04/C8

Topic: B.07. Synaptic Plasticity

Support: Guangdong Science and Technology Department Grant 2017B030314026
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Title: Increased neuropeptide VGF expression through post-transcriptional auto-feedback mechanisms improves cognitive functions

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Abstract: The expression of VGF (nonacronymic), a secreted neuropeptide precursor, can be induced in the brain by hippocampus-dependent learning and physical exercise. TLQP-62, a 62 amino acid peptide derived from the C-terminal region of the VGF precursor, has been shown to enhance neuronal activity in both cultured hippocampal neurons and hippocampal slices, and its direct administration to the hippocampus *in vivo* additionally results in increased neurogenesis, antidepressant-like effects, and memory enhancement in rodent models. While *Vgf* gene expression can be robustly regulated via CREB-dependent transcriptional activation in response to neuronal depolarization or growth factor treatment, for example, little is known about post-transcriptional regulatory mechanisms of VGF expression. Here we show that TLQP-62 can rapidly increase VGF translation in the absence of measurable increases in VGF mRNA levels, via an mTOR-dependent signaling pathway. Luciferase reporter-based assays suggest that the mouse 3'-untranslated region (3'UTR) of VGF mRNA reduces protein expression compared to the 3'UTR of mouse Gapdh. Consistent with the translational repression of VGF mRNA that is conferred by its 3' UTR, truncation of the endogenous VGF mRNA 3'UTR, results in dramatic elevation of VGF protein levels both in cultured neurons and mouse brains. Phenotypic analysis of this *Vgf* 3'UTR-truncated mouse model reveals enhanced memory performance, and anxiolytic and antidepressant-like effects, consistent with increased VGF expression. Our results identified a rapid, transcription-independent induction of VGF protein levels that is triggered by TLQP-62 peptide treatment, *in vitro*, and contextual fear memory training, *in vivo*. Moreover, we noted similar rapid induction of several other related chromogranin and secretogranin proteins

following memory training, suggesting that the rapid, positive feedforward increase in the synthesis of dense core vesicle secreted proteins could be a general mechanism to replenish stores that have been released in response to neuronal activation.

Disclosures: **W. Lin:** None. **C. Jiang:** None. **J. Wu:** None. **Y. Zhao:** None. **X. Ye:** None. **S.R. Salton:** None.

Poster

648. Transcription and Translation in Plasticity I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 648.05/C9

Topic: B.07. Synaptic Plasticity

Support: Canada First Research Excellence Fund, awarded to McGill University for the Healthy Brains for Healthy Lives initiative
CIHR PG 389378
NSERC DG 2017-04730
FRQS CB Sr 254033

Title: Differential role of presynaptic translation in evoked and spontaneous release

Authors: *H. H.-W. WONG, P. J. SJÖSTRÖM;
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Abstract: The roles of postsynaptic molecules in neurotransmission have been well characterized and constitute important neuroscience principles. However, due in part to low accessibility, less is known about the contribution of the presynaptic terminal to long-term changes in neurotransmission. Axonal local protein synthesis (PS) has emerged as a major mechanism to regulate localized growth responses during development. This efficient process allows proteins to be strategically synthesized at the right time and place to optimally carry out biological functions. Latest evidence is pointing to potential roles of local PS in mature neurons, raising the possibility that axonal local PS may contribute to neurotransmission.
Using quadruple patch clamp, we explored the acute effect of PS inhibition on spontaneous and evoked excitatory release onto layer-5 pyramidal cells in acute visual cortex slices from P11-16 C57BL/6 mice. Acute PS inhibition with cycloheximide (CHX) wash-in increased the rate of spontaneous release after 10-20 minutes (140% ± 16%, n = 9 vs. 96% ± 8% in control, n = 8, $p < 0.05$), consistent with rapid, local PS. Although the rate of spontaneous release was upregulated for as long as monitored (~7 hours; 1.7 ± 0.3 Hz, n = 33 vs. 1.1 ± 0.1 Hz in control, n = 91, $p < 0.01$), it was not correlated with CHX incubation time ($r = 0.13$, $p = 0.5$, n = 33), suggesting that basal PS serves as a constitutive regulatory mechanism to maintain spontaneous release. We eliminated a possible postsynaptic contribution by intracellular CHX loading, while additionally

showing that the rate was increased by CHX wash-in during postsynaptic CHX loading (139% ± 14%, n = 10 vs. 85% ± 7% in CHX-loading control, n = 9, $p < 0.01$).
Spontaneous release rate is commonly used as a metric of presynaptic release probability. We therefore speculated that PS inhibition would upregulate evoked release as well. Surprisingly, CHX wash-in reduced EPSP amplitude (59% ± 8%, n = 8 vs. 97% ± 2% in control, n = 12, $p < 0.001$) by reducing release, as evidenced by analysis of the change in paired-pulse ratio (ΔPPR: 0.18 ± 0.06, n = 8 vs. -0.0066 ± 0.02 in control, n = 12, $p < 0.01$) and coefficient of variation ($1/CV^2$ normalized: 37% ± 6% vs. 106% ± 28% in control, $p < 0.05$). PS inhibition thus differentially affected evoked and spontaneous release.
Taken together, our findings demonstrate specific roles of presynaptic translation in tuning neurotransmission. Moreover, presynaptic translation confers a dichotomy in activity-dependent and activity-independent neurotransmitter release mechanisms.

Disclosures: H.H. Wong: None. **P.J. Sjöström:** None.

Poster

648. Transcription and Translation in Plasticity I

Location: Hall A

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Program #/Poster #: 648.06/C10

Topic: B.07. Synaptic Plasticity

Support: NIH grant NS034007
NIH grant NS047384
NIH grant HD082013
NIH training grant T32MH019524

Title: Characterization of the mTORC1 effector PDCD4 in activity dependent translation and memory

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Abstract: The formation of eukaryotic initiation 4F (eIF4F), a critical, rate limiting step in cap dependent translation initiation, is relevant to both normal memory function and disease. Increased expression of eukaryotic initiation factor 4E (eIF4E) or deletion of its repressor eukaryotic factor 4E binding protein 2 (4E-BP2) causes autistic endophenotypes in mice. Inhibitors of either the interaction of eIF4E with eukaryotic initiation factor 4G (eIF4G) or the eukaryotic initiation factor 4A (eIF4A) have also been shown to affect protein synthesis in brain slices and to disrupt long-term potentiation. Targeting eIF4A, the DEAD box helicase in eIF4F, in cancer cells decreases translation of specific targets and reduces cell growth, showing promising preclinical efficacy. In cells eIF4A1 is inhibited by programmed cell death 4 (PDCD4)

which can be phosphorylated by S6K1 and broken down by the proteasome pathway in cancer cells to permit protein synthesis and cell growth. Our data show that PDCD4 is also down regulated by neuronal stimulation and that the pathway responsible for this regulation is both S6K1- and proteasome-dependent in a similar manner as seen in cancer. Moreover, in contrast to non-neuronal cell types, PDCD4 is present in the cell body as well as dendrites and its overexpression in neurons causes a decrease in dendrite complexity. The localization and down-regulation of PDCD4 implicates the importance of PDCD4 and eIF4A1 as mTORC1 effectors in not only activity-dependent translation but also synaptic plasticity and memory function. To test this idea we have begun to examine synaptic function and behavior and memory processes in PDCD4 knockout mice. In summary, our findings indicate that PDCD4 acts as a downstream effector of mTORC1 and thus, is an important regulator of activity-dependent translation.

Disclosures: I. Kats: None. **F. Longo:** None. **E. Klann:** None.

Poster

648. Transcription and Translation in Plasticity I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 648.07/C11

Topic: B.07. Synaptic Plasticity

Support: 1R21NS104249

Title: Mitochondria dependent metabolic programming drives long term potentiation and synaptic maturation

Authors: *H. ROLYAN[1], P. MIRANDA[2], H.-A. PARK[2], S. SACCHETTI[2], K. ALAVIAN[4], N. MNATSAKANYAN[2], P. LICZNERSKI[5], H. IMAMURA[6], H. NOJI[7], J. SHEPHERD[8], A. CHAVEZ[9], S. ZUKIN[10], E. JONAS[3];
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Abstract: Long-term potentiation (LTP) and depression (LTD) are mechanisms of inherent synaptic plasticity of neurons and support the storage and recovery of memories in the mammalian brain. The ability to potentiate a synapse long-term declines significantly in neurodegenerative disorders. In keeping with deficiencies in synaptic plasticity, degenerating neurons display acute and chronic mitochondrial dysfunction, suggesting that dysregulated mitochondria play a role in synaptic dysfunction, separately from their role in apoptotic cell

death. Our previous work has shown that the anti-apoptotic protein Bcl-xL not only prevents apoptosis, but also potentiates long-term synaptic responses. Here, we present that Bcl-xL is required for dramatic changes in ATP levels in hippocampal neurons during LTP stimulation and progression. Using fluorescence imaging with a FRET based ATP construct (ATeam) in live hippocampal neurons, we find that LTP induction causes a sharp decrease in ATP levels followed by a persistent long-term increase in ATP production, suggesting that intense synaptic stimulation requires neurons to be metabolically more efficient. In agreement with this, the late phase increase in ATP levels is associated with decreases in oxygen consumption by single neurons and with maturation of dendritic spines. The LTP-associated increase in ATP levels and maturation of dendritic spines is blocked by application of Bcl-xL specific inhibitors and also by inhibition of mitochondrial ATP synthase activity. Bcl-xL inhibition also prevents the LTP induced increase in surface glutamate receptor insertion. In hippocampal slice recordings, inhibition of Bcl-xL impairs early stage LTP and prevents late stage LTP. Our findings suggest that long-term changes in mitochondrial efficiency brought on by activity-dependent Bcl-xL translocation to mitochondria are required for LTP and shed light upon the role of mitochondrial metabolic plasticity in acute induction and long-term maintenance of learning and memory processing. If such mitochondria-dependent metabolic changes fail to occur, synaptic dysfunction and neurodegeneration may ensue.

Disclosures: **H. Rolyan:** None. **P. Miranda:** None. **H. Park:** None. **S. Sacchetti:** None. **K. Alavian:** None. **N. Mnatsakanyan:** None. **P. Licznerski:** None. **H. Imamura:** None. **H. Noji:** None. **J. Shepherd:** None. **A. Chavez:** None. **S. Zukin:** None. **E. Jonas:** None.

Poster

648. Transcription and Translation in Plasticity I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 648.08/C12

Topic: B.07. Synaptic Plasticity

Support: NIH grant DP1NS096787
NIH grant R01MH080047
Max Planck Florida Institute for Neuroscience

Title: *In vivo* imaging of the coupling between neuronal and CREB activity in the mouse brain

Authors: ***T. LAVIV**[1], B. SCHOLL[1], P. PARRA-BUENO[1], B. FOOTE[1], C. ZHANG[2], L. YAN[1], J. CHU[2], R. YASUDA[1];
[1]Max Planck Florida Inst., Jupiter, FL; [2]CAS Key Lab. of Hlth. Informatics & Res. Lab. for Biomed. Optics and Mol. Imaging, Shenzhen Inst. of Advanced Technol., Shenzen, China

Abstract: Sensory experiences exert long-term modifications of neuronal circuits by regulating activity-dependent transcription programs, which are vital for regulation of long-term plasticity and learning. However, it has not been possible to precisely determine the interplay between neuronal activity patterns and transcription factor activity. Here we present a technique to image *in vivo* signaling of CREB, an activity-dependent transcription factor important for synaptic plasticity, using 2-photon fluorescence lifetime imaging (2pFLIM) with new FRET biosensors. Combination of red-shifted CREB sensor and GCaMP imaging allowed simultaneous imaging of CREB and calcium dynamics at single cells. With this approach, we explored how experience shapes the interplay between CREB and neuronal activity in the visual cortex of awake mice. We found that dark rearing augmented the sensitivity and persistence of visually evoked CREB activity, thereby shifting the threshold for neuronal activity-transcription coupling. This technique will allow to unravel the transcriptional dynamics underlying experience-dependent plasticity in the brain.

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Poster

648. Transcription and Translation in Plasticity I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 648.09/C13

Topic: B.07. Synaptic Plasticity

Title: Genome-wide gene expression profiling of spinal cord in a mouse model of neuropathic pain

Authors: *S. UTTAM[1], M. PARISIEN[2], S. JAFARNEJAD[3], M. AMIRI[1], F. BEAUDRY[4], L. DIATCHENKO[5], A. KHOUTORSKY[5];
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Abstract: Acute pain serves as a protective mechanism, guiding the organism away from actual or potential tissue injury. In contrast, chronic pain is a debilitating condition without any obvious physiological advantage. This supports the notion that, the transition to, and the maintenance of chronic pain rely on different gene expression patterns to support biochemical and structural changes within the pain pathway. Gene expression can be regulated at various levels including transcription and translation. While transcriptomics in pain is widely studied, there have been only very few studies aimed at identifying translationally regulated genes. Regulation of mRNA

translation has emerged as an important step in the control of protein expression in the cell. However, mRNAs whose translation is altered in different stages of chronic pain remain largely unknown. In this study we perform genome-wide translational profiling using Ribosome profiling in parallel with transcription profiling using RNA-Seq of dorsal spinal cord in a mouse model of chronic neuropathic pain. We also performed proteomics to assess the relative contribution of transcription and translation regulation toward protein levels. We perform this multi-level gene expression profiling at early and late time points to investigate the difference in gene expression pattern, between the induction and the maintenance stages of chronic pain. Interestingly, preliminary analysis shows that, while both transcription and translation regulation are exerted in the early stage, transcriptional regulation subsides by the late stage, and a new pattern of translation regulation emerges.

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Poster

648. Transcription and Translation in Plasticity I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 648.10/C14

Topic: B.07. Synaptic Plasticity

Support: National Institute Of Mental Health, R43MH119989

Title: Brain-wide measurement of neuronal activity at cellular resolution

Authors: C. LO[1,2], R. AZEVEDO[1,2], A. A. KEISER[1], M. PETERS[3], M. A. WOOD[1], S. P. GANDHI[1,2], *D. G. WHEELER[2,4];
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Abstract: Environmental stimuli initiate a cascade of activity-dependent signaling events that alter gene expression in specific sets of neurons. This process of excitation-transcription coupling drives activity-dependent expression of immediate-early genes (IEGs) such as c-Fos, Arc and Egr1 (Zif268). Using *in situ* hybridization, immunostaining or transgenic reporter animals, these genes have been used as surrogate markers for neuronal activity driven by environmental stimuli. For instance, much recent work has exploited the activity-dependence of c-Fos to mark neuronal ensembles associated with memory traces. However, while traditional IEGs such as Fos have played an invaluable role in identifying activity-dependent circuitry, the expression of these genes may not be entirely tuned to neuronal activity alone. Traditional IEGs are transcribed in response to synaptic activity and Ca^{2+} entry, but also in response to growth

factor signaling, neurotrophins and neuromodulators. In contrast, the more recently identified IEG, Npas4, is selectively driven by neuronal activity, suggesting that it may be a purer marker of neuronal activation *in vivo*. We have developed a recombinant rabbit monoclonal antibody against Npas4 and demonstrated specific immunoreactivity in stimulated primary neurons and in tissue from WT and *npas4* KO mice. To increase the throughput of whole-brain histological imaging for IEGs, we are taking advantage of recent developments in tissue clearing, fluorescence light sheet imaging and computational alignment and cell detection. For tissue clearing, we optimized the iDISCO tissue clearing method for whole brain immunostaining. For imaging, we have developed the Mesoscale Imaging System used with the ZEISS Lightsheet Z.1 microscope, improving spatial resolution and imaging speed, allowing for visualization of an entire mouse brain in less than 3 hours. Further, we have developed machine learning-based methods that mediate the identification and quantification of individual immunostained cells across the entire intact mouse brain and the automated quantification of cell densities in >1,200 brain regions defined by the annotated Allen Brain Atlas. We are combining the use of our recombinant Npas4 Ab and our whole-brain imaging methodologies to provide a regional analysis activity-dependent gene induction in response to visual stimuli and contextual fear conditioning. We are also performing direct comparisons of neuronal activity pattern snapshots determined with Npas4 and c-Fos immunoreactivity. These studies will provide a powerful tool for measuring neuronal activity throughout the entire mouse brain.

Disclosures: **C. Lo:** A. Employment/Salary (full or part-time):; Translucence Biosystems LLC. **R. Azevedo:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Translucence Biosystems LLC. **A.A. Keiser:** None. **M. Peters:** None. **M.A. Wood:** 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.; Translucence Biosystems LLC. **S.P. Gandhi:** 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.; Translucence Biosystems LLC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Translucence Biosystems LLC. **D.G. Wheeler:** A. Employment/Salary (full or part-time):; Translucence Biosystems LLC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Translucence Biosystems LLC.

Poster

648. Transcription and Translation in Plasticity I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 648.11/C15

Topic: B.07. Synaptic Plasticity

Title: Cell-specific recruitment of unique patterns of activity-regulated genes in individual neurons

Authors: *C. V. NGUYEN[1], E. A. PATTIE[1], M. TIPPANI[1], D. J. HILER[1], S. R. SRIPATHY RAO[1], Y. WANG[1], N. J. EAGLES[1], B. J. MAHER[1,2,3], A. E. JAFFE[1,2,4,5,6], S. C. PAGE[1], K. M. MAYNARD[1], K. MARTINOWICH[1,2,3];
[1]The Lieber Inst. For Brain Develop., Baltimore, MD; [2]Dept. of Psychiatry and Behavioral Sci., [3]The Solomon H. Snyder Dept. of Neurosci., [4]Dept. of Mental Hlth., [5]Dept. of Human Genet., [6]Dept. of Biostatistics, Johns Hopkins Sch. of Med., Baltimore, MD

Abstract: Activity Regulated Genes (ARGs), including *Bdnf, Arc, Fos* and *Egr1*, are expressed in a rapid, transient manner following a variety of stimuli. Increased expression of these genes results in the initiation of well-characterized gene expression programs that support neuronal activity. As such, expression of these genes is commonly used as a proxy for demarcating activated neurons following behavior or other stimulation. However, whether unique patterns of ARGs are recruited in a cellular- and stimulus-specific manner is not well understood. Moreover, limited evidence exists to explain how unique combinations of ARGs are recruited to mark ensembles of activated neurons. To address this question, we examined ARG expression patterns using multiplex single-molecule RNA fluorescent *in situ* hybridization (smFISH) in mouse cortex following induction of widespread neuronal activity with electroconvulsive seizures. We found that the ARGs *Arc* and *Bdnf* are sometimes expressed in non-overlapping neuronal populations and differentially regulated by neuronal activity. To evaluate whether ARGs tag different ensembles of activated neurons *in vitro*, we similarly examined the expression patterns of ARGs in mouse cortical neuron cultures using smFISH following potassium chloride-induced depolarization (PCID). ARG expression following PCID has been shown to be altered in iPSC-derived neurons from schizophrenic patients, suggesting that examination of ARG expression in patient-derived human models is important. By performing RNAseq on human iPSC-derived neurons through the neural progenitor cell stage and early neuronal development, we found that a specific activity-regulated *BDNF* isoform containing untranslated exon 1 increases over development. We then investigated the response of human iPSC-derived neurons to PCID using qPCR for various ARGs. Induction of *BDNF* from both the activity-dependent exon 1 and exon 4 transcripts in human iPSC derived neurons following PCID is low, but expression of other ARGs, including *ARC, FOS* and *EGR1,* is upregulated. Similar to experiments in mouse cultures, multiplex smFISH was used to investigate activity-induced regulation of ARGs at single cell resolution in hiPSC-derived neurons across time. Our data suggest that differential ARG patterns represent dynamic molecular signatures, marking recruitment of neurons to specific ensembles.

Disclosures: C.V. Nguyen: None. **E.A. Pattie:** None. **M. Tippani:** None. **D.J. Hiler:** None. **S.R. Sripathy Rao:** None. **Y. Wang:** None. **N.J. Eagles:** None. **B.J. Maher:** None. **A.E. Jaffe:** None. **S.C. Page:** None. **K.M. Maynard:** None. **K. Martinowich:** None.

Poster

648. Transcription and Translation in Plasticity I

Location: Hall A

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Program #/Poster #: 648.12/C16

Topic: B.07. Synaptic Plasticity

Support: NIH R56 Grant MH113923
AHA Grant 19PRE34380056
NIH T32 Grant GM105538

Title: Proteomic landscape of genetically targeted neural systems

Authors: *V. DUMRONGPRECHACHAN, L. BUTLER, Y. KOZOROVITSKIY;
Neurobio., Northwestern Univ., Evanston, IL

Abstract: Neuromodulation is an essential process that regulates neuronal excitability, synaptic processing, and circuit activity across the vertebrate brain. Neuromodulators trigger complex intracellular signalling cascades resulting in effects that span multiple timescales. We hypothesized that long-term effects of neuromodulation involve changes in the proteomic landscape in a cell-type specific manner. However, current genetically-targeted proteomic approaches are limited to a timescale of a few days and are not optimal to investigate initial changes in the proteome with a timescale of hours. Here, we created a new Cre-dependent peroxidase reporter mouse line using CRISPR/Cas9 approach. In conjunction with exogenous biotin tag, genetically-encoded peroxidase can rapidly take snapshots of the proteome at earlier time points (hours). We validated Cre-dependent expression and activity by crossing the reporter line to various Cre-driver lines including VGlut2-Cre and VGAT-Cre. We showed that the proteome of Cre-positive cells were selectively labelled and enriched for mass spectrometry identification and quantification. Finally, we plan to use this novel approach to investigate changes in the proteomic landscape of glutamatergic and GABAergic neurons in the medial prefrontal cortex in response to rapidly-acting antidepressant ketamine.

Disclosures: V. Dumrongprechachan: None. **Y. Kozorovitskiy:** None. **L. Butler:** None.

Poster

648. Transcription and Translation in Plasticity I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 648.13/C17

Topic: B.07. Synaptic Plasticity

Support: Medical Research Council grant MR/L021064/1
BBSRC ICP studentship BB/M503356/1

Title: Sex differences in estradiol regulation of local protein synthesis and synaptic proteome

Authors: *D. P. SRIVASTAVA[1], P. RAVAL[2], S. MOSS[3], N. BRANDON[4];
[1]Inst. of Psychiatry, Psychology and Neuroscien, London, United Kingdom; [2]Inst. of Psychiatry Psychology and Neuroscience, King's Col. London, London, United Kingdom; [3]Tufts Univ., Boston, MA; [4]AstraZeneca, Cambridge, MA

Abstract: Estrogens, particularly 17beta-estradiol (estradiol), have repeatedly been shown to have long-lasting influences over learning and memory. The mechanisms underlying estrogenic-facilitation of memory are driven partly through activation of signalling cascades, resulting in modulation of synaptic structure and function. However, growing evidence indicates that estradiol can also rapidly modulate local protein synthesis (translation); the ability to produce nascent proteins near or at synapses, independent of gene transcription. However, the molecular and cellular mechanisms that underlie estradiol's ability to regulate local protein synthesis and subsequently, the consequence of modulating local protein translation of synaptic function and whether male and female brains utilise the same signalling mechanism to regulate this process are unknown. Using a combination of Surface Sensing of Translation (SUnSET) and fluorescent non-canonical amino acid tagging (FUNCAT) assays, we demonstrate that estradiol increases protein synthesis in acute hippocampal slices prepared from 10-12 week old male and ovariectomized (OXV'ed) female mice. This increase in protein synthesis was found to be independent of gene transcription indicting a local protein synthesis mechanism. Consistent with this, treatment with estradiol increased the number of active ribosomal complexes along dendrites and at synapses. Concurrently, an increase in the amount of newly synthesised protein was detected at synapses following estradiol treatment. This was further reflected by an increase in select synaptic proteins and an increase of these proteins at dendritic spines. Critically, the signalling pathways required for estradiol-induced protein synthesis differed between males and OVX'ed females. Surprisingly, this was not always reflected when individual proteins were examined, suggesting that estradiol employs both distinct and common signalling pathways to regulate the local synthesis of specific synaptic proteins. Taken together, our study suggests that the rapid modulation of local protein synthesis by estradiol may result in an increase in synaptic function in male and females and thus, contribute to the facilitation of cognition offered by estrogens; this however, occurs via distinct signalling mechanisms between sexes.

Disclosures: D.P. Srivastava: None. **P. Raval:** None. **S. Moss:** F. Consulting Fees (e.g., advisory boards); AstraZeneca. **N. Brandon:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); AstraZeneca.

Poster

648. Transcription and Translation in Plasticity I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 648.14/C18

Topic: C.08. Ischemia

Support: JSPS (KAKEN No.18K16555)

Title: Expression of mitochondrial uncoupling protein 4 in association with ATP-dependent k^+channel opening in neuron

Authors: *Y. FUKUSHI, C. SUN, S. YAMAMOTO;
Hamamatsu Univ. Sch. of Med., Hamamatsu, Japan

Abstract: Objective: Our previous study had shown that electrical stimulation of cerebellar fastigial nucleus (FN) before middle cerebral artery occlusion (MCAO) induced ischemic tolerance in rats, and increased UCP4 expression in the cerebral cortex [1, 2]. UCP4 is an uncoupling protein localized in the inner mitochondrial membrane and principally expressed in the central nervous system. It is expected that the expression of UCP4 might have related to the acquisition of cerebral ischemic tolerance; however, the mechanism of the UCP4 expression is still under discussion. We hypothesized that the UCP4 expression is regulated through an ATP dependent K^+ (kATP) channel opening. The objective of this study is to determine whether kATP channel opening induce expression of UCP4 in the neuronal cells. **Method:** For primary cultured cortical neurons, 1-day-old Wistar rat was used. The cerebral cortex was dissected and minced, then dissociated by the pipetting and suspended the culture medium. After one-week incubation, UCP4-promotor tdTomato (red fluorescence protein) reporter vector plasmid (UCP4-tdTomato) was transfected in the neurons. Then, expression of UCP4 was observed with the incubation fluorescence microscope for 30 hours with or without 500 μM diazoxide administration. For SHR rat (12-week), UCP4-tdTomato plasmid was transfected by intraventricular injection. One day after the transfection, diazoxide (10 mg/kg) was injected intraperitoneally. Two days after the injection, the brain slices were prepared, and the expression of UCP4 was observed with the fluorescence microscope. **Results:** UCP4 was up-regulated 1.3 times higher 24h after the administration of 500 μM diazoxide as compared to that without the administration. On the other hand, UCP4 expression was suppressed by 1 μM glibenclamide of kATP channel blocker with 500 μM diazoxide. In SHR rat brain, UCP4 expression was also induced by 10 mg/kg diazoxide administration. **Conclusion:** kATP channel opening induced the UCP4 expression in the neuronal cells. This result supports the hypothesis that the FN stimulation activates kATP channel opening and induces UCP4 expression in the event of ischemic tolerance in rat brain. **References**: [1] D J. Reis, Brain Research 780, 161-165, 1998. [2] S. Koizumi, The annual meeting of society for neuroscience 2011.

Disclosures: **Y. Fukushi:** None. **C. Sun:** None. **S. Yamamoto:** None.

Poster

648. Transcription and Translation in Plasticity I

Location: Hall A

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Program #/Poster #: 648.15/C19

Topic: B.07. Synaptic Plasticity

Title: Transcript-specific BDNF expression defines unique activity-induced neuronal ensembles: Impact on neural plasticity

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Abstract: Brain-derived neurotrophic factor (BDNF) is an activity-dependent protein in the neurotrophin family that plays a vital role in neuronal growth and survival, synaptic plasticity, and behavior. Bdnf has a complex gene structure, with nine unique promotors that drive transcription of at least 20 distinct transcripts with unique 5' non-coding exons that encode an identical BDNF protein. Previous data from our group and others have shown that expression of these transcripts is regulated by independent, stimulus-specific mechanisms. For example, promoters I and IV contribute significantly to activity-dependent transcription of exon I and exon IV-containing transcripts, respectively. This regulation of Bdnf transcription results in spatial and temporally specific translation of BDNF protein and is thought to underlie the varied roles of BDNF in neuronal development and plasticity. However, it remains unclear whether individual cells preferentially transcribe Bdnf from one promoter over another. While transcript-specific Bdnf expression has been well-studied in rodent models, less is known about how well conserved Bdnf transcriptional regulation remains in human model systems, such as induced pluripotent stem cell (iPSC)-derived neuron. Using RNAscope single-molecule fluorescent *in situ* hybridization, we demonstrate that Bdnf exon (ex) 1 and ex4-containing transcripts are dynamically regulated following induction of widespread neuronal activity in largely non-overlapping neuronal populations in mouse cortex. To extend these findings, we examined Bdnf ex1 and ex4-containing transcript expression at single cell resolution in mouse cortical neurons and human iPSC-derived neurons at baseline and following induction of neuronal activity. To explore how selective elevation of ex1 or ex4-containing Bdnf transcripts impacts neuronal structure and network activity, we employed a recently developed CRISPR activator system to drive transcript-specific expression of Bdnf in single cells to examine transcript-specific effects

on dendrite branching and network dynamics. Our findings provide further support that, in both rodent and human-derived models, BDNF produced from different activity-regulated promoters may have unique functions in neurodevelopment, plasticity, and behavior.

Disclosures: **E. Pattie:** None. **A.S. Kardian:** None. **C.V. Nguyen:** None. **S.V. Bach:** None. **M. Tippani:** None. **A. Jaffe:** None. **J.J. Day:** None. **K.R. Maynard:** None. **S.C. Page:** None. **K. Martinowich:** None.

Poster

648. Transcription and Translation in Plasticity I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 648.16/C20

Topic: B.07. Synaptic Plasticity

Support: F32-MH112304
DP1-Da039650
R00-DA034681

Title: Distinct roles of Bdnf 1 and Bdnf 4 transcript variant expression in hippocampal neurons

Authors: *S. V. BACH[1], D. HOSEIN[1], D. WILLIAMS[1], L. IANOV[1], N. CARULLO[1], C. G. DUKE[2], J. J. TUSCHER[1], B. W. HENDERSON[3], J. H. HERSKOWITZ[5], J. J. DAY[4]; [1]Univ. of Alabama at Birmingham, Birmingham, AL; [2]Sch. of Med., UAB, Birmingham, AL; [3]Neurol., [4]Neurobio., Univ. of Alabama At Birmingham, Birmingham, AL; [5]Neurol., The Univ. of Alabama At Birmingham, Birmingham, AL

Abstract: *Brain-derived neurotrophic factor* (*Bdnf*) plays a critical role in brain development, neuronal differentiation, dendritic growth, and synaptic plasticity. Aberrant *Bdnf* regulation is implicated in numerous psychiatric and neurocognitive disorders, such as depression, schizophrenia, drug addiction, Rett syndrome, and memory impairments. The rodent *Bdnf* gene contains nine 5' non-coding exons (I-IXa) and one 3' coding exon (IX). Transcription of different *Bdnf* variants (which all code for the same BDNF protein) is initiated at unique promoters upstream of each exon. However, the functional significance of each *Bdnf* transcript is still unknown. Here we show that *Bdnf* mRNAs *I* and *IV* are the most responsive transcripts to neuronal stimulation or inactivation. Using single-molecule RNA fluorescent *in situ* hybridization (FISH) we show that they spread to different cellular compartments upon neuronal depolarization with potassium chloride. To investigate functional roles of *Bdnf* variants *I* and *IV,* we use a CRISPR/dCas9 transcriptional modulation system in which dCas9 fused to either a transcriptional activator (VPR) or a repressor (KRAB-MeCP2) is targeted to distinct *Bdnf* promoters, resulting in selective transcript upregulation or repression, respectively. Using this bi-directional regulation of endogenous *Bdnf* transcription, we are investigating

electrophysiological and morphological changes of hippocampal neurons. Microelectrode Array (MEA) recordings indicate that simultaneous upregulation of *Bdnf I* and *IV* variants increases neuronal action potential frequency and burst frequency. Dendritic spine analyses indicate that upregulation of *Bdnf* variant *I*, but not *IV*, increases mushroom spine density and decreases thin spine density. Whole genome RNA-sequencing reveals that upregulation of *Bdnf I* or *IV* variants increases expression of immediate early genes and genes implicated in synaptic plasticity, but also results in distinct gene expression changes that are specific to each transcript variant. Taken together, our data suggest that *Bdnf I* and *IV* are highly responsive to pharmacological stimulation and may have diverse contributions to neuronal excitability, dendritic spine development, and gene expression profiles in cultured hippocampal neurons. In addition to addressing a poorly understood mechanism in *Bdnf* transcriptional regulation, our work illustrates functional feasibility for endogenous *Bdnf* manipulation for the development of potential gene therapies against psychiatric and neurocognitive disorders.

Disclosures: S.V. Bach: None. **D. Hosein:** None. **D. Williams:** None. **L. Ianov:** None. **N. Carullo:** None. **C.G. Duke:** None. **J.J. Tuscher:** None. **B.W. Henderson:** None. **J.H. Herskowitz:** None. **J.J. Day:** None.

Poster

648. Transcription and Translation in Plasticity I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 648.17/C21

Topic: B.07. Synaptic Plasticity

Support: KAKENHI, 19H03325, 16H06460

Title: Physiological stimuli-dependent BDNF promoter activity in cortical cells revealed by live imaging with luciferase assay

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Abstract: In the developing cortex, firing and synaptic activity is known to remodel neuronal circuits via activity-dependent gene expression. However, what physiological neuronal activity efficiently regulates the gene expression is almost unknown. To address this issue, we studied the promoter activity of brain-derived neurotrophic factor (BDNF), which is a well characterized activity-dependent gene, in living individual cortical cells by applying various physiological stimulation. Cortical slices from neonatal mouse and rat brains were cultured for two weeks. To visualize the promoter activity, a luciferase (luc) vector containing a BDNF exon4 promoter was transfected sparsely into upper layer neurons. The luc signals were observed by an EMCCD camera every 30 minutes for up to 24 hr. For conventional electrophysiological stimulation, a

pair of platinum electrodes were penetrated into the cortical slices, and various stimuli (0.1-60 Hz) were applied. Optogenetic stimulation with channel rhodopsin 2 (ChR2) was also used for relatively low frequency stimulation (0.1-10 Hz). For this, a ChR2-YFP vector was transfected into upper layer cells by *in utero* electroporation prior to culturing. First, the promoter activity was confirmed to be stable for several hours before stimulation. After high frequency electrical stimulation (>2 Hz), the luc signals in a large fraction of cells began to increase within a few hours and peaked around 6 to 8 hr after stimulation (2-6 fold increase). In particular, theta burst and 20 Hz stimuli were effective. In contrast, low frequency stimulation (0.1 and 1 Hz) did not increase the luc signals in most observed cells. A similar frequency-dependent increase was also found in the luc signals by optogenetic stimulation, indicating that synaptic responses contribute to the increase in the promoter activity. Moreover, the luc signals did not change in the presence of glutamate receptor blockers even after high frequency stimulation. Taken together, the present live imaging study of the luc signals in individual cells demonstrates that synaptic inputs with preferential frequency efficiently induces BDNF promoter activity in developing cortical neurons.

Disclosures: Y. Miyasaka: None. **N. Yamamoto:** None.

Poster

648. Transcription and Translation in Plasticity I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

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Topic: B.07. Synaptic Plasticity

Support: NIH Grant MH119628

Title: Gene expression levels of the BDNF pathway in glutamatergic neurons from animal models with social deficits

Authors: *M. FAIN[1], B. BEASLEY[2], R. ABENS[2], K. SCOTT[2], G. WESLEY[2], M. CHANDLEY[2];
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Abstract: Autism spectrum disorder (ASD) is a neurological developmental disability affecting communication and other social behaviors. ASD currently affects 1 in 59 children with males affected more frequently at a rate of 1 in 42. It has been postulated that an imbalance between the excitatory and inhibitory systems may be at the core of neuronal dysfunction in ASD. Increased excitatory glutamatergic markers and reduced inhibitory markers have been observed in the neuropathology of the disorder. Brain derived neurotrophic factor (BDNF) and the receptor TrkB were evaluated to determine if markers of impaired synaptic health may be present in brain tissue from mouse models that display social behavior deficits. BDNF binding to the receptor TrkB is

responsible for downstream signaling that facilitates synaptic plasticity and maintenance. Previous studies in human ASD from our laboratory have found that *NTRK2* expression (encodes TrkB receptor) in glutamatergic neurons is reduced in anterior cingulate cortex from donors diagnosed with ASD when compared to typically developing control donors. In this study, laser capture microdissection was used to obtain enriched populations of glutamatergic neurons from the cingulate cortex using male mice (postnatal day 21). Gene expression levels for *BDNF* and *NTRK2* in these neurons were compared to wild type control mice (C57BL/6J) using tissue from three mouse models (maternal immune activation, BTBR, and valproic acid) of social behavior deficits. A secondary goal of this study was to determine if comparable gene expression levels could be obtained between nested QPCR and quantitative endpoint PCR. For the nested QPCR method, twenty cycles of PCR were performed using reverse transcribed cDNA with Prime5 HotStart Master Mix followed by a subsequent QPCR reaction using Powerup sybr-based enzyme on the BioRad CFX96 RT detection system. No significant gene expression differences were found in *NTRK2* expression levels between groups, but expression levels of *BDNF* in only the BTBR model was significantly decreased ($p < 0.05$). The second method used the same starting cDNA for PCR amplification but was quantified using the Agilent tape station 2200 and no significant differences between *BDNF* or *NTRK2* were determined in any model. Behavioral analysis of mouse littermates matured to adulthood used in the study demonstrated expected behavioral changes between wild type and models in marble burying and sociability measures. Further analysis of additional genes in the BDNF signaling cascade in the mouse models could help establish a parallel between human BDNF abnormalities in ASD and brain development linked to social behaviors.

Disclosures: **M. Fain:** None. **B. Beasley:** None. **R. Abens:** None. **K. Scott:** None. **G. Wesley:** None. **M. Chandley:** None.

Poster

648. Transcription and Translation in Plasticity I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 648.19/C23

Topic: B.07. Synaptic Plasticity

Title: Neuronal activation can modulate enhancer activity through *de novo* DNA methylation

Authors: *T. KAMEDA[1], T. IMAMURA[1], T. TAKIZAWA[2], F. MIURA[1], T. ITO[1], K. NAKASHIMA[1];
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Abstract: External stimuli cause gene expression changes in the brain, and such changes are important for memory formation and learning. Contrary to the notion that non-dividing cells

exhibit low epigenetic dynamics, recent studies have shown that neuronal activation can induce epigenetic changes, including DNA demethylation, for gene induction. Here we show that neuronal activity-dependent DNA methylation also impose a considerable effect on gene expression memory formation. In order to examine the degree to which DNA methylation changes upon neuronal stimulation, we conducted DNA methylome analysis using post-bisulfite adapter-tagging method for primary cultured neurons that were hyper-activated by the treatment with bicuculline/4-aminopyridine. We identified 531 and 669 regions where methylation and demethylation respectively occurred upon stimulation. Many of these regions were located relatively far from gene promoters. Using publicly available ChIP-seq data for H3K4me1, accumulation of H3K4me1 was observed at the differentially methylated regions, raising the possibility that not only DNA demethylation but also DNA methylation occur at a set of enhancer regions to regulate downstream gene expressions. To test this hypothesis, we examined the enhancer activity of selected differentially methylated regions using a reporter assay system with a CpG-free luciferase. We found that DNA methylation at the differentially methylated regions impaired enhancer activity, and supply of a DNMT inhibitor, RG108, or simultaneous knockdown of *Dnmt1* and *Dnmt3a,*reversed the DNA methylation status from hyper-methylated to hypo-methylated. Our results suggest that rapid *de novo* DNA methylation occurs depending on neuronal activity in a set of enhancer regions and modulate their transcriptional activity through DNA methylation machinery including DNMT1 and DNMT3a.

Disclosures: **T. Kameda:** A. Employment/Salary (full or part-time):; Japan Society for the Promotion of Science. **T. Imamura:** None. **T. Takizawa:** None. **F. Miura:** None. **T. Ito:** None. **K. Nakashima:** None.

Poster

648. Transcription and Translation in Plasticity I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 648.20/C24

Topic: B.07. Synaptic Plasticity

Title: Activity dependent regulation of CaMKII and local RNA translation machinery in the postsynaptic density

Authors: *Y. JOO, D. R. BENAVIDES;
Dept. of Neurol., Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: The ser/thr kinase calcium/calmodulin-stimulated protein kinase II (CaMKII) is essential in signaling pathways important for synaptic plasticity that underlie learning and memory. RNA transport and local translation are crucial for neuronal signal transmission and synaptic plasticity. Dysfunction of CaMKII and RNA metabolism have been implicated in numerous neuronal disorders. Synaptic accumulation of CaMKII is triggered by neuronal

activity, and local Ca^{2+} signaling induces translation of CaMKII. However, the timecourse for activity-induced regulation of CaMKII in the postsynaptic density (PSD) remains to be fully elucidated. We used dissociated rat primary neuron culture, proteomics, pharmacology, and immunoblotting to investigate the translational mechanisms of CaMKII regulation in the PSD. We discovered changes in total protein and phosphorylation states in the PSD following brief NMDA or KCl treatment. These data suggest that activity-dependent regulation of local RNA translation is induced in the PSD. This study may contribute to understanding of the underlying pathophysiology of neurological disorders and pathways for novel therapeutics.

Disclosures: Y. Joo: None. **D.R. Benavides:** None.

Poster

648. Transcription and Translation in Plasticity I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 648.21/C25

Topic: B.07. Synaptic Plasticity

Support: F31-MH114431
R01-DA017392
R01-MH081935
NS-083085

Title: Presynaptic protein synthesis supports structural and functional plasticity at excitatory hippocampal mossy fiber synapses

Authors: *H. R. MONDAY[1], Y. J. YOON[2], R. H. SINGER[2], P. E. CASTILLO[1];
[2]Anat. & Structural Biol., [1]Albert Einstein Col. of Med., Bronx, NY

Abstract: Activity dependent changes at synapses critically underlie information storage in the brain. Protein synthesis is required for long-lasting plastic changes of the postsynaptic compartment, but whether and how local protein synthesis contributes to presynaptic structure and function remains unclear. We recently reported that presynaptic protein synthesis is required for functional plasticity of a subset of inhibitory interneuron terminals. In order to test the role of protein synthesis in excitatory presynaptic terminals, we examined the hippocampal mossy fiber (MF)-CA3 synapse which expresses robust presynaptic functional plasticity, has notably large and complex boutons, and is known to undergo structural plasticity upon experience. Using electrophysiology, we first confirmed that long-term potentiation (MF-LTP) requires protein synthesis and showed that transected MF axons are capable of MF-LTP, suggesting that protein synthesis in the soma is not required for plasticity. Using high-resolution microscopy, we found that MF-LTP is associated with an enhancement of bouton volume that was protein synthesis-dependent. Importantly, we demonstrate that MF boutons are capable of synthesizing protein

locally. By selectively labeling ribosomes in the presynaptic neuron, we also show that MF boutons and axons contain ribosomes. Lastly, given that the Fragile X mental retardation protein (FMRP), a critical regulator of translation, is highly expressed in mossy fiber boutons, we tested whether conditional presynaptic KO of FMRP results in changes at the MF synapse. Presynaptic KO of FMRP resulted in a loss of the activity-dependent structural and functional plasticity. Together, these results indicate that presynaptic protein synthesis critically regulates bouton structure and function at diverse synapse types in the mature brain. This capability could underlie input-specificity of presynaptic plasticity and may represent a novel mechanism that regulates memory formation.
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Poster

648. Transcription and Translation in Plasticity I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

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ControlExtraData.DynamicPosterDisplay:
Dynamic Poster
Topic: B.07. Synaptic Plasticity

Support: NIH Grant NS083085
NIH GrantF31 MH109267
NIH Grant MH081935
NIH Grant DA017392

Title: Real-time imaging of activity-regulated arc gene transcription in acute hippocampal slices

Authors: *S. DAS[1], P. J. LITUMA[2], P. E. CASTILLO[2], R. H. SINGER[1,3];
[1]Anat. and Structural Biol., [2]Dominick P. Purpura Dept. of Neurosci., Albert Einstein Col. of Med., Bronx, NY; [3]Janelia Res. Campus, Ashburn, VA

Abstract: Spatio-temporal control of gene expression in a neuronal network is an essential element of memory formation. For immediate early genes (IEGs) strongly linked to behavior, this regulation initiates at the level of transcription. Arc (activity-regulated cytoskeletal associated), or Arg3.1 is one such IEG playing crucial roles in synaptic plasticity and memory consolidation. Although the distribution of Arc mRNA is known, it has not been possible to follow the temporal behavior of these mRNAs in tissue. To this end, we generated a transgenic mouse, where the endogenous Arc gene is tagged in its 3′UTR with an array of bacteriophage-derived stem loops that bind to fluorescent coat proteins. This approach allows the visualization

of actively transcribing Arc loci and mRNAs in real time both in cultured neurons and in acute hippocampal slices. Using optogenetic stimulation with channelrhodopsins (ChR2 in cultures, and ChIEF in slices), we have developed an all-optical method of triggering and measuring Arc transcription in tissue. By modulating the frequency of opto-stimulation we identified the minimal threshold required for transcription induction to be 25Hz. In addition, pairing optogenetics with antagonists for synaptic transmission allowed us to delineate the contribution of synaptic versus somatic inputs to trigger transcription. Furthermore, following activity, long-term imaging of Arc transcription revealed novel features - the immediate early phase is followed by subsequent reactivation phases in a subset of neurons without any additional stimulation. Our results provide unprecedented temporal insights into activity-regulated IEG transcription and these transcriptional signatures have implications in long-term memory consolidation.

Disclosures: S. Das: None. **P.J. Lituma:** None. **P.E. Castillo:** None. **R.H. Singer:** None.

Poster

648. Transcription and Translation in Plasticity I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 648.23/C27

Topic: B.07. Synaptic Plasticity

Support: NIH Grant R01ES028738

Title: Two functionally distinct signaling cascades are required to efficiently couple neuronal activity with immediate early gene transcription

Authors: *R. N. SAHA[1], B. GUTIERREZ[3], R. POSTON[2], C. DUNN[4];
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Abstract: We have recently provided evidence that neuronal activity patterns induce different subsets of activity-induced immediate early genes (IEGs) [Tyssowski et al. (2018)]. Brief activity selectively induces a small subset of the activity-regulated gene program - rapid IEGs - that are mechanistically distinct from the later IEGs (delayed IEGs) in their open chromatin state with preloaded TFs and RNA Polymerase II (Pol2) at the regulatory regions and their requirement of MAPK/ERK signaling. However, further work in our laboratory has shown that MAPK/ERK signaling is not sufficient for optimal expression of most rapid IEGs and minimal expression of many delayed IEGs. This suggests the involvement of additional signaling cascades in the process. We have identified that neuronal activity induces the Calcineurin/CRTC1/CREB signaling cascade in parallel to MAPK/ERK pathway and both these two pathways then function together to provide the complete IEG transcriptional response.

Blocking the Calcineurin/CRTC1 pathway pharmacologically or genetically impairs optimal transcription of most rapid IEGs (two exceptions) and several delayed IEGs. Functionally, these two pathways are non-redundant and have distinct functions. While the primary function of the MAPK pathway is to regulate Pol2 recruitment and activity during elongation, the Calcineurin/CRTC1 pathway regulates the epigenetic landscape of regulatory regions (promoters and enhancers) via CBP/p300 HAT activity. Together, these two signaling cascades efficiently relay the information from the membrane for a proficient transcriptional response in the nucleus.

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Poster

649. In Vivo Analyses of Epilepsy Models

Location: Hall A

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Program #/Poster #: 649.01/C28

Topic: B.10. Epilepsy

Support: NIH NINDS R01 NS038572-17
NIH NINDS R01 NS082046-08

Title: Contrasting effects of pathologic and experimentally induced dentate granule cell hyperactivity on spatial tuning specificity in hippocampal CA1 cells

Authors: *S. A. PARK[1], H. TAKANO[1], J. B. KAHN[2], D. A. COULTER[1,2];
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Abstract: The dentate gyrus (DG) plays a crucial role in cognition by regulating hippocampal network activity. In pathological conditions such as epilepsy, where the DG is hyper-excitable, a dysregulation of hippocampal activity could affect cognitive abilities. To better understand how altered DG function affects downstream processing we examined cellular activity in the CA1 hippocampal region when normal DG function is perturbed. For this purpose, we implemented an in vivo approach and performed two-photon calcium imaging in the CA1 of awake, behaving mice traversing a virtual reality (VR) environment. Our experimental setup allowed us to monitor the activity of CA1 pyramidal cells and assess their spatial tuning with regard to the animal's position within the virtual environment. Compared to controls, the CA1 region in epileptic mice that had experienced pilocarpine-induced status epilepticus (SE), which generates chronic hyperexcitability in dentate granule cells (DGCs), had fewer place cells and a lower spatial tuning specificity. Some SE mice exhibited synchronous network activity in the CA1 region, considered to be interictal burst events. No synchronous network activity was observed in any control mice (n=12). We also investigated how spatial tuning in the CA1 region is affected by experimentally enhancing DGC excitability using chemogenetic approaches. CaMKIIa.hM3D

was expressed in the dorsal DG of Thy1-GCaMP6 mice which were treated with clozapine-N-oxide (CNO) 30 min before VR navigation to induce DGC hyperexcitability. Counterintuitively, increasing DGC excitability by CNO enhanced the spatial coding. The number of place cells increased and spatial tuning specificity improved. Enhanced spatial coding was observed in both 2.5m (short) and 5m (long) VR tracks, but with a less profound change when animals navigated a short track compared to the long track. This might be attributed to ceiling effects, since at baseline, spatial coding was poorer in the long track compared to the short track. These contrasting effects on CA1 cells following the modulation of DG excitability experimentally vs. by epilepsy development suggest that distinct factors not under experimental control may disrupt CA1 spatial coding in epilepsy.

Disclosures: **S.A. Park:** None. **H. Takano:** None. **J.B. Kahn:** None. **D.A. Coulter:** None.

Poster

649. In Vivo Analyses of Epilepsy Models

Location: Hall A

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Program #/Poster #: 649.02/C29

Topic: B.10. Epilepsy

Support: National Key R&D Program of China 2017YFC1307500
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Title: Differential neural activities in multiple rats brain regions in Lithium-pilocarpine-induced state epilepsy model

Authors: *Q. WANG[1,2,3], W. SHAN[1], H. YANG[1], A. GUO[1], J. WU[1,4];
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Abstract: Purpose: To confirm different regional brain activities characterized in Lithium-pilocarpine-induced status epilepticus model
Methods: we induced seizures and status epilepticus in Lithium-pilocarpine model. Regional brain activities were evaluated by EEG and c-Fos immunolabeling. ZnT3 immunostaining was performed to observe hippocampal mossy fiber sprouting within 7 days after induction of status epilepticus.
Results: EEG recordings showed distinctive features of activation in different brain areas. With the aggravation of behavioral manifestations of seizures, the frequency and amplitude of the

discharges on EEG were increasing gradually. Status epilepticus was eventually induced and sustained. The labeling of c-Fos was enhanced in the medial prefrontal cortex, hippocampal CA1, CA3, and dentate gyrus, and in the striatum. For each brain region, prominent c-Fos labeling was observed at 2h and 4h after induction of status epilepticus and diminished at 24h. In the chronic phase after SE induction, mossy fiber sprouting was observed at 7 days after SE accompanied by the dynamic evolution of epileptic EEG activities.
Conclusions: These findings validated Lithium-pilocarpine-induced status epilepticus as a seizure model with a specific spatial-temporal profile of neural activation. Hippocampal mossy fiber spouting might be associated with spontaneous seizures in the chronic phase.

Disclosures: Q. Wang: None. **W. Shan:** None. **H. Yang:** None. **A. Guo:** None. **J. Wu:** None.

Poster

649. In Vivo Analyses of Epilepsy Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 649.03/C30

Topic: B.10. Epilepsy

Title: Enhanced susceptibility to pentylenetetrazol-induced seizure in forebrain excitatory neuron-specific connective tissue growth factor knockout mice

Authors: *C.-Y. TSAO, C.-Y. CHEN, L.-J. LEE;
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Abstract: Connective tissue growth factor (CTGF) plays critical roles in the development and regeneration of various connective tissues. In fact, CTGF is also expressed in the nervous system, especially under pathological conditions such as epileptic insult. However, the role of CTGF in epileptogenesis has not yet been studied. In order to elucidate the function of CTGF in the nervous system, we generated forebrain excitatory neuron-specific *Ctgf* knockout (Fb*Ctgf* KO) mice, in which *Ctgf* gene is removed under the expression of *Emx1-Cre*. In the present study, pentylenetetrazol (PTZ) was administrated intraperitoneally in a single dose of 30, 50 or 60 mg/kg to both control and Fb*Ctgf* KO adult male mice. The responses following PTZ injection were classified into hypoactivity, partial clonus, general clonus and tonic-clonic seizures. The behaviors of mice after the PTZ treatment were recorded for 30 mins and the lethality, occurrence of each seizure response and latencies to the first responses were analyzed. No significant difference was noted between control and Fb*Ctgf* KO at the dosage of 30 mg/kg. Higher lethality rate was evident in Fb*Ctgf* KO mice at higher dosages. The latencies to the first sign of hypoactivity and general colonus were shorter in Fb*Ctgf* KO mice compared with controls. Our result indicated an enhanced susceptibility to PTZ-induced seizure in mice lacking *Ctgf*, indicating a role of CTGF involved in the neuronal mechanism of epileptogenesis.

Disclosures: **C. Tsao:** None. **C. Chen:** None. **L. Lee:** None.

Poster

649. In Vivo Analyses of Epilepsy Models

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Program #/Poster #: 649.04/C31

Topic: B.10. Epilepsy

Support: NIH Grant R35NS097287

Title: Global correlates of local epileptiform activity in a chemically-induced seizure model

Authors: ***P. J. STEFFAN**, D. A. MCCORMICK;
Inst. of Neurosci., Univ. of Oregon, Eugene, OR

Abstract: Localization-related epilepsies are a commonly diagnosed neurological disorder. Although focal-onset seizures can secondarily generalize throughout the brain, the mechanism behind this transition remains unclear. A preliminary question in addressing this mechanism is to ask if spatiotemporal patterns of localized epileptiform activity are reflected in global readouts of arousal and behavioral state. Here we demonstrate that focal epileptiform activity is highly coordinated with key external biomarkers of global arousal and behavioral state in animals treated with focal cortical application of the $GABA_A$ antagonist picrotoxin. Electrophysiology *in vivo* demonstrates that the emergence of chemically-induced focal seizures causes pupil diameter and whisking motion to become highly correlated to inter-ictal activity. Further, wide-field fluorescence imaging demonstrates that the extent of spread of epileptiform activity is related to the magnitude of pupil dilation. This is true of inter-ictal spikes as well as focal and secondarily generalized seizures (i.e. ictal activity). These results suggest that even before a focal-onset seizure spreads throughout the brain, local epileptiform activity is already being reflected in the animal's global arousal and behavioral state. How local information comes to be represented in such global signals is of interest for future study as a possible mechanism for secondary generalization. Further, the coordination of external biomarkers to epileptiform activity may prove useful for covert seizure detection and closed loop stimulation paradigms.

Disclosures: **P.J. Steffan:** None. **D.A. McCormick:** None.

Poster

649. In Vivo Analyses of Epilepsy Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 649.05/C32

Topic: B.10. Epilepsy

Support: NS040337
NS044370

Title: Single seizure induced retrograde amnesia in mice: Mechanisms

Authors: *A. A. NAIK, J. KAPUR;
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Abstract: Seizures can cause retrograde amnesia but underlying mechanisms are poorly understood. It is proposed that engram cells and circuits are engaged in acquisition, consolidation and retrieval of memories. We tested whether, single seizure and spatial learning activate CA1 pyramidal neurons and if so, do the CA1 ensembles activated by seizure overlap with those of spatial memory. We developed a model of single seizure retrograde amnesia. C57bl/6 mice (6-8 week, n=12) were trained for delayed discrete trial rewarded alternation task on T-maze to engage working memory. Animals then received pentylenetetrazole (PTZ; 40mg/kg, i.p.) to induce seizure or saline; they were tested the following day. We used TRAP mice expressing tamoxifen-dependent CreERT2 under cfos-promoter for activity-dependent labelling of CA1 pyramidal neurons with tdTomato following either a seizure or working memory acquisition. Entire hippocampus was sectioned (40µm), imaged and TRAPed (tdT+ve) CA1 neurons were counted. Mice that experienced a seizure following training made fewer correct choices on probe day than saline treated controls supporting retrograde amnesia. Seizure induced activation in CA1 as significantly more tagged CA1 pyramidal neurons were present following a seizure compared to saline controls (PTZ; 293.4±22.53, saline; 124.6±16.05, $P<0.001$). Similarly, untrained home cage controls demonstrated sparse CA1 labelling, whereas, significantly more TRAPed CA1 neurons in T maze group demonstrate CA1 activity following spatial memory (untrained; 113.0 ± 6.90, trained; 231.4 ± 18.42, $P<0.001$). The activation pattern was not spatially restricted as tagged pyramidal neurons were present in dorsal as well as ventral hippocampus. Individual sections with CA1 region contained 4 to 5 tagged neurons following either training or seizure with 1 to 3 in respective controls. We hypothesized same set of pyramidal neurons may be activated as positions of these tagged CA1 neurons from seizure and trained mice appeared to be similar on visual examination. Ongoing experiments are aimed to test this potential overlap. This study may shed light on the mechanisms of retrograde amnesia.

Disclosures: A.A. Naik: None. **J. Kapur:** None.

Poster

649. In Vivo Analyses of Epilepsy Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 649.06/C33

Topic: B.10. Epilepsy

Title: Losartan affects seizure threshold and progression by decreasing blood brain barrier disruption

Authors: *S. MCDERMOTT[1], G. LANGUREN[1], N. P. SABETFAKHRI[1], J. M. RAKOTOMAMONJY[2], A. D. GUEMEZ-GAMBOA[3];
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Abstract: Blood-brain barrier (BBB) disruption is a key element in the pathogenesis of epilepsy. Previous studies have shown that BBB disruption allows immune cells, inflammatory mediators, and albumin to infiltrate the brain parenchyma, lower the seizure threshold, and promote epileptogenesis. However, the mechanisms underlying the complex interplay between BBB disruption and brain inflammation, and subsequent effects on seizure susceptibility and progression, remain unclear. In this study, we use a GABAA inhibitor, flurothyl, to determine whether seizure-induced BBB permeability and inflammation affect the seizure threshold and seizure progression. Our results show that the BBB remains intact during flurothyl-induced myoclonic jerks (MJ), but is disrupted upon reaching generalized tonic-clonic seizures (GTCS). We observe an increase in neuronal activity, cell death, and astroglial activation following flurothyl-induced GTCS. In addition, increased BBB permeability contributes to seizure progression, but does not correlate with changes in seizure threshold. Treatment with an FDA-approved drug, Losartan, inhibits BBB disruption, leading to an increased latency to GTCS and slower seizure progression. Losartan-treated mice also show a decrease in neuronal activity, cell death, and reactive astrogliosis. Altogether, these results suggest that inflammation and neuronal excitability due to an increase in BBB disruption occurring between the first MJ and GTCS contribute to seizure progression.

Disclosures: S. McDermott: None. **G. Languren:** None. **N.P. Sabetfakhri:** None. **J.M. Rakotomamonjy:** None. **A.D. Guemez-Gamboa:** None.

Poster

649. In Vivo Analyses of Epilepsy Models

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Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 649.07/C34

Topic: B.10. Epilepsy

Support: , CONACYT-SEP-CB 250930.

Title: Effect of deep microelectrodes implantation surgery on physiological and pathological behaviors in rats: A temporal analysis

Authors: *G. A. CHIPRES-TINAJERO, M. A. NUNEZ-OCHOA, L. H. SAT-DÁVILA, G. M. CAMBEROS-CAMARENA, L. G. MEDINA-CEJA;
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Abstract: Wake-sleep cycle and exploratory are considered important behaviors to intact or sham animals that are usually not affected by experimental protocols in which several neurosurgeries are carried out, as well as in animal's model of neural diseases in which the impact of surgeries in the pathological phenomena that is studied is reduced; in epilepsy models some electrophysiological parameters such as Fast Ripples (FR) oscillations are associated with the disease and are studied without regard to surgery effect, even in specific brain areas in which circuits are associated with these behaviors. We analyzed the effects of microelectrodes implantation surgeries in the hippocampus of rats on physiological and pathological behaviors, in this last behavior considering: a) relationship between latency of first spontaneous and recurrent seizure and time on seizures over 3-5 Racine scale per day before and after surgeries, and b) correlation between the number of fast ripples (FR) recorded and the number and severity of seizures events in the same day. Male Wistar rats (210-300 g) were grouped in Sham and epileptic (n = 7, each group); to induce epilepsy, rats were injected with a single dose of pilocarpine hydrochloride (2.4 mg/2µl; i.c.v.). Sham and epileptic rats were implanted with deep microelectrodes in the CA1, CA3 and dentate gyrus; both groups were EEG recorded during 5 days; the behaviors were analyzed by video monitoring (24hours/7days), 15 days before and 15 days after the surgery. Quiet wakefulness, sleep and exploratory activity as physiological behaviors and convulsive behaviors according the Racine scale as pathological behaviors were analyzed. Epileptic animals showed a significant decrease in sleep time and exploratory activity compared with Sham group after surgery, while a reduction in quiet wakefulness period and an increase in the sleep and exploratory behavior time was observed in animals of Sham group after surgery; the rats with short latency to the first spontaneous and recurrent seizure (≤60 days) showed high variability in terms of total mean seizure time per day in contrast with epileptic animals with long latencies. Surgery increased the average time of seizures in scale 4 per day and the number of seizure events in 4 and 5 scales. No significant correlations between the

occurrence of FR and scales in epileptic animals were observed. In conclusion, surgery affects physiological as pathological behaviors in both Sham and epileptic groups; however a correlation between the severity of seizures and FR activity was not found in the present study. Support contributed by the grant from LMC, CONACYT-SEP-CB 250930.

Disclosures: G.A. Chipres-Tinajero: None. **M.A. Nunez-Ochoa:** None. **L.H. Sat-Dávila:** None. **G.M. Camberos-Camarena:** None. **L.G. Medina-Ceja:** None.

Poster

649. In Vivo Analyses of Epilepsy Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 649.08/C35

Topic: B.10. Epilepsy

Support: Science Foundation Ireland FutureNeuro Centre Grant

Title: Profiling of neuronal and microglial argonaute-2 bound microrna during epileptogenesis and in chronic epilepsy reveals cell-type specific contribution to disease

Authors: *G. P. BRENNAN[1], N. NGUYEN[2], T. HILL[2], E. BRINDLEY[2], M. DIVINEY[2], M. HEILAND[2], A. BATOOL[2], D. C. HENSHALL[2];
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Abstract: *Introduction:* Epilepsy is a chronic neurological disorder characterized by spontaneous recurrent seizures and affects between 50-60 million people worldwide. Acquired temporal lobe epilepsy, induced by brain insult such as TBI, stroke or status epilepticus is the culmination of altered molecular and cellular function regulated by global changes in gene networks in numerous cell types. Recently it has emerged that microRNAs (small non-coding RNAs) are involved in the development of acquired temporal lobe epilepsy. How they shape the neuronal and microglial response to an epilepsy-inciting event however is unclear. Here we generate an inducible transgenic reporter mouse which allows genome-wide profiling of the miRnome from both neurons and microglia in healthy, epileptogenic and epileptic mice. *Methods:* A transgenic mouse line homozygous for a FLAG-tagged-Ago2 gene (Rosa-Stop$^{fl/fl}$-Flag-Ago2 were crossed with two different inducible cre-recombinase mouse lines, one with a Cx3cr1 microglial specific promoter and one with a Thy1 neuronal promoter producing two specific genotypes *Cx3cr1-cre$^{tg/tg}$;Rosa-Stop$^{fl/fl}$-Flag-Ago2, Thy1-cre$^{tg/+}$;Rosa-Stop$^{fl/fl}$-Flag-Ago2* respectively. Upon the administration of tamoxifen these mice then express Flag-tagged Ago2 in either microglia or neurons. Epilepsy was induced by injecting kainic acid directly to the amygdala of adult mice, a sham injection of PBS was administered to control animals. Hippocampus was harvested from epileptogenic animals (24h post KA) and chronically epileptic animals (2 weeks post KA) and from time matched control animals. Immunoprecipitation for

Flag followed by RNA isolation was performed to isolate Ago2-bound miRNAs from neurons or microglia. Sequencing libraries were generated from immunoprecipitated miRNAs and from total cellular miRNA and sequenced on an Illumina miSeq. *Approach for statistical analysis:* Count based miRNA expression data was generated by mapping to mouse miRBase. Principal component analysis (PCA) was used to reveal simplified dynamics within the data and identify clustering of samples. Differential miRNA expression between groups employed by using Bayesian moderations and an adjusted p-value set at 5%. *Results and Conclusions:* Initial characterisation of Flag-Ago2 mice revealed accurate identification of neuronal and microglial enriched miRNAs providing proof of concept for our sequencing studies. Neuronal and microglial miRNA profiles differed in both healthy brain and in epilepsy. Differential miRNA expression was a prominent feature and distinguishable between epileptogenic and epileptic tissue compared to control mice.

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Poster

649. In Vivo Analyses of Epilepsy Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 649.09/C36

Topic: B.10. Epilepsy

Title: Comparison of the effects of three antiepileptic substances in a genetic animal model of absence seizure

Authors: *E. ESNEAULT, A. SOYER, G. PEYON, V. CASTAGNE;
Porsolt, Le Genest Saint Isle, France

Abstract: Absence-type generalized seizures are particularly prevalent in children and often have a genetic origin. The WAG/Rij rat is a well-characterized genetic model of absence seizure. These animals develop non-convulsive seizures accompanied by neuropsychological and neurocognitive symptoms, with age. The aim of this study was to compare the efficacy of three antiepileptic substances: Ethosuximide (ETX), the standard treatment; levetiracetam (LEV); and valproate (VPA). We also evaluated comorbidities including neuropsychological and cognitive performances in WAG/Rij rats. Six month old rats were implanted with epidural electrodes placed over the fronto-parietal cortex. After a two-week period of recovery, video-EEG recordings were performed over periods of 4 hours, the first hour was used as a baseline session, and the following 3 hours of recording after administration of the antiepileptic drugs. In order to evaluate comorbidities, the rats were assessed in the Y-maze and social recognition tests for cognitive performances, and in the elevated plus maze (EPM) and forced swim (FST) tests for neuropsychological evaluation. ETX (50 and 100 mg/kg) and VPA (100 and 200 mg/kg) dose-

dependently decreased the number and the duration of spike and wave discharges (SWD). ETX and VPA fully suppressed SWD at high doses (200 and 300 mg/kg, respectively). The effects of LEV were of lower magnitude as compared with ETH for the same doses. With LEV, the number of SWD was decreased down to approximately 50 percent as compared with vehicle-treated control rats, and this corresponded to a ceiling effect observed at 100 and 200 mg/kg. Moderate spatial memory deficits were noted in the Y-maze test whereas no abnormal behaviour was observed in the EPM or the FST in eight-month old rats. These results confirm the efficacy of ETX and VPA to antagonize absence seizure in WAG/Rij rats. In humans, ETX remains the gold standard treatment for this type of seizure, while VPA is used more when absence seizure is accompanied of tonico-clonic convulsions. LEV showed a moderate efficacy against absence seizure. Slight cognitive dysfunction in WAG/Rij rats were observed in absence of clear evidence for an abnormal neuropsychological status. The results suggest that the strain of WAG/Rij rats may be particularly useful for evaluating absence seizure as well as comorbid cognitive deficits. This chronic genetic model is reliable and predictive to evaluate potential new treatments against absence seizure. Memory impairments observed in these animals reinforce the translational value of this model.

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Poster

649. In Vivo Analyses of Epilepsy Models

Location: Hall A

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Program #/Poster #: 649.10/C37

Topic: B.10. Epilepsy

Support: UID/NEU/04539/2019
POCI-01-0145-FEDER-028261

Title: Tracking neurometabolic markers during seizure activity in awake rodents

Authors: ***A. LEDO**[1,2], C. F. LOURENÇO[1,2], G. A. GERHARDT[3], J. LARANJINHA[1,2], R. M. BARBOSA[1,2];
[1]Fac. of Pharmacy, Univ. of Coimbra, Coimbra, Portugal; [2]Ctr. for Neurosci. and Cell Biol., Coimbra, Portugal; [3]Neurosci. Dept., Univ. of Kentucky Med. Ctr., Lexington, KY

Abstract: Synaptic communication is an energy demanding process, accounting for ca. 40% of energy consumption in the cerebral cortex. Under physiological conditions, glucose metabolism is highly compartmentalized between neurons and astrocytes. Although it is consensual that neural cells rely mainly on glucose/lactate to fuel neurotransmission, it is still a matter of debate how these substrates are used and supplied to each cell type. The pathways of bioenergetic dysfunction during disease are even more unclear, hindering therapeutic development.

Neurometabolic dysfunction is a critical pathophysiological aspect of the epileptic brain and appears to share many of the self-propagating features that are typical of epileptogenic processes. To understand the mechanisms of neurometabolic (de)coupling it is critical to monitor the fluxes of key metabolic markers (such as glucose, oxygen, lactate, pyruvate) in the living brain, under physiological stimulation and during aberrant synaptic firing (ex: seizures). One attractive strategy for in vivo monitor of such compounds consists in the use of micro(bio)sensors coupled to fast electrochemical techniques. Here we have used ceramic-based platinum microelectrode arrays (MEA) for direct recording of pO_2 and glucose/lactate oxidase based MEAs as biosensors to record changes in these substrates in the CNS of chronically implanted **freely-moving** rats during pilocarpine-evoked *status epilepticus*. Furthermore, by employing fast sampling amperometry (100Hz acquisition) we have concurrently recorded brain electrical activity in the form of LFP-related currents, a surrogate signal of LFP. We have found that Induction of *status epilepticus* by intrahippocampal injection of pilocarpine (1.2 mg in 1 microL) induces biphasic changes in pO_2 in the hippocampus. The initial dip at seizure onset (ΔO_2= -4.5 ± 0.7 µM) was followed by a prolonged hyperoxygenation phase (ΔO_2 = +10.4 ± 2.9 µM). Analysis of LFP-related currents at the site of pO_2 recording further revealed that the O_2 dip may precede observable change in high frequency power. This has high potential for translation into the clinical setting supported on intracranial grid or strip electrodes.

Disclosures: A. Ledo: None. **C.F. Lourenço:** None. **G.A. Gerhardt:** None. **J. Laranjinha:** None. **R.M. Barbosa:** None.

Poster

649. In Vivo Analyses of Epilepsy Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 649.11/C38

Topic: B.10. Epilepsy

Support: ERC Starting Grant, Epilepsy Controlled with Electronic Neurotransmitter Delivery (EPI- Centrd)
Chaire d'excellence A*MIDEX

Title: Electric field orientation-dependence of evoked seizures and foci localisation using temporal interference and implantable electrodes

Authors: *E. RUSINA[1], S. SAFIEDDINE[1], R. POULKOURAS[1], F. MISSEY[1], B. BOTZANOWSKI[1], E. ACERBO[1], Y. ZILBERTER[1], M. DONAHUE[2], A. WILLIAMSON[1]; [1]Aix-Marseille Univ., Marseille, France; [2]Mines Saint-Etienne, Saint-Etienne, France

Abstract: Temporal lobe epilepsy (TLE) is the most common type of partial epilepsy among adults worldwide. Various animal models have been created in attempt to mimic the disease with

similar behavioural, electrophysiological, and morphological symptoms. In our study we used the kainic acid (KA) model of TLE to evoke seizures in male adult C57BL/6 mice. To evoke and to localise seizure foci we used a novel method of temporal interference (TI) electrical stimulation and electric field orientation-dependence, combined with *in vivo* EEG recording and post-mortem histological examination to confirm epileptic activity onset, originating from the CA3 field of the hippocampus. TI is based on the principle of interference between 2 electric fields, where 2 pairs of electrodes are placed on the skull or on the dura mater at precise coordinates and electrical stimulation is applied with a slight difference in frequency between each pair (2 kHz and 2.01 kHz), thus creating an oscillation within each electric field. By overlapping, these fields target accurately precise brain locations located far from the cortex surface without a penetrating electrode, and help to localise an epileptic focus. We used a computational model to calculate stereotaxic coordinates at the desired location for electrode placement, so that upon electrical stimulation, CA3 would be targeted. We have also modified an existing TI stimulation protocol, by placing the electrodes directly on the dura mater, via removal of the bone layer, which acts as a barrier for electric stimuli to penetrate the brain tissue. We have shown that TI can be successfully used in a virtual model of a mouse brain, and that, by altering the field orientation, significantly different results are achieved. For instance, we have found that if an electrode pair is oriented along the axons, the stimulation results in a greater depolarisation rate compared to the perpendicular orientation. Altogether, these findings may provide breakthrough in epilepsy research, allowing the targeting and stimulation of a seizure focus with an efficient, minimally invasive technique.

Figure 1. Temporal interference

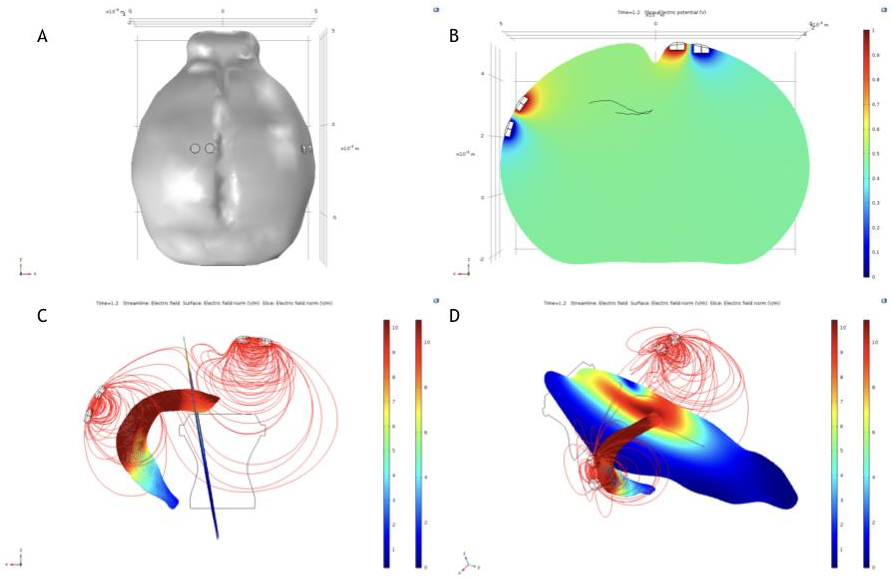

Fig 1. A. General outline of the TI setup. 2 pairs of electrodes are placed on the top of the cortex. B. Coronal view of the mouse brain with implanted electrodes. C. Electric fields generated by electrical stimulation, overlapping in the zone of the hippocampus. D. Electric field surface.

Disclosures: **E. Rusina:** None. **S. Safieddine:** None. **R. Poulkouras:** None. **F. Missey:** None. **B. Botzanowski:** None. **E. Acerbo:** None. **Y. Zilberter:** None. **M. Donahue:** None. **A. Williamson:** None.

Poster

649. In Vivo Analyses of Epilepsy Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 649.12/C39

Topic: B.10. Epilepsy

Title: Continuous *in-vivo* tissue oxygen recording for spontaneous seizure and spreading depolarization

Authors: *J. LIU, F. BAHARI, S. LÓPEZ, C. CURAY, B. J. GLUCKMAN;
The Pennsylvania State Univ., State College, PA

Abstract: Both brain slice (Ingram 2013) and in-vivo measurements (Farrell 2016) have demonstrated that tissue oxygenation (PO_2) varies with seizure dynamics. In recent work (Bahari bioRxiv) we have demonstrated in two very different chronic animal models of epilepsy, that spontaneous seizures are frequently accompanied by spreading depolarization (SD) events. Revealing the SD required the implementation of a recording system with near-DC sensitivity and sufficient dynamics range.

Theoretical modeling work at the single neuron level has unified a full range of neuronal dynamics that includes normal spiking, seizure, spreading depolarization, and even wave-of-death (Wei 2014) by including conservation constraints of ionic species, tracking extracellular concentrations of ionic analytes, cell swelling, and including tissue oxygenation, which is critical for fueling ionic pumps. Such modeling implicates tissue oxygenation as a critical parameter to understand the interactions between spontaneous seizures and SD. However, to date, there has not been simultaneous study In Vivo of chronic spontaneous seizures and PO_2 with sufficient sensitivity to observe SD.

We have now incorporated a floating 3-electrode potentiostat and accompanied waveform generation into our DC-sensitive recording system. The new system is capable of fulfilling chronic biopotential recording during seizure/SD and at the same time performing a range of different electrochemical measurements, and particularly for PO_2.

Here, we show the validation of both fast-scan cyclic voltammetry and constant voltage amperometry results and preliminary results for continuous In-Vivo oxygen concentration dynamics, and preliminary findings from chronic recordings from the tetanus toxin model of temporal lobe epilepsy.

This system provides a platform to study oxygen concentration dynamics, and predictions on evolution, and the ability to intervene with both seizure and spreading depression dynamics.

Ingram. *et al, Journal of Neurophysiology* 112: 205-212 (2014).
Farrell, J. S. *et al, eLife* 5: 1-24 (2016).
Bahari, F. *et al*, bioRxiv 455519; **doi:** https://doi.org/10.1101/455519 (2018).
Wei, Y. *et al, Journal of Neuroscience*, 34(35), 11733-11743 (2014).

Disclosures: J. Liu: None. **F. Bahari:** None. **S. López:** None. **C. Curay:** None. **B.J. Gluckman:** None.

Poster

649. In Vivo Analyses of Epilepsy Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 649.13/C40

Topic: B.10. Epilepsy

Support: AOD18013-001-00000

Title: Evaluation of modulation of cannabinoid receptor 1 (CB1R) for the alleviation of organophosphate-induced status epilepticus and mortality

Authors: *B. M. WINNER, S. W. O'BRIEN, P. B. DUBEE, S. E. WOLFE, K. E. KELLY, C. H. PHUNG, K. T. PAGARIGAN, M. R. EISEN, P. M. BODNER, M. R. NELSON, P. M. MCNUTT;
USAMRICD, Gunpowder, MD

Abstract: The acute toxicity of organophosphorus (OP) compounds is primarily a result of acetylcholinesterase inhibition in the central and peripheral nervous systems, which manifests as seizure, respiratory failure and neurotoxicity. Without aggressive and early treatment, OP-induced seizures rapidly transition to refractory status epilepticus (SE), characterized by sustained seizure activity that is resistant to anticonvulsant drugs. A high proportion of survivors of SE subsequently develop spontaneous recurrent seizures (SRS), which are also refractory to anti-epileptic drugs. Here we evaluated the potential for the endocannabinoid (eCB) system to act as an “on-demand” neuroprotective pathway by evaluating the effects of the CB1R positive allosteric modulator (PAM) ZCZ-011 on severity, latency and duration of SE and SRS in soman-exposed rats. In preliminary studies, we demonstrated that ZCZ-011 (20 mg/kg; i.p.) delayed latency to behavioral seizure versus vehicle. We also observed improved 10 d survival in the ZCZ-011 group versus vehicle (94% versus 60%, respectively). We are currently characterizing the functional effects of ZCZ-011 and other CB1R PAMs and agonists on local field potentials in telemeterized rats during and following soman exposure to more comprehensively assess whether agonism of the eCB pathway can reduce the severity of SE and/or recurrence of SRS. Taken together, these early results reveal a potential therapeutic target for acute and chronic OP-induced neurological effects.

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Poster

649. In Vivo Analyses of Epilepsy Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 649.14/C41

Topic: B.10. Epilepsy

Support: Conacyt-Mexico No. 003236 to CVMP

Title: Diabetic hyperglycemia increases the severity of lithium-pilocarpine-induced SE in male Wistar rats

Authors: *C. V. MERIDA PORTILLA[1], F. CHENA BECERRA[2], K. P. RAMOS RIERA[1], C. MORGADO-VALLE[3], L. BELTRAN-PARRAZAL[4], L. LOPEZ-MERAZ[5];
[1]Ctr. de Investigaciones Cerebrales, Univ. Veracruzana, Xalapa, Ver, Mexico; [2]Doctorado en Investigaciones Cerebrals, [3]Univ. Veracruzana, Xalapa, Mexico; [4]Univ. Veracruzana, Xalapa-Enriquez, Mexico; [5]Cice, Univ. Veracruzana, Xalapa, Mexico

Abstract: Diabetes Mellitus type II (DMII) is a metabolic disorder characterized by hyperglycemia and associated with beta-cell dysfunction and insulin resistance.
Clinical and experimental studies have shown comorbidity between DM and epilepsy, including a higher incidence of status epilepticus (SE). SE is a neurological emergency with high a mortality rate, characterized by continuous epileptic activity for along 30 minutes. However, the association between DMII and epilepsy is not fully understood. Therefore, the aim of this study was to analyze the severity of SE in male Wistar rats with DMII. To induce DMII, three-days-old (P3) rats were given a subcutaneous injection of streptozotocin (STZ) (100mg/kg) (n=6); control rats received an equal volume of citrate buffer (pH 4.5) (n=8). Glycemia was monitored at P30, P60, and P90 in both experimental groups. Rats were injected intraperitoneally with lithium chloride (3mEq/kg, i.p.) and 18 h later, at P90, SE was induced by injection of pilocarpine hydrochloride (30mg/kg, s.c.). Motor seizures were carefully monitored and evaluated using the Racine's scale: 0 = 1 abnormality; 1=Mouth and facial movements; 2=Head nodding; 3=Forelimb clonus; 4=Rearing; 5=Rearing and falling. Latency, duration, and frequency of seizures and SE were also evaluated. Time course of glycemia showed that control rats had normal glucose levels along with the study (114±3 mg/dL), whereas STZ-treated rats had hyperglycemia from P60 (198±20 mg/dL) to P90 (287±3 mg/dL). Diabetic rats had more stage V seizures (5.8±0.4) than control rats (2.8±0.3). However, STZ rats had increased latency to the first stage V seizure (44.3±1.6 min) and to SE (48.3±1.7 min) when compared to the control group (22.12±0.96 min and 27.6±0.31 min, respectively). The duration of stage V seizures didn't

show differences between STZ (1.2±0.1 min) and control (0.95±0.1 min) rats. These data suggest that the presence of DMII may increase SE severity.
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Disclosures: C.V. Merida portilla: None. **F. Chena becerra:** None. **K.P. Ramos riera:** None. **C. Morgado-Valle:** None. **L. Beltran-Parrazal:** None. **L. Lopez-Meraz:** None.

Poster

649. In Vivo Analyses of Epilepsy Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 649.15/C42

Topic: B.10. Epilepsy

Support: NIH Grant R01 NS097762

Title: Optogenetic dissection of striatal outputs modulates absence-like spike and wave discharges

Authors: *S. HYDER, P. FORCELLI;
Pharmacol. & Physiol., Georgetown Univ., Washington, DC

Abstract: Absence epilepsy is a prevalent childhood epilepsy characterized by non-convulsive generalized seizures. These seizures are generated in corticothalamocortical loops. Nuclei of the basal ganglia (BG), while not sites necessary for generation of absence seizures, may be capable of modulating this seizure activity. Supporting this hypothesis, several basal ganglia nuclei can be either stimulated or inhibited to suppress seizures in a variety of preclinical seizure models. Here, we employed an optogenetic approach to determine the pathways by which the striatum modulates spike and wave discharges (SWDs) evoked by gamma-butyrolactone (GBL). Adult rats were stereotaxically injected bilaterally with activating (hChR2(H134R) or Chronos) or inhibitory (ArchT) opsins into the dorsal striatum and fiber optics were placed at the same sites. Epidural electrodes were placed over frontal and parietal cortices to monitor SWDs. Following post-operative recovery, seizures were evoked by systemic administration of GBL. We compared pan-striatal activation and inhibition to selective activation of DRD1-expressing direct pathway neurons and selective inhibition of DRD2-expressing indirect pathway neurons. We tested animals on a within-subject basis at baseline and with photostimulation. We also compared “open loop” stimulation to “closed loop” stimulation modes, in which stimulation was delivered only upon detection of a seizure. Pan-neuronal striatal activation suppressed SWDs in wild-type rats. Optogenetic activation of the direct pathway neurons was without effect on SWDs. Optogenetic silencing of indirect pathway neurons suppressed SWDs both in open-loop and closed-loop stimulation paradigms.

Disclosures: **S. Hyder:** None. **P. Forcelli:** None.

Poster

649. In Vivo Analyses of Epilepsy Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 649.16/C43

Topic: B.10. Epilepsy

Support: Swiss National Foundation grant # 177873
Tiny Blue Dot foundation grant # 133AAG3451

Title: Spectral correlates of loss of responsiveness during partial vs. secondarily generalized seizures

Authors: C. PAPANTONATOS[1], C. KOZMA[1], U. GORSKA[2], T. BUGNON[1], A. STRUCK[3], G. TONONI[1], M. BOLY[3], *E. JUAN[1];
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Abstract: Both complex partial (CPS) and generalized tonic-clonic (GTC) seizures lead to loss of responsiveness (LOR), causing serious risks of injury in patients with epilepsy. However, mechanisms of LOR during seizures are poorly understood. Here we aim to investigate in more details the spectral signatures characterizing the dynamics of LOR in CPS and GTC.
Intracranial recordings of 15 GTC and 13 CPS were obtained from 12 patients (7 male, median age 33 years, range 18-59). Two patients had both CPS and GTC. All CPS were from temporal origin; this was the case in 6/15 GTC (2 frontal and 7 parietal origin). Responsiveness was assessed through video review and scoring. The ictal period was split based on generalization onset in GTC (i.e. before/after behavioral tonic phase); CPS were split in two equal parts. We used a three-way ANOVA to contrast CPS vs. GTC in three brain regions (seizure onset zone [SOZ], parietal and frontal areas) during the two ictal periods, focusing on high-gamma and delta power. P values were corrected for multiple comparisons using false discovery rate.
GTC lasted on average 164 seconds, with generalization occurring ~38 sec after seizure onset. CPS lasted on average 110 sec. Both CPS and GTC were characterized by impairment in responsiveness but of different degrees: while 10/13 (77%) CPS showed preserved visual pursuit, all GTC followed a stereotypical sequence of events, with staring and severe LOR preceding head turn and screaming. Only 2/15 (13%) GTC showed a transient period of visual pursuit before this stereotypical sequence (10/13 CPS vs. 2/15 GTC; Fisher's exact test: $p = 0.002$). During the second ictal period, LOR remained partial in CPS, while it was complete in all GTC. Before generalization, both GTC and CPS showed increased high-gamma power in the SOZ, significantly stronger in GTC than CPS ($p < 0.001$), while delta power decreased to a similar extent. In parietal regions, GTC showed increased high-gamma and delta power as

compared to CPS ($p < 0.001$). In frontal regions, delta and high-gamma power changes did not differ between GTC and CPS. After generalization, GTC showed further high-gamma and delta power increase in all brain regions, unlike CPS ($p < 0.001$).
While both CPS and pre-generalization GTC show altered responsiveness, LOR was more severe in GTC. This behavioral difference was accompanied by stronger high-gamma increase in the SOZ, as well as stronger increase in high-gamma and delta power in parietal regions. Our results suggest a broader posterior cortical involvement accompanying more severe LOR in GTC as compared to CPS.

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Poster

649. In Vivo Analyses of Epilepsy Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 649.17/C44

Topic: B.10. Epilepsy

Support: Golshani/Houser R01NS099137

Title: Dissecting the role of temporal lobe epilepsy related parvalbumin+ and somatostatin+ interneuron loss in place cell dysfunction

Authors: ***C. YANG**[1], I. MOLLINEDO GAJATE[3], L. CHEN[4], L. PAGE-HARLEY[5], D. J. CAI[6], D. AHARONI[2], T. SHUMAN[7], P. GOLSHANI[8];
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Abstract: Temporal lobe epilepsy (TLE) is associated with significant cognitive difficulties but the mechanisms underlying these deficits are not understood. We have previously shown that the number of CA1 place cells as well as the precision and stability of place-specific firing decreases in the pilocarpine model of TLE. As TLE has been previously associated with parvalbumin (PV+) and somatostatin (SOM+) interneuron loss, we asked whether decreased activation of these neurons contributed to the altered spatial coding in CA1. We expressed the inhibitory DREADD hM4Di in PV+ or SOM+ interneurons in CA1 using AAV5-Syn-DIO-hM4Di-mCherry injections into CA1 of PV-Cre or SOM-Cre animals, respectively. We performed patch clamp recordings from PV+ or SOM+ neurons in slices, and showed that CNO application significantly decreased the excitability of the hM4di expressing neurons. To determine whether decreased activation of PV+ or SOM+ neurons contributed to poor spatial coding of CA1

pyramidal neurons, we also virally expressed the calcium sensor GCAMP6f in CA1 neurons and used a miniaturized microscope (UCLA Miniscope) to follow the activity patterns of CA1 neurons as animals ran back and forth on a linear track with or without inhibition of PV+ or SOM+ neuronal firing. PV-Cre or SOM-Cre mice expressing FLEXed hM4di were injected with CNO or vehicle solution 45 minutes prior to running on the track while we performed calcium imaging of CA1 neurons. We found no differences in the information content (specificity of each neuron coding of spatial location), stability (reliability of neuron firing at the spatial location across trials), and in proportion of neurons that were place cells compared between animals that received CNO or Vehicle. These findings suggest that decreased activity of CA1 PV+ or SOM+ neurons likely does not significantly contribute to the place cell dysfunction recorded in TLE. Epilepsy-related changes to the activity patterns of CA1 inputs or desynchronization of activity arriving in CA1 may play a more important role than loss of PV+ or SOM+ interneurons.

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Poster

649. In Vivo Analyses of Epilepsy Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 649.18/C45

Topic: B.10. Epilepsy

Support: CURE Taking Flight Award
AES Junior Investigator Award

Title: Deficits in place cell stability and precision have distinct time courses during the progression of pilocarpine-induced epilepsy

Authors: *L. PAGE-HARLEY[1], Y. FENG[1], L. M. VETERE[1], C. R. LEE[2], D. J. CAI[1], P. GOLSHANI[3], D. B. AHARONI[3], T. SHUMAN[1];
[1]Neurosciences, Icahn Sch. of Med. at Mount Sinai, New York, NY; [2]UCSD, San Diego, CA; [3]Neurol., UCLA, Los Angeles, CA

Abstract: Temporal lobe epilepsy (TLE) is associated with debilitating cognitive deficits in human patients and rodent models, but the underlying changes to circuit function that disrupt cognition remain poorly understood. Pilocarpine-treated epileptic mice have disrupted spatial coding in hippocampus, as place cells have less precise and less stable firing patterns compared to those from healthy controls. However, the time course of when spatial coding deficits emerge and how they relate to seizure onset has not been explored. In the pilocarpine-status epilepticus model, seizures take weeks to develop and progressively increase throughout the animal's life. Here we investigated spatial coding in dorsal CA1 of pilocarpine-treated epileptic mice in the

weeks after epileptogenesis in order to determine how stability and precision in spatial coding are altered during the progression of epilepsy. We used *in vivo* calcium imaging with open-source miniature microscopes (Miniscopes) paired with chronic EEG recordings to track spatial coding and seizure activity from 3-8 weeks after pilocarpine. All pilocarpine-treated mice had seizures throughout our recordings which progressively increased from 3 to 8 weeks after pilocarpine. Surprisingly, we found that the stability of spatial coding was initially normal 3-5 weeks after pilocarpine, despite the mice already having seizures throughout that time. Deficits in spatial stability did not emerge until 6-8 weeks after pilocarpine. In contrast, the precision of spatial coding (information content) was reduced in epileptic mice throughout the 3-8 weeks after pilocarpine. Thus, there was a clear dissociation between the precision and stability of the hippocampal place code deficits in epilepsy. In addition, neither of these measures correlated with seizure frequency, suggesting that independent circuit mechanisms lead to altered precision and stability of spatial coding in epilepsy.

Disclosures: L. Page-Harley: None. **Y. Feng:** None. **L.M. Vetere:** None. **C.R. Lee:** None. **D.J. Cai:** None. **P. Golshani:** None. **D.B. Aharoni:** None. **T. Shuman:** None.

Poster

649. In Vivo Analyses of Epilepsy Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 649.19/C46

Topic: B.10. Epilepsy

Title: The ketogenic diet attenuates post-ictal hypoxia

Authors: *R. C. GOM[1], D. BHATT[1], R. M. MYCHASIUK[2], J. M. RHO[3], G. TESKEY[1]; [1]Cell Biol. & Anat., [2]Neurosci., Univ. of Calgary, Calgary, AB, Canada; [3]Alberta Children's Hospital, Univ. of Calgary, Calgary, AB, Canada

Abstract: Rationale: The ketogenic diet (KD) has shown efficacy as an anticonvulsant and results in numerous metabolic changes which influence physiological processes. More recently the KD has been shown to downregulate COX-2 expression and subsequent production of vasoactive prostanoids. Recent evidence has determined that postictal hypoxia, a stroke-like event that follows seizures, is COX-2 dependent. However, the effect of the ketogenic diet on postictal hypoxia is completely unknown. Here we tested the hypothesis that the KD can prevent severe postictal hypoxia using a repetitively induced seizure model (electrical kindling). **Methods:** Young adult Long-Evans rats weighing between 250-300 g at the start of experimentation were used in this study. We measured local tissue oxygenation in the hippocampus before, during and following electrically-induced seizures in awake, freely-moving rats. In the experimental group, the traditional ad libitum diet was replaced with a high fat/protein diet (6:1 fat to protein ratio consisting of lard, butter, corn oil, casein, and a vitamin

and mineral mix) that was maintained 14 days prior to seizure elicitation to ensure systemic ketosis (elevated blood ketone concentration >1.00mmol/L). Seizures were elicited at a suprathreshold (100 μA above previously determined threshold) current on a fixed schedule. In addition to observing changes in postictal hypoxia, measurements including weight change, seizure duration, seizure thresholds, and blood ketones were taken before and after the kindling protocol. **Results and Conclusions:** The KD attenuated postictal hypoxia by raising baseline oxygen levels. As expected, weight gain was reduced in diet exposed rats and a notable increase in blood ketones was measured. Regular chow and KD-treated rats had no significant difference in seizure duration however KD rats had a higher seizure threshold relative to rats receiving regular chow. These preliminary experiments illustrate that metabolic changes with the KD increased baseline oxygen levels rather than neurovascular responses to seizures and may provide another possible treatment to prevent severe postictal hypoxia.

Disclosures: R.C. Gom: None. **D. Bhatt:** None. **R.M. Mychasiuk:** None. **J.M. Rho:** None. **G. Teskey:** None.

Poster

649. In Vivo Analyses of Epilepsy Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 649.20/C47

Topic: B.10. Epilepsy

Title: Dynamic changes in hippocampal oxygen levels following febrile seizures

Authors: *S. HARRIS[1], A. GEORGE[1], K. BARRETT[2], M. H. SCANTLEBURY[1], G. TESKEY[3];
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Abstract: *Rational:* Febrile seizures are the most common convulsive event, occur in childhood, and are preceded by inflammation and fever (above 38.3 ^{o}C). Febrile seizures can have long-term negative consequences such as memory deficits and an enhanced predisposition to develop temporal lobe epilepsy. Human adults with brief self-generated seizures and animals with induced brief seizures display a period of low brain oxygen levels after seizures terminate (postictal hypoxia) that can be prevented by administering either COX-2 blockers or L-type calcium channel antagonists. Animals with traumatic-induced seizures or seizures induced with chemical convulsants typically results in hyperoxia. It is currently unknown what the dynamic oxygen profiles are during and following febrile seizures. Here we examined oxygen dynamics in the hippocampus in two juvenile seizure models; hyperthermic seizures and febrile seizures. *Methods:* Eight-day old rat pups were implanted with an electrode to monitor electrographic activity and an optrode to measure local oxygen in the dorsal hippocampus. In the febrile model

pups received one injection of 400 µg/kg lipopolysaccharide (LPS) per day for 5 days. In the hyperthermic model no injections were given. At 12 days of age rat pups were subjected to exogenous heat in a heated dry air chamber, a common method to elicit seizures. Once a behavioural seizure occurred the pup was removed and allowed to recover while hippocampal oxygen levels and local field potentials were monitored.
Results and Conclusions: Infant rats typically display lower baseline oxygen levels in the hippocampus than their adult counterparts. However, in 12/20 pups we also observed a further drop in oxygen followed by a period of higher than baseline oxygen levels. 8/20 young rats did not show hippocampal hypoxia and only displayed higher than baseline oxygen levels following a hyperthermic convulsion. We have found that oxygen levels in the rat pup hippocampus following a hyperthermic convulsion were variable, with both increased and decreased levels observed. This research provides insight into the oxygen dynamics in the developing brain during common childhood convulsive events.

Disclosures: S. Harris: None. **A. George:** None. **K. Barrett:** None. **M.H. Scantlebury:** None. **G. Teskey:** None.

Poster

649. In Vivo Analyses of Epilepsy Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 649.21/C48

Topic: G.02. Motivation

Title: Expression of Scn1a in brain regions related to sexual motivation

Authors: *A. CROCKETT[1], H. MARTIN[1], S. SANCHEZ[1], S. B. DUTTON[2];
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Abstract: Individuals with epilepsy commonly report sexual dysfunctions, including an inability to orgasm, lack of sexual motivation, and erectile dysfunctions. These behaviors are reported at a higher percentage in patients with epilepsy compared to the general population. Currently, little information is available on the role that epilepsy plays on the specific brains regions that underlie these quality of life altering behaviors. The amygdala, nucleus accumbens, and medial preoptic area have been established as important brain regions for modulating sexual behaviors, particularly the motivational aspects. The present study examines the expression of the voltage-gated sodium channel $Na_v1.1$ in these regions of female R1648H (RH) GEFS+ mice. The RH mouse model of GEFS+ is an established line that recapitulates many of the symptoms patients with the condition present, including spontaneous seizures, increased susceptibility to febrile seizures, increased anxiety and altered cognition. In this current study, we determined the relative distribution of $Na_v1.1$ in inhibitory and excitatory cells in the amygdala, nucleus accumbens, and medial preoptic area and identified alterations in their expression. These results

suggests a potential mechanism for the altered sexual behavior seen in patients with epilepsy, and possibly other neurological disorders.

Disclosures: **A. Crockett:** None. **H. Martin:** None. **S. Sanchez:** None. **S.B. Dutton:** None.

Poster

649. In Vivo Analyses of Epilepsy Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 649.22/C49

Topic: B.10. Epilepsy

Support: DFG IS63/10-1

Title: Early postnatal cellular and network perturbations in the hippocampus of mice with a genetic $Na_v1.2$ channelopathy

Authors: *K. ULRICH[1], Y. LIU[2], M. BARBONI[3], M. SAMEHNI[1], S. MARGUET[1], R. M. NEVES[1], I. JAKOVCEVSKI[1], M. STOCKEBRAND[1], B. ENGELAND[1], H. BECK[3], H. LERCHE[2], T. KELLY[3], D. ISBRANDT[1];
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Abstract: Neuronal network perturbations during early life such as those caused by ion channel dysfunctions can lead to neurodevelopmental disorders including epileptic encephalopathies (EE). Mutations in the *SCN2A* gene encoding the voltage-gated sodium channel alpha subunit $Na_v1.2$ are associated with a broad spectrum of epilepsies, ranging from benign phenotypes to severe EE including cognitive impairment. To investigate the mechanisms of epileptogenesis, we generated a knock-in mouse model harboring the missense mutation *Scn2a* (p.A263V), which was previously identified in a patient with neonatal onset, therapy-resistant seizures and resulted in a gain-of-function of heterologously expressed Nav1.2 channels. Homozygous and heterozygous A263V knock-in mice were viable but showed reduced body weight, increased mortality and behavioral deficits, which manifested as early as postnatal day P7. At this age, animals also exhibited increased cFos immunoreactivity in the hippocampus indicating increased neuronal activity. Furthermore, surviving mice showed spontaneous behavioral seizures. Hippocampal local field potential (LFP) silicone probe depth recordings from head-fixed awake neonatal mice revealed ictal network activity as early as P2, which evolved in frequency content, amplitude and duration during the first two postnatal weeks. Hippocampal CA1 pyramidal neurons exhibited an increased action potential firing frequency in in-vitro patch-clamp recordings from P21-28 mutant mice. We are characterizing the developmental and regional specificity of changes in neuronal excitability in CA3 and CA1 neurons from P10-14 and P21-28

mice. Characterization of somatic neuronal excitability in the hippocampal CA1 and CA3 regions in acute slices indicated increased somatic excitability in hetero- and homozygous mutants. Together, these results indicate a disease onset shortly after birth during early stages of hippocampal network maturation. Therefore, preventive therapeutic approaches would need to be targeted to the first postnatal weeks.

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Poster

649. In Vivo Analyses of Epilepsy Models

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Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 649.23/C50

Topic: B.10. Epilepsy

Support: DFG KFO219
DFG TP13
SFB1089

Title: Loss of I_h in forebrain during a critical period of striatal synaptogenesis results in somatomotor dysfunctions and antipsychotic-responsive hyperactivity

Authors: *A. MERSEBURG[1], S. SANDKE[2], I. JAKOVCEVSKI[1], A. NEU[3], Z. HUANG[4], M. SHAH[4], S. MARGUET[1], R. MELO NEVES[1], J. ROEPER[5], F. MORELLINI[2], D. ISBRANDT[1]; [1]Univ. of Cologne/ DZNE Bonn, Cologne, Germany; [2]Ctr. for Mol. Neurobio. Hamburg, Hamburg, Germany; [3]Univ. Clin. Hamburg Eppendorf, Hamburg, Germany; [4]UCL Sch. of Pharm., Univ. Col. London, London, United Kingdom; [5]Goethe Univ. Frankfurt, Frankfurt, Germany

Abstract: Hyperpolarization-activated, cyclic nucleotide-gated subunits (HCN) 1 to 4 mediate I(h), which is suggested to contribute to development-dependent network activity and maturation of the CNS. *De novo* mutations in *HCN1* are associated with early infantile epileptic encephalopathies (EIEE), and other neurodevelopmental disorders, including autism spectrum disorder. HCN channel-mediated currents are subject to developmental regulation over the course of pre- and postnatal development, including subunit composition, subcellular location and underlying current properties. Studies aimed at investigating I(h) function during brain development are limited when using knockout mouse models that target only specific subunits of the HCN1-4 family. Here, we present an approach that is designed to functionally and conditionally ablate I(h), independent of subunit composition, by controlling the expression of a dominant-negative HCN subunit (HCN-DN) with the Tet-off doxycycline (Dox) system and

CaMKIIα promoter-regulated expression in forebrain projection neurons in double transgenic mutant mice. This strategy allowed us to ablate I(h) independent of the underlying developmental expression pattern. We show that lifelong I(h) loss starting around birth is associated with impaired somatomotor development in neonatal mutants and psychomotor disturbances, including behavioral hyperactivity paired with stereotyped circling, and motor deficits in adult mutants. Notably, restricting I(h) loss to an early postnatal period, i.e., to the first three weeks of life, had more severe consequences than lifelong ablation of I(h) in that these mice also exhibited cognitive symptoms, indicating the presence of developmental changes that are not reversible by simple re-introduction of I(h). Of note, the locomotor hyperactivity could not be ameliorated by the administration of the psychostimulant methylphenidate which is a common treatment for ADHD hyperactivity. Instead, I(h)-deficient mutants responded to blocking D2-like dopamine receptors (D2R) with the typical antipsychotic haloperidol, or to the specific D2R blocker eticlopride. In addition, DREADD-mediated activation of indirect-pathway, D2R-expressing medium spiny neurons in the striatum of mutant animals strongly ameliorated the locomotor hyperactivity. Together, our results suggest that developmental I(h) loss in forebrain projection neurons caused persistent changes in cortico-striatal circuits and associated motor behaviors, resulting in a phenotype that is reminiscent of neurodevelopmental co-morbidities in disorders such as EIEE.

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Poster

649. In Vivo Analyses of Epilepsy Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 649.24/C51

Topic: B.10. Epilepsy

Support: NIH NINDS R21 NS106434-01

Title: *In vivo* optical imaging and simultaneous electrophysiological recording from hippocampal CA1 neurons with transparent graphene electrodes arrays

Authors: N. DRISCOLL[1], B. MURPHY[1], F. VITALE[2,3], ***H. TAKANO**[4,2];
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Abstract: High-frequency oscillations (HFOs), when observed in electroencephalograms, have been proposed as a biomarker for epilepsy and, thus could potentially be used to identify the seizure onset zone. Understanding the cellular origin of HFO generation in animal models of

epilepsy is important for establishing HFOs as a biomarker for potentially improving both diagnostic and surgical precision. Multicellular calcium imaging allows characterizing the dynamic properties of multiple cells (>200 neurons) and provides information on functional connectivity and signal propagation through analysis of ordered temporal firing patterns. Because of the large number of cells that can be simultaneously probed with this technique, it can also provide the ability to isolate an unusual cellular population in pathological tissues. Unfortunately, because of the nature of calcium ion probing molecules, the temporal resolution is poor. To overcome this limitation, we demonstrated that a transparent electrode made of graphene can be used to record local field potentials (LFPs) and simultaneously image activities of multiple neurons via calcium imaging. We recorded 4AP-induced seizure activity simultaneously on the graphene electrodes and through calcium epifluorescence imaging in anesthetized GCaMP6-expressing mice (Jax #025776, Jackson Laboratory). More recently, we developed a transparent graphene electrode array/cannula assembly and implanted it *in vivo* to conduct imaging/recording of hippocampal CA1 pyramidal neurons. We implanted the electrode/cannula assembly consisting of 3 mm (O.D.) stainless steel tube with microelectrode arrays with a 4x4 grid of 50x50 µm2 graphene contacts in Thy-1 GCaMP6 mice. We recorded hippocampal CA1 activity simultaneously on the graphene electrodes and through calcium imaging by two-photon microscopy at cellular resolution. We apply this innovative multimodal, multiscale technology to kainate-induced cortical injury model to elucidate the dynamics of seizure generation and propagation at the cellular level.

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Poster

649. In Vivo Analyses of Epilepsy Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

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Topic: B.10. Epilepsy

Support: NIH Grant 1R01NS094668

Title: *In vivo* 2-photon assessment of dentate gyrus network function in the kainate mouse model of medial temporal lobe epilepsy

Authors: *F. T. SPARKS[1], Z. LIAO[2], I. SOLTESZ[3], A. LOSONCZY[2];
[2]Neurosci., [1]Columbia Univ., New York, NY; [3]Sch. of Med., Stanford Univ., Stanford, CA

Abstract: Temporal lobe epilepsy (TLE) is characterized by spontaneous recurrent seizures, and is the most common form of adult epilepsy. In light of efforts spent characterizing this disease, effective treatments and a cure have remained elusive. TLE develops over a latent period that comprises structural and functional changes to the hippocampus (HPC) including neuronal loss,

reactive gliosis, inflammation and neurogenesis. Epileptic seizures result in aberrant HPC neurogenesis, characterized by an increase in neural progenitor proliferation, production of ectopic granule cells, mossy fibre sprouting, neuronal hypertrophy and persistence of hilar basal dendrites on adult-born granule cells (abGCs). The intrinsically low excitability of the dentate gyrus (DG) acts to gate pathological activity from propagating through the HPC, and the breakdown of the DG gate is hypothesized to contribute to TLE. Evidence for the role of adult born neurons in the pathogenesis of TLE is lacking, though recent evidence suggests development of recurrent microcircuits possibly driven by aberrant abGC connectivity within the DG and CA3 abGC-GC-mossy cell (MC) populations. To assess the role of abGCs in TLE related electrographic activity, we used genetic cell-type specific labeling of newborn cells and MCs, and monitored DG neural activity in a unilateral HPC kainic acid mouse model of TLE. Using *in vivo* 2-photon calcium multi-plane imaging with concurrent local field potential (LFP) recording while mice explored a linear treadmill environment, we were able to visualize DG network dynamics during seizure events characterized by electromyography. abGC activity levels tend to increase at seizure initiation, followed by mature GCs, MCs and interneurons. MC and interneuron activity persists beyond that of all GCs as seizures terminate and the DG enters a period of general quiescence. These observations suggest that abGCs may play a leading role in seizure genesis. This possibility is supported by recent evidence linking pharmacological inhibition of abGCs with a general decrease in epilepsy related pathological LFP activity.
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Disclosures: **F.T. Sparks:** None. **Z. Liao:** None. **I. Soltesz:** None. **A. Losonczy:** None.

Poster

649. In Vivo Analyses of Epilepsy Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 649.26/C53

Topic: B.10. Epilepsy

Title: Ca^{2+} imaging in seizured brain of novel zebrafish model

Authors: *L. SHIGEMITSU, K. OGINO, H. HIRATA;
Dept. of Chem. and Biol. Sci., Aoyama Gakuin Univ., Sagamihara, Japan

Abstract: A chronic brain disorder, epilepsy, is pathologically characterized by sudden spasm and/or loss of consciousness and is caused by hyperexcitability of the brain. The excess excitability can be induced by the efflux of chloride ion from neurons in the brain. One of the causes of epilepsy is the increase of chloride reversal potential induced by the loss of KCC2, which is known as a potassium-chloride cotransporter, consequently resulting in the excess activation of neural networks. Zebrafish have two paralogs of KCC2 gene (KCC2a and KCC2b), which were generated by ancestral gene duplication and both are expressed by the CNS. Here,

we found that KCC2a-KCC2b double knockout mutant (DKO) zebrafish exhibits the epileptic phenotype when exposed to LED flash light. However, how this epilepsy is triggered by external optical stimuli remain unclear. Therefore, we aimed to elucidate the location of focal area of the seizured brain in larval zebrafish. First, we established a motor assay to induce epilepsy following exposure to red flash light. Second, to visualize neural activity in seizured brain, we prepared KCC2a-KCC2b DKO zebrafish larvae (5 dpf) by genome editing crossed with a GCaMP transgenic for visualization of brain activity in the CNS. Finally, we performed *in vivo* calcium imaging and analyzed the increase of fluorescence intensity in five regions of the brain; cerebellum, diencephalon, telencephalon, optic tectum and hindbrain. Surprisingly, we found that all of the brain regions in KCC2a-KCC2b DKO larvae showed higher and persistent activity compared to that in wild-type larvae. Our spatial and temporal analysis also revealed that functionally reversed inhibitory transduction generates excess neural activity, which is different from a simple enhancement of neuronal excitability induced by PTZ. Taken together, we established a new pathologically relevant epilepsy model in zebrafish.

Disclosures: L. Shigemitsu: None. **K. Ogino:** None. **H. Hirata:** None.

Poster

649. In Vivo Analyses of Epilepsy Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 649.27/C54

Topic: B.10. Epilepsy

Support: UC Davis MIND Institute IDDRC grant (U54 HD079125)

Title: Using zebrafish as a tool to study SLC7A5, a gene implicated in autism spectrum disorder and epilepsy

Authors: *A. COLON-RODRIGUEZ[1], J. M. URIBE SALAZAR[1], A. SRIRAM[1], P. LEIN[2], L.-E. JAO[3], M. Y. DENNIS[4];
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Abstract: Autism spectrum disorder (ASD) affects 1 in 59 children according to the Center for Disease Control with many cases caused by often-unknown genetic alterations. Mutations of ion channels and/or transporters are commonly found to be an underlying factor. For example, mutations in *SLC7A5*, a gene encoding the large amino acid transporter LAT1, have recently been identified in patients with ASD, motor impairment, developmental delay, microcephaly and intractable seizures. Recent studies using conditional knockout *Slc7a5* mice showed that mutants exhibit decreased neuronal inhibition, microcephaly, decreased exploratory behavior, and motor delay compared to wildtype animals. We hypothesize that loss-of-function mutations of *slc7a5* in

zebrafish will recapitulate neurological phenotypes observed in patients and mouse models. Using zebrafish allows us to conduct experiments in higher throughput due to their high fecundity and rapid embryonic development. To generate mosaic F_0 mutants at high efficiency, we used a pooled CRISPR gene editing approach. Subsequent morphological and behavioral analyses were performed of 5 days post fertilization (dpf) mutant- and mock-injected zebrafish. Our results show a significant decrease in head size ($p=0.0002$) and increase in locomotor activity ($p=0.004$) in the presence of a $GABA_A$ antagonist (PTZ) between our mosaic mutant *slc7a5* zebrafish compared to our control fish. These phenotypes recapitulate the results observed in the conditional knockout rodent model and patients. Ongoing studies include validation of identified defects in stable lines carrying null mutations of *slc7a* as well as characterization of additional phenotypes, including seizures via electroencephalograms and neurodevelopmental defects. The results of this study will lay the groundwork to (1) identify neurodevelopmental alterations caused by *slc7a5* mutations in zebrafish and (2) develop tools that we will continue to use as we move forward to characterize unknown disease-related mutations in a higher-throughput manner.

Disclosures: **A. Colon-Rodriguez:** None. **J.M. Uribe Salazar:** None. **A. Sriram:** None. **P. Lein:** None. **L. Jao:** None. **M.Y. Dennis:** None.

Poster

650. Tau: Animal and Cellular Models II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 650.01/C55

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

Support: ASRP-NI to SGW

Title: Anatomical staging of a rat pretangle model of sporadic Alzheimer’s disease

Authors: *S. G. WALLING[1], M. WASEF[2], A. GHOSH[3], G. MARTIN[4], C. W. HARLEY[2], Q. YUAN[5], D. M. SKINNER[6];
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Abstract: Persistently phosphorylated tau (pPhtau), is associated with neurofibrillary tangles, a hallmark of Alzheimer’s disease (AD). pPhtau is first localized to the locus coeruleus (LC) in young adults, and progresses to insoluble tau and tangles in later stages of AD tauopathy (Braak et al., 2011). We have modelled the LC pretangle stages of sporadic AD in male and female TH-Cre rats by infusing an adenoassociated virus (AAV) with a pseudophosphorylated human tau

gene, htauE14 (Karen Ashe plasmid, Addgene) into the LC. To examine the expression and transfer of LC-htauE14 to modulatory regions and cortical structures, as predicted by Braak, rats were infused with 1μL of AAV9-hEF1a-DIO-eGFP-htauE14-WPRE (Virovek, CA) into the LC bilaterally, or controls (sham/vehicle). Brain tissue was examined for GFP and human tau at 1-mo (T1) post-infusion (p.i.) and at 3-mo intervals (T2-5). GFP antibody (ThermoFisher, rabbit, 1:5000) and an antibody against human tau (HT7, ThermoFisher, mouse, 1:5000) was used to detect eGFP-htauE14 in free floating coronal (LC) and horizontal forebrain sections using a DAB-metal kit (ThermoFisher). Images were collected using a Zeiss BX-2 microscope and converted to grayscale for densitometry measurement (MCID, UK). Relative optical density measurements (ROD) were collected from htauE14 LC infused male and female rats and compared to ROD measurements of control rats (sham, vehicle infused). Results: At T1 (1-1.5 mo p.i.) GFP- ROD measurements were increased in the LC, dorsal raphe, and lateral entorhinal cortex in htauE14 infused rats over control rats. Positive transneuronal transfer of GFP was observed in pyramidal and non-pyramidal cells of the hippocampal complex (specifically, parasubiculum). HT7-ROD measurement mirrored the GFP increases whereby HT7-ROD was also higher in the LC, dorsal raphe, and lateral entorhinal cortex compared to control rats. These results demonstrate the successful uptake and expression of AAV-eGFP-htauE14 in LC neurons in the pretangle AD model, and further characterize transfer to modulatory (raphe) and cortical brain regions at the first period outlined (T1).

Disclosures: S.G. Walling: None. **M. Wasef:** None. **A. Ghosh:** None. **G. Martin:** None. **C.W. Harley:** None. **Q. Yuan:** None. **D.M. Skinner:** None.

Poster

650. Tau: Animal and Cellular Models II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 650.02/C56

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

Support: ASRP-NI to SGW

Title: Behavioural staging of a rat pretangle model of sporadic Alzheimer’s disease (AD): Longitudinal effects of locus coeruleus htauE14 on tests of pattern separation

Authors: *D. M. SKINNER[1], M. WASEF[2], T. CASSELL[2], V. HARVEY[2], H. BAKER[2], H. DICKS[2], A. POMROY[2], A. GHOSH[3], G. M. MARTIN[2], C. W. HARLEY[4], Q. YUAN[3], S. G. WALLING[4];
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Abstract: Persistently phosphorylated tau (pPtau), the precursor to the neurofibrillary tangles (NFTs) found in Alzheimer's disease (AD), is first found in the locus coeruleus (LC) in young adulthood (Braak et al., 2011). Soluble pPtau (pretangle) progresses to insoluble pPtau and NFTs in more advanced stages of tauopathy in higher cortical regions in AD. Given that the LC is implicated in the earliest stages of tau dysfunction, we have modelled the pretangle stages of AD in TH-Cre rats by infusing an adenoassociated virus (AAV) with a pseudophosphorylated human tau gene (htauE14, Karen Ash, Addgene) into the LC. To examine the effects of htauE14 on LC function, we assess performance on two pattern separation tasks longitudinally. TH-Cre rats infused with 1μL AAV9-hEF1a-DIO-eGFP-htauE14-WPRE (Virovek, CA) bilaterally into the LC, and controls (sham, vehicle or AAV-eGFP) were tested on olfactory and spatial pattern separation tasks at 1-mo post-infusion (p.i.), and 3-mo intervals thereafter (to 13-mo p.i.). LC-piriform dependent olfactory discrimination (OD) tests were assessed at two levels of difficulty, using the methods of Tronel and Sara (2003): Simple OD (SOD; almond vs banana) and a Difficult OD (DOD; heptanol vs 50:50 heptanol:octanol). OD tests took place in an open field with 3 scent infused sponges (1-S^+, 2-S^-) for FrootLoop reinforcement. Rats were given 6 training trials with the S^+ location changed on each trial and tested 48-hr later. At T1 (1-mo p.i.) there were no differences in %correct or place errors (nosepoke in previously reinforced location) for sex or htau condition in the SOD. However, preliminary data suggest female htauE14 infused rats had a lower %correct compared to female control rats in the DOD. Male htauE14-infused and control rats did not differ in the %correct choice. In the spatial separation task, rats were trained for 10 trials/day to discriminate between reinforced (S+) and non-reinforced (S-) arms in adjacent locations on a radial arm maze (RAM). No differences in trials to criterion (9/10 correct) between sex or htau condition were found at T1. Data at this staging period suggests the effects of LC-htauE14 on pattern separation first produces deficits in olfactory DOD (female) rather than deficits in spatial separation (adj-RAM).

Disclosures: D.M. Skinner: None. **M. Wasef:** None. **T. Cassell:** None. **V. Harvey:** None. **H. Baker:** None. **H. Dicks:** None. **A. Pomroy:** None. **A. Ghosh:** None. **G.M. Martin:** None. **C.W. Harley:** None. **Q. Yuan:** None. **S.G. Walling:** None.

Poster

650. Tau: Animal and Cellular Models II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 650.03/C57

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

Support: ASRP-NI2SGW

Title: Behavioural staging of a rat pretangle model of sporadic Alzheimer's disease (AD): Longitudinal testing of AD phenotype

Authors: *M. A. WASEF[1], A. GHOSH[2], G. MARTIN[3], C. W. HARLEY[5], Q. YUAN[6], D. M. SKINNER[4], S. G. WALLING[5];
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Abstract: The locus coeruleus (LC) is implicated in the earliest stages of tauopathy and Alzheimer's disease (AD). Persistently phosphorylated tau is first localized to the LC in young adulthood in pretangle stages and the progression to insoluble tau and neurofibrillary tangles in cortical structures is associated with the progression of sporadic AD (Braak et al., 2011). We modelled the pretangle stages of AD in TH-Cre rats by infusing an adenoassociated virus (AAV) with a pseudophosphorylated human tau gene (htauE14) into the LC. To examine the effects of LC-htauE14, we assessed cognitive performance longitudinally in rats to mimic the repeated testing to assess cognitive impairment used in humans. Rats infused with 1μL of AAV9-hEF1a-DIO-eGFP-htauE14-WPRE (Virovek, CA) into the LC bilaterally, or controls (sham/vehicle/AAV-GFP), were tested at 1-mo (T1) post-infusion (p.i.) and 3-mo intervals (T2-5), on 4 behavioural tests. Spontaneous alternation in a Y-maze was used as a test of spatial working memory and no differences between sex or condition were found at T1 in the % alternation, or number of arm entries in an 8-min exposure. Novel object recognition was assessed in the same Y-maze. All rats were more likely to spend time in the arm containing a novel object compared to the arm containing a familiar object, 24-hr after initial exposure. In the cued platform version of the Morris Water Maze no differences were observed in escape latencies. In the hidden platform version, male htauE14 rats had significantly longer escape latencies than male controls at T1. By the last day of testing, no differences were found between male groups. There were no differences between female htauE14 and control groups in the hidden platform task, and there were no sex or group differences in the no-platform probe. In the What-Where-When episodic memory task, 2 5-min exploration trials (ITI 5-min) each with 2 distinct objects in distinct locations were followed by a 5-min test in which all 4 previously explored objects were presented, 2 in the same (static) locations and 2 in novel (switched) locations. No differences were found across sex or htau condition. These results detail subtle changes in the LC-htauE14 AD phenotype at the earliest behavioural staging interval (T1).

Disclosures: M.A. Wasef: None. **A. Ghosh:** None. **G. Martin:** None. **C.W. Harley:** None. **Q. Yuan:** None. **D.M. Skinner:** None. **S.G. Walling:** None.

Poster

650. Tau: Animal and Cellular Models II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 650.04/C58

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

Title: Study of spatial memory impairment and hippocampal neurodegeneration in okadaic acid induced rat model of Alzheimer's disease

Authors: *M. CHIGHLADZE[1], G. BESELIA[2], M. DASHNIANI[1], M. BURJANADZE[1], N. CHKHIKVISHVILI[1], L. KRUASHVILI[1], T. NANEISHVILI[3];
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Abstract: Alzheimer's disease (AD) is a neurodegenerative disease that causes progressive cognitive and behavior impairment in the elderly. It is widely believed that changes in the cerebral activity of protein phosphatases have been implicated in the pathogenesis of AD. Okadaic acid (OA) is a potent and selective inhibitor of protein phosphatases. Because of its property to inhibit phosphatase activity, OA is associated with protein phosphorylation and has been proved to be a powerful probe for studying the various regulatory mechanisms and neurotoxicity (intracerebral injection of OA, would provide a useful model of Alzheimer's disease). In the present study, we evaluated and compared effect of intracerebroventricular (ICV) and intrahippocampal bilateral microinjection of okadaic acid (OA) on spatial memory function assessed in one day water maze paradigm and hippocampal structure in rats. Rats were divided in following groups: Control(icv) - rats injected ICV with artificial cerebrospinal fluid (aCSF); Control(hipp) - rats injected intrahippocampally with aCSF; OA(icv) - rats injected ICV with OA; OA(hipp) - rats injected intrahippocampally with OA. At the end of the behavioral experiments OA treated and control rats were deeply anesthetized with pentobarbital and perfused through the ascending aorta with 300 ml saline followed by 600 ml 4% paraformaldehyde in 0.1 M phosphate buffer (pH 7.4)). The surviving pyramidal cells in the hippocampus of rats were visualized by Nissl staining. The number of the hippocampal pyramidal cells in Nissl staining sections was counted at X 400 magnification. Nissl staining of hippocampal sections showed that the pyramidal cell loss in OAhipp group is significantly higher than that in the OAicv . The results of our behavioral experiments showed that all rats exhibited a decreased latency to find the hidden platform across the eight training trials and OA treatment did not affects probe-test performance 30m after training. In marked contrast, the present experiments indicate that OA treatment affects probe-test performance 24 h after training. These findings suggest that OA treatment did not affect learning process and short-term spatial memory but induced impairment in spatial long-term memory. OA-induced spatial memory impairment may be attributed to the hippocampal cell death. Based on these results OA induced memory deficit and hippocampal cell loss in rat may be considered as a potential animal model for preclinical evaluation of antidementic drug activity.

Disclosures: M. Chighladze: None. **G. Beselia:** None. **M. Dashniani:** None. **M. Burjanadze:** None. **N. Chkhikvishvili:** None. **L. Kruashvili:** None. **T. Naneishvili:** None.

Poster

650. Tau: Animal and Cellular Models II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 650.05/C59

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

Title: Generation of human iPSC derived cerebral organoids to model Alzheimer's disease

Authors: *D. LEE[1], J.-C. PARK[1], S.-H. HAN[3], M. BYUN[4], D. YI[4], J. LEE[5], D. LEE[2], I. MOOK-JUNG[1];
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Abstract: Alzheimer's disease(AD) is a devastating neurodegenerative disorder which leads to cognitive impairment and consequent behavioral abnormalities in patients. As in many diseases that afflict the central nervous system, progress in AD research has been largely hampered by difficulty in acquiring adequate human samples and inevitable limitations of animal models. Utilization of brain organoids could possibly surpass these hurdles by providing *in vitro* models of human origin that reliably represent pathological conditions of an AD brain.
Participants of the study were classified into Alzheimer’s disease(AD)/mild cognitive impairment(MCI)/cognitively normal(CN) groups by pre-established standards based on PiB/Tau/FDG PET & MRI imaging data. From patients’ blood samples we extracted peripheral blood mononuclear cells(PBMCs) and solely activated T cells for efficient introduction of transcription factors. Sendai viruses encoding four Yamanaka factors were infected to these cells to generate induced pluripotent stem cells(iPSCs). Then we aggregated iPSCs to form embryoid bodies and cultured them in suspension. Addition of defined growth factors at specific time points led to the differentiation of distinct cell types in organoids. Prolonged culture in suspension ultimately resulted in the maturation of cerebral organoids. We performed immunohistochemistry experiment with these organoids and observed major hallmarks of AD: amyloid beta plaques and neurofibrillary tau tangles. Secreted proteins such as amyloid beta 40, amyloid beta 42, total tau, and phospho-tau from organoids were detected by ELISA which showed a marked difference between AD and control group. These findings suggest that organoids are capable of recapitulating pathophysiology observed *in vivo*. Employing the system, we further aim to investigate how AD/control organoids differ in reacting to various environmental stimuli.

Disclosures: D. Lee: None. **J. Park:** None. **S. Han:** None. **M. Byun:** None. **D. Yi:** None. **J. Lee:** None. **D. Lee:** None. **I. Mook-Jung:** None.

Poster

650. Tau: Animal and Cellular Models II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 650.06/C60

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

Support: Arizona Alzheimer's Research Consortium
Barrow Neurological Foundation
NIH P01 AG014449
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BrightFocus Foundation

Title: Characterization of the molecular interplay between amyloid, nuclear splicing proteins and tau isoforms in Down syndrome hiPSC cortical neurons

Authors: *S. E. PEREZ, I. LORENZINI, J. LEVY, C. BURCIU, R. SATTLER, E. J. MUFSON;
Barrow Neurolog. Inst., Phoenix, AZ

Abstract: Despite the presence of neurofibrillary tangle (NFT) and beta amyloid (Aβ) pathologies in the brain of adults with Down syndrome (DS), only two-thirds develop dementia (DSD+). Recently, we demonstrated a greater number of NFTs compared to amyloid plaques in the frontal cortex (FC) of DSD+ compared to non-demented DS (DSD-) individuals (Perez et al., 2019). However, the cellular and molecular mechanisms that underlie the increase in tau pathology between these two groups remain unknown. Recent studies suggest that alteration in nuclear splicing proteins play a role in NFTs in DS (Hales et al., 2014). Preliminary studies by our group found a reduction in the nuclear splicing factors SR splicing factor 2 (SRSF2 or SC35), SR repetitive matrix protein 2 (SRRM2) and heterogeneous nuclear (hn) RNP A2B1 in FC neurons in DS. Furthermore, we found an increase in extranuclear U1-70k small nuclear ribonucleoproteins (snRNP), which was associated with NFTs in FC neurons in DSD+ compared to DSD-. Functionally, dysregulation of splicing proteins has been associated with changes in the ratio of three (3R) and four (4R) microtubule-repeat tau isoforms, which is linked to NFT formation in various tauopathies. To examine the role of amyloid in tauopathies and dysregulation of splicing proteins we used trysomic and dysomic human induced pluripotent stem cells (hiPSCs) obtained from a one month-old mosaic DS case, which were differentiated into cortical neurons (CN). At day 65 of differentiation, hiPSCs-CNs were treated with 0.1 µM $A\beta_{25-35}$ for three days. Cells were then fixed and processed for the visualization of SRSF2, SRRM2, U1-70k, hnRNP A2B1, the early tau phosphorylation marker AT8 ($pSer^{202}/Thr^{205}$), 3R tau and MAP 2 using standard immunofluorescence techniques. Preliminary observations derived from non-$A\beta_{25-35}$ treated disomic and trysomic hiPSCs-CNs revealed that MAP 2-

positive neurons displayed immunoreactivity for the splicing proteins U1-70k, hnRNP A2B1, SRRM2, SRSF2 and tau markers AT8 and 3R. In addition, we found a reduction in hnRNP A2B1 and 3R immunofluorescence in $A\beta_{25-35}$ treated disomic and trysomic hiPSC-CNs. AT8 fluorescence was reduced in trysomic compared to disomic hiPSC-CNs independent of $A\beta_{25-35}$ treatment. No changes were observed for U1-70k across treatments and cell lines. These preliminary data suggest that Aβ affects select splicing proteins and tau markers in both disomic and trysomic hiPSCs-CNs, suggesting that DS-derived hiPSC-CNs provide a robust human *in vitro* model to study the molecular mechanisms behind the interactions of amyloid, tau and RNA splicing.

Disclosures: S.E. Perez: None. **I. Lorenzini:** None. **J. Levy:** None. **C. Burciu:** None. **R. Sattler:** None. **E.J. Mufson:** None.

Poster

650. Tau: Animal and Cellular Models II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 650.07/C61

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

Title: Tauopathy induced degradation of Per2 leads to circadian rhythm disruption in Alzheimer's disease

Authors: *H. KIM[1], A. KIM[2], J. PARK[3], S. CHO[4], I. MOOK-JUNG[5];
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Abstract: Alzheimer's disease (AD) is the most common type of dementia. Pathologies of Alzheimer's disease are represented by amyloid plaque, neuro-fibrillary tangle (NFT) and gliosis. NFT, majorly consist of pathological tau protein, is highly correlated with cognitive impairment in AD. Recently, sleep deprivation and circadian rhythm disruption show high correlation with AD pathology. Previously, molecular mechanism of circadian rhythm disruption by amyloid beta (Aβ) was revealed. Focus of this study is molecular mechanism of circadian rhythm disruption in AD especially with tauopathy. AD pathology model mice ($ADLP^{Tau}$) were used in this study. $ADLP^{Tau}$ has hTau P301L and showing tauopathy, not amyloid pathology. $ADLP^{Tau}$ shows tauopathy and circadian rhythm disruption. Specifically, phase delay and body temperature of $ADLP^{Tau}$ mice was altered from wild type. In mRNA level, several clock gene oscillation was disrupted. In protein level, Per2 core clock protein was decreased in entire time point. From this results, degradation of Per2 induced by tauopathy was investigated and we

suggest this for major underlying mechanism of circadian rhythm disruption in AD and tauopathy.

Disclosures: H. Kim: None. **A. Kim:** None. **J. Park:** None. **S. Cho:** None. **I. Mook-Jung:** None.

Poster

650. Tau: Animal and Cellular Models II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 650.08/C62

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

Title: aβ accelerates uptake of extracellular tau via endocytic pathway

Authors: *K. SUH[1], D. KIM[2], I. MOOK-JUNG[3];
[1]Seoul Natl. Univ., Seoul, Korea, Republic of; [2]Seoul Natl. University, Grad. Sch., Seoul City, Chongno-Gu, Korea, Republic of; [3]Seoul Natnl Univ. Col. Med., Seoul, Korea, Republic of

Abstract: In Alzheimer’s disease (AD), pathological tau protein propagates along the neuronal circuit in highly conserved pattern. As accumulation of Aβ precedes the formation and propagation of tau, pre-existing Aβ may affect the propagation of tau. However, clear relationship between Aβ and tau propagation is poorly understood. To confirm the effect of Aβ on tau propagation, we constructed a novel mouse model for AD, ADLP^{APT} mice, which expresses both Aβ and human tau. We observed the accelerated tauopathy affected by Aβ in ADLP^{APT} mice. However, Aβ pathology is not affected by the presence of pathological tau, indicating that Aβ can work as an accelerant for the propagation of tau but not vice versa. Using neuronal cell line, we found that secretion of tau is not accelerated in presence of Aβ, while uptake of extracellular tau is accelerated in Aβ dependent manner. Extracellular tau is internalized via endocytic pathway. Taken together, we show that Aβ facilitates the propagation of tau by increasing neuronal uptake of extracellular tau, and the internalized tau induces formation of neurofibrillary tangles and cytotoxicity in receptor neurons, thereby promoting neuronal cell death.

Disclosures: K. Suh: None. **D. Kim:** None. **I. Mook-Jung:** None.

Poster

650. Tau: Animal and Cellular Models II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 650.09/C63

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

Title: Transfer of a healthy microbiota reduces amyloid and tau pathology in an Alzheimer's disease animal model

Authors: *H. CHOI[1], M.-S. KIM[2,3], Y. KIM[4], W. KIM[5], S. PARK[5], D. LEE[4], D. KIM[4], H. KIM[4], H. CHOI[4], D.-W. HYUN[3], J.-Y. LEE[3], E. CHOI[5], D.-S. LEE[5], J.-W. BAE[3], I. MOOK-JUNG[1,4];
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Abstract: Cerebral amyloidosis and severe tauopathy in the brain are key pathological features of Alzheimer’s disease (AD). Despite a strong influence of the intestinal microbiota on AD, the causal relationship between the gut microbiota and AD pathophysiology is still elusive. Using a developed ADLP^{APT} transgenic mouse model of AD showing both amyloid plaques and neurofibrillary tangles, we found that the composition of the gut microbiota in ADLP^{APT} mice differed from that of healthy wild-type (WT) mice. Interestingly, suppression of gut microbial activity in antibiotics (ABX)-treated ADLP^{APT} mice did not attenuate Aβ deposition, tau pathology, reactive gliosis and cognitive impairment, however, frequent transfer of the fecal microbiota from WT mice into ADLP^{APT} mice or ABX-treated ADLP^{APT} mice ameliorated their pathogenic features. These results implicated that gut microbial community and gut microbiota-derived factors might contribute to the pathogenesis of AD. It suggested that the restoration of intestinal microbiota and the maintenance of healthy microbiota is one of factors to consider clinical treatment for AD patients.

Disclosures: H. Choi: None. **M. Kim:** None. **Y. Kim:** None. **W. Kim:** None. **S. Park:** None. **D. Lee:** None. **D. Kim:** None. **H. Kim:** None. **H. Choi:** None. **D. Hyun:** None. **J. Lee:** None. **E. Choi:** None. **D. Lee:** None. **J. Bae:** None. **I. Mook-Jung:** None.

Poster

650. Tau: Animal and Cellular Models II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 650.10/C64

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

Support: ARDRAF Award No. 17-2

Title: Examination of olfactory dysfunction in the 3xTg-AD model of Alzheimer's disease

Authors: *D. A. MITRANO[1], **P. PEARCE**[2], S. HOULE[2], B. LOCKHART[2], I. CONTRERAS[2], R. SCHENDZIELOS[3], R. QUINTANILLA[3], L. S. WEBB[3];
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Abstract: Alzheimer’s disease (AD) is an incurable neurodegenerative disease in which the risk of development increases with age (Alzheimer’s Association, 2019). People with the disease are plagued with deficits in their short-term memory and a chronic reduction in basic social skills such as speech (Faith, 2014). Histologically, many of these deficits are caused by the formation of amyloid-β plaques and phosphorylated tau tangles in regions of the brain associated with memory, such as the hippocampus (Choi et al., 2014). However, one of the earliest clinical symptoms of AD is the loss of olfactory detection and discrimination, which is possibly due to dysfunction of the olfactory bulb, through the degeneration of the neurons located there (Zou et al., 2016). To determine if mice expressed the same olfactory dysfunction seen in human AD, 3xTg-AD mice were run in a buried food test and were then compared to their background and parental strains. Results showed that over 52 weeks, the 3xTg-AD mice took significantly longer to find the buried food than the control strains. The olfactory bulbs of the 52-week-old mice were removed, sliced and stained using Congo red for further histological analysis. The slices were observed with a confocal microscope’s polarized lens to observe both birefringence and non-birefringence to look for amyloid deposits. Significantly more amyloid deposits were observed in the 52-week-old 3xTg-AD mice when compared to the other strains of mice. Continued observation of the olfactory bulbs also revealed that a greater number of 3xTg-AD females than males developed the amyloid deposits showing sex differences in the phenotype of the trans Alzheimer’s genes.

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Poster

650. Tau: Animal and Cellular Models II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 650.11/C65

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

Title: Tau alters temporoammonic pathway via GABAergic transmission in early taupathy

Authors: *E. JUNG[1,2], S. CHOI[3,4], S.-E. LEE[5], S. CHANG[5], S.-Y. CHOI[3,4], I. MOOK-JUNG[1,2];
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Abstract: The entorhinal cortex (EC) is one of the most vulnerable brain region that is attacked during the early stage of Alzheimer's disease. Accumulation of abnormally hyperphosphorylated tau in the EC is the earliest pathological hallmarks in AD patients and neurofibrillary tangles are known to spread in a hierarchical pattern during disease progression. However, the neuronal function of tau is still unknown despite its probable influence on specific neural circuits in the early Alzheimer's disease. We found that accumulation of pathological tau begins in the lateral entorhinal cortex (LEC), followed by the hippocampal CA1 region of 2- to 3-month-old tau mice. In early tauopathy (<3 months), CA1 pyramidal neurons had reduced the neuronal excitability and decreased c-fos immunoreactivity was observed in both LEC and CA1 area. In the present study, we report that the release probability (Pr) of inhibitory synapse at temporoammonic pathway (EC-CA1) is increased and GAD2, VGAT and $GABA_A$ Receptor β3 levels were increased in 3-month-old tau model mice. All these results suggest that the possibility that tau alters temporoammonic pathway by modulating GABAergic synaptic transmission in the early tauopathy.

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Poster

650. Tau: Animal and Cellular Models II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 650.12/C66

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

Support: NIH Grant 1R15AG058197-01
PSC CUNY 60290-00 48
Donation from Jeff Lin

Title: Tau uptake is mediated by muscarinic receptors

Authors: V. MOROZOVA[1], L. S. COHEN[2], A. E.-H. MAKKI[2], ***A. SHUR**[3], G. R. PILAR[4], A. EL IDRISSI[2], A. ALONSO[5];
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Abstract: Alzheimer's disease and associated tauopathies are characterized by the presence of neurofibrillary tangles composed of hyperphosphorylated tau proteins. Tau is a microtubule-associated protein located in neuronal axons. This protein has recently been found in the extracellular space, but the role of extracellular tau is not yet known. Avila et al. (2008) has shown that tau has a high binding affinity for M1- and M3- type muscarinic receptors. Based on this finding, we hypothesize that tau uptake is mediated by muscarinic receptors. We demonstrate that normal and pathological tau can be taken up by HEK293 cells and neurons. Uptake of normal tau in neurons enhances neuronal process formation, but pathological human tau (PH-Tau) uptake results in the disruption process formation and accumulation of aggregates in the somatodendritic compartment. Hyperphosphorylated tau (AD P-Tau) had similar effects to PH-Tau on the cultured neurons. To explore whether specific subtypes of muscarinic receptors are implicated in tau uptake, HEK293 cells and cerebellar neuronal cultures were pre-incubated with broad muscarinic receptor antagonist atropine and selective M1 receptor antagonist pirenzepine prior to the addition of tau. Uptake was blocked by up to 80%. Pre-incubation with M2 and M4 receptor antagonists AF DX116 and PTX failed to block tau uptake. Furthermore, we showed that CHO cells do not express muscarinic receptors, and therefore cannot uptake either form of tau unless transfected with M1- and/or M3-type receptors. Interestingly, we found that our transgenic mouse model that conditionally expresses PH-Tau showed increased M1 muscarinic receptors compared to control. Similar results were observed in primary cerebellar cultures treated with PH-Tau. Based on our results, tau uptake is mediated by muscarinic receptors and induces different morphological consequences in neurons based on the phosphorylation state of the protein.

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Poster

650. Tau: Animal and Cellular Models II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 650.13/C67

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

Title: The effect of synaptic adhesion molecules on *in vitro* tau propagation model

Authors: *Y. NEMOTO, Y. HORI, T. TOMITA;
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Abstract: One of the distinct hallmarks of Alzheimer disease (AD) is neurofibrillary tangles, which is consisted of the aggregated tau protein. Because the spreading of tau pathology through brain correlates with the cognitive decline, understanding the mechanism of tau spreading has been highlighted. Recently, several studies proposed the tau propagation theory as a model of spreading tau pathology. In this model, tau propagation occurs between anatomically connected neurons, suggesting that neuronal synapses play an important role in the tau propagation. One of the synapse organizers is neuroligin (NL), which is the postsynaptic adhesion molecule. Human NL family is comprised of NL1, 2, 3, 4X and 4Y. NL1 specifically localizes at excitatory synapses, whereas NL2 and 4 at inhibitory synapses. Overexpression of NLs induces the formation of functional synapse with specific properties depending on the NL isoform *in vitro*. Moreover, previous report revealed that the synapse formation by overexpression of NL1 facilitated the tau propagation. However, the effects of synapse formation by other NLs on tau propagation remain unclear. To examine the roles of induced synapses by NLs on tau propagation, we developed the *in vitro* tau propagation model using co-culture system using murine primary neurons overexpressing full-length tau and HEK293 cells harboring tau aggregates. Immunocytochemical analysis revealed that the co-culture with HEK293 cells with tau aggregates induced the accumulation of tau in the primary neuron. In addition, tau in the primary neurons acquired the insolubility in the co-culture system, indicating that the aggregated tau seed was propagated from HEK293 cells to the neurons to induce the tau aggregation. Next, we overexpressed each NL isoform in HEK293 cells with tau aggregates to elucidate the effects of synaptic properties on tau propagation. We found that the levels of insoluble tau in the neurons was selectively increased by NL2-mediated inhibitory synapse formation. These results suggested that the tau propagation is modulated by the synaptic properties induced by different NL isoforms. Further molecular and cellular studies would clarify the mechanistic role of NLs in the tau propagation and the etiology of AD.

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Poster

650. Tau: Animal and Cellular Models II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 650.14/C68

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

Support: Cosmos Club
Sigma Xi

Title: Blood transfusion from young wildtype mice alters behavior in old Alzheimer's disease mice with hTau

Authors: *C. M. HERNANDEZ, K. A. PEDEMONTE, R. E. BARKEY, J. O. SANCHEZ, B. JOHNSON, J. M. FLINN;
George Mason Univ., Fairfax, VA

Abstract: Aging is characterized by a decline in synaptic plasticity and cognitive functions. This is intensified in Alzheimer’s disease (AD) by the buildup of amyloid plaques and tau tangles in the brain. There are limited treatments for AD, therefore the exploration of new alternatives is warranted. In a recent study, plasma was transfused from young wildtype (WT) mice to older mice containing human APP, which lead to improvement in spatial learning and memory tasks and an increase in synaptic plasticity (Middeldorp et al. 2016). Since mice with h-tau were not included in this design, we have transfused plasma from young WT mice to older transgenic mice with h-Tau (P301L/CaMKII). Previous studies in our lab have shown that these mice have learning and memory impairments in mice (Craven et al. 2018). Nesting and burrowing are innate behaviors in mice that have been shown to be impaired in AD, and they parallel activities of daily living in AD patients. Circadian rhythm is disrupted in AD mice, which are less active during the last four hours of dark cycle (Boggs et al. 2017). This study examined burrowing, nesting, circadian rhythm, based on 24-hour activity, in four groups: old WT mice injected with a) young plasma or b) saline, and old h-tau mice injected with c) young plasma or d) saline. Preliminary results show that plasma transfusions rescued the deficits in activities of daily living seen in older h-tau mice. Old h-tau mice with plasma built significantly better nests ($p<.05$), and burrowed more ($p<.05$) than those with saline; no effects were seen in old WT mice. Old h-tau mice had impaired circadian rhythms which were corrected with plasma transfusion, demonstrated by an increase of wheel-running activity during the last four hours of the dark cycle. Further examination will include tau staining in the brain, and protein expression of phosphorylated tau and total tau using western blotting. This study expands our understand of the behavioral and biochemical effects of young blood transfusion of AD.

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Poster

650. Tau: Animal and Cellular Models II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 650.15/C69

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

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Limitless Worldwide, LLC

Title: You are what you eat: High methionine and western diet impacts on Alzheimer's disease mouse model cognition and MRI

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Abstract: Introduction: Lifestyle choices contribute to nearly all of the 10 leading causes of death in the United States, and Alzheimer’s disease (AD) is no exception. Links from AD to metabolic and inflammatory diseases give dietary and lifestyle contributions to the disease further traction. Using established AD mouse lines we hypothesized that dietary insults would have a deleterious effect on the cognitive ability of our experimental mice. This effect would be caused by oxidative damage and iron dysregulation which we would visualize using experimental Ultra-short Echo Time MRI scanning techniques. Methods: We bred 74 total mice into cohorts of PSEN1 and Tau transgenes, with C57BL6 wild-types as controls. Mice received Methionine enriched or Western diets as insults, and rescue cohorts received diets enriched with Metformin. At time-points of 2 months (baseline), 3 months and 6 months, behavioral data was collected using a radial arm maze for 10, 5 minute trials each day for 2 weeks. The baited arm was changed after each testing period. Trials were recorded using a GoPro HERO4 and analyzed using ANYMaze software. Mice were scanned using a 3T Siemens MRI scanner to acquire 2D T2 weighted turbo-spin echo scans, 3D Gradient Echo scans, and Ultra Short Echo 3D Cone

images. ROI's were set on bilateral hippocampi and normalized to a water standard included in the scan. All statistics were analyzed using SPSS. Results: There was a statistically significant difference in mean time ($F(15, 8.683) = 15.183$, $p < 0.0005$), mean distance ($F(15, 8.683) = 7.309$, $p = 0.0003$), and mean errors ($F(15, 8.683) = 6.613$, $p = 0.0004$) in the maze, between the control and western diets. There was also a significant difference in mean failed (the subject failed to complete the task in 5 minutes) trials ($F(15, 8.683) = 13.333$, $p < 0.0005$) between controls and western diets. Significant interaction effects were also seen between genotype and treatment administered with each of the measures (time [$p = 0.003$], distance [$p = 0.037$], errors [$p = 0.033$], and failed trials [$p < 0.0005$]). Metformin rescue cohorts showed some improved cognitive ability, predominantly with co-administration of methionine. It did, however, have deleterious effects when administered alone. The MRI sequences showed some sensitivity to differences in brain tissue between control and western diets when measured using 3D CONE echo times of 1.2ms, but this requires further investigation and analysis. Conclusion: Western diet exacerbates the cognitive decline seen in AD transgenic mouse models, and metformin shows potential as a treatment, but not in healthy individuals. New MRI techniques also show promise as improved diagnostic tools.

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Poster

650. Tau: Animal and Cellular Models II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 650.16/C70

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

Support: NHI Grant NIA00051

Title: Effect of treadmill exercise training on anxious-depressive-like behavior in transgenic Alzheimer rat

Authors: ***L. YANG**, C. WU, Y. LI, Y. DONG, L. DONOVAN TUCKER, Q. ZHANG; Dept. of Neurosci. and Regenerative Med., Augusta Univ., Augusta, GA

Abstract: **PURPOSE:** This study aimed to examine the effects of treadmill training on anxious-depressive-like behaviors of transgenic Alzheimer rats in the early stage of Alzheimer's disease (AD) and provided the evidence of exercise in alleviating fear memory deficits. **METHODS:** Male 2-month-old TgF344-AD and wild-type (WT) rats were divided into WT, AD and AD + treadmill exercise (Exe) groups. After 8 months of exercise, the Passive Avoidance test (fear memory), Barnes Maze task, Novel Object Recognition test and Objection Location test

(hippocampus-dependent spatial learning/recognition memory) were used to measure learning and memory function. The Open Field test and Elevated Plus maze were performed to measure anxiety-like behavior. The sucrose preference test and forced swim test were conducted to determine the depression-like behavior of transgenic Alzheimer rats. **RESULTS:** The results of Passive Avoidance test revealed that treadmill exercise significantly alleviated the defective fear memory in AD rats ($p < 0.01$). The Barnes Maze, Novel Object Recognition test, and Object Location test revealed that the 12-month TgF344-AD rats did not develop significant hippocampus-dependent spatial learning and recognition memory deficits compared with WT animals ($p \geq 0.05$). Intriguingly, TgF344-AD animals displayed significant anxiety-like behavior compared with WT animals ($p < 0.05$), which was reversed by treadmill exercise ($p < 0.05$). TgF344-AD animals also displayed depression-like behavior compared with WT animals as measured by sucrose preference test and forced swim test, which could be effectively improved following exercise training ($p < 0.05$). **CONCLUSION:** Long-term exercise training alleviated anxious-depressive-like behavior and improved fear memory in transgenic AD rats, supporting exercise is an effective approach to prevent anxiety, depression and fear-related memory deficits in the early stages of AD pathogenesis. **Key Words**: Treadmill exercise; Anxiety; Depression; Learning and memory; TgF344-AD rat

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Poster

650. Tau: Animal and Cellular Models II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 650.17/C71

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

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NRF-2018M3A9H3021707

Title: Harnessing intramolecular rotation to enhance two-photon imaging of Aβ plaques through minimizing background fluorescence

Authors: *H. CHOI[1], J. SHIN[2], P. VERWILST[2], S. KANG[3], J. HAN[4], N. KIM[3], J. CHOI[3], M. OH[3], J. HWANG[5], D. KIM[3], J. KIM[2], I. MOOK-JUNG[1];
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Hee Univ., Seoul, Korea, Republic of; [4]Hyupsung Univ., Hwasung-si, Korea, Republic of; [5]Daegu-Gyeongbuk Med. Innovation Fndn., Daegu, Korea, Republic of

Abstract: The aggregation of Aβ-proteins in senile plaques is a critical event during the development of Alzheimer's disease, and the postmortem detection of Aβ-rich proteinaceous deposits via fluorescent staining remains one of the most robust diagnostic tools. In animal models, fluorescence imaging can be employed to follow the progression of the disease and among imaging methods two-photon microscopy (TPM) has emerged as one of the most powerful. To date, several near-infrared-emissive two-photon dyes with a high affinity for Aβ-fibrils have been developed, but there has often been a tradeoff between excellent two-photon cross sections and large fluorescence signal to background ratios. In the current work, we introduced a TICT-based de-excitation pathway, resulting in a remarkable fluorescence increase of ~167-fold in the presence of Aβ-fibrils, while maintaining an excellent two-photon cross section, allowing high contrast *ex vivo* and *in vivo* TPM imaging. Overall, the results suggest that adopting TICT de-excitation in two-photon fluorophores may represent a general method to overcome the probe brightness vs. probe signal to background tradeoff.

Disclosures: H. Choi: None. **J. Shin:** None. **P. Verwilst:** None. **S. Kang:** None. **J. Han:** None. **N. Kim:** None. **J. Choi:** None. **M. Oh:** None. **J. Hwang:** None. **D. Kim:** None. **J. Kim:** None. **I. Mook-Jung:** None.

Poster

650. Tau: Animal and Cellular Models II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 650.18/C72

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

Title: The dog as a preclinical species for the evaluation of Tau antibodies

Authors: *H. BORGHYS[1], D. DHUYVETTER[2], C. THEUNIS[3], K. VAN KOLEN[4], M. H. MERCKEN[1];
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Abstract: Hyperphosphorylated and aggregated tau are among the main characteristics of Alzheimer's disease (AD) pathology and it is known that pathological tau can spread from cell to cell, continuously progressing the disease. Immunotherapy with anti-tau antibodies is currently investigated as treatment approach acting on this tau spreading hypothesis.
We evaluated the dog as a preclinical species for the pharmacokinetic/pharmacodynamic (PK/PD) properties of tau antibodies. Phosphorylated tau (pTau) was measured as PD biomarker in cerebrospinal fluid (CSF) sampled from the lateral ventricle (LV) in conscious dogs and from

the cisterna magna (CM) in anesthetized dogs. In addition, levels of antibodies were measured in serum and CSF. Baseline pTau levels at the 2 sample sites were compared in a separate study. The results show a decrease in pTau for both tested antibodies. It was also noted that the variability was lower in the samples from the CM making this sample site more suitable then the LV.
It is concluded that the dog is a suitable preclinical species to evaluate and compare PK/PD properties of Tau antibodies.

Disclosures: **H. Borghys:** A. Employment/Salary (full or part-time):; Janssen. **D. Dhuyvetter:** A. Employment/Salary (full or part-time):; Janssen. **C. Theunis:** A. Employment/Salary (full or part-time):; Janssen. **K. Van Kolen:** A. Employment/Salary (full or part-time):; Janssen. **M.H. Mercken:** A. Employment/Salary (full or part-time):; Janssen.

Poster

651. Alzheimer's Disease: Energy Homeostasis

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 651.01/C73

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

Support: NIA U01-AG031115
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Title: Allopregnanolone potentiates bioenergetic capacity and restructures mitochondrial reticulum in neurons and astrocytes

Authors: *T. WANG, S. CHEN, Z. MAO, R. D. BRINTON;
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Abstract: We previously demonstrated that the neurosteroid allopregnanolone (Allo) promotes neural stem cell regeneration, reverses neurogenic, metabolic and cognitive deficits and reduces Alzheimer’s disease (AD) pathology in a mouse model of AD. To determine the cell-type specific mechanisms of Allo in regulating brain energy metabolism, we assessed the effect of Allo on mitochondrial bioenergetic profile and their morphological changes in rat E18 hippocampal neurons and astrocytes.
In E18 hippocampal neurons, Allo treatment significantly reversed supplement depletion-induced (2%B27/NBM) decrease in mitochondrial maximal- and spare respiratory capacity and axonal and dendritic length and count. In parallel, in E18 hippocampal astrocytes, Allo rescued serum depletion-induced (10% Charcoal stripped-FBS/DMEM : F12) decline in mitochondrial spare respiratory capacity through increasing MT-encoded OXPHOS gene expression. Allo

treatment reduced the population of less efficient swollen globule mitochondria in both neurons and astrocytes. Specifically in astrocytes, Allo decreased the number of hyperfused tubule mitochondria and increased small globule mitochondria. The effect of Allo on re-structuring supplement depletion-induced mitochondrial reticulum in both neurons and astrocytes was further supported by the restoration of the balance between Drp1 and Opa1 expression, which are key regulators for mitochondrial fission and fusion, respectively.
Outcomes of our findings further support therapeutic development of Allo to reverse bioenergetic deficits and mitochondrial inefficiency that can emerge in early phases of AD, with mitochondrial dynamics being a potentially key targeted mechanism.

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Poster

651. Alzheimer's Disease: Energy Homeostasis

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 651.02/C74

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

Title: Nobiletin effect on brain mitochondria as a neuroprotective mechanism

Authors: *N. SHARIKADZE[1,2], N. JOJUA[2], M. SEPASHVILI[2], E. ZHURAVLIOVA[2,3], D. MIKELADZE[2,3];
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Abstract: Citrus flavonoid nobiletin has anticancer, antiviral, neuroprotective, anti-inflammatory activities and depending on the cell types exhibits both pro- or anti-apoptotic properties that suggest the effect of this compound on the central metabolic systems, such as mitochondrial bioenergetics. The aim of our study was to investigate the influence of nobiletin on brain mitochondrial bioenergetics and determine the target molecules, involving in nobiletin-induced alterations. Here we analyzed mitochondrial enzymes activities and estimated of respiration rate, mitochondrial membrane potential, ROS production were performed in bovine brain mitochondria to evaluate the direct effect of nobiletin on the mitochondrial bioenergetics. Additionally, were made isolation and characterization of nobiletin-bound mitochondrial protein to identify the main target molecule.We have found that nobiletin decreases oxygen consumption in the presence of glutamate and malate and increases in the presence of succinate. In parallel, nobiletin increases NADH oxidation, alpha-ketoglutarate dehydrogenase activities and alpha-ketoglutarate-dependent production of ATP. Additionally, nobiletin reduces the production of peroxides in the presence of complex I substrates and does not change succinate-driven peroxide formation. Besides, nobiletin induces transient elevation of membrane potential followed by mild depolarization. Affinity purified nobiletin binding proteins revealed one major anti-NDUFV1

positive protein with 52 kD and NADH: ubiquinone oxidoreductase activity. We propose that nobiletin may act as a mild uncoupler, which through activation of a-KGDH-complex and acceleration of matrix substrate-level phosphorylation maintain membrane potential at a normal level. This switch in mitochondrial metabolism could elevate succinate-driven oxygen consumptionthat may underlay both pro-and anti-apoptotic effects of nobiletin.

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Poster

651. Alzheimer's Disease: Energy Homeostasis

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 651.03/C75

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

Title: The role of synaptic vesicle protein 2a on mitochondrial morphology and autophagy

Authors: *J. REICHERT[1], M. CHRIST[2], M. JÖRG[1], A. KERN[2], C. W. BEHL[2], K. FRIEDLAND[1];
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Abstract: Synaptic Vesicle Protein 2a (SV2a) is a transmembrane protein mainly located on synaptic vesicles and involved in transmitter release via its calcium dependent interaction with SNARE complex proteins especially Synaptotagmin-1. SV2a is the postulated target of the anticonvulsant drug Levetiracetam (LEV), which was found to enhance the cognition of Alzheimer’s disease patients and slow down progression of Alzheimer’s disease (AD). These effects are discussed to be mediated due to LEVs efficient silencing of excitotoxic neuronal hyperexcitability which occurs in early stages of AD and is likely to contribute to neurodegeneration. Additionally, our group found LEV to affect mitochondrial morphology, increase ATP levels and mitochondrial membrane potential (MMP), which is surprising as in literature SV2a is claimed to neither be a mitochondrial protein nor to bind to mitochondria or to regulate mitochondrial function. Therefore, to this day the underlying mode of action on mitochondria remains elusive and needs further investigation. It is also interesting that in an epilepsy model of *c. elegans* LEV was found to reduce paralysis although *c. elegans* as an invertebrate does not possess SV2a but its evolutionary precursor Synaptic Vesicle 2-Related Protein (SVOP-1). To shape light on the mode of action of LEV on mitochondria our group first analyzed proteomics of isolated mitochondria and detected SV2a which gave rise to our idea that SV2a must either be a mitochondrial protein or an interactor. To further investigate whether SV2a is a mitochondrial protein or interactor we perform confocal microscopy and Super-Resolution GSDIM microscopy on SH-SY5Y cells to check for colocalization of SV2a with mitochondria. Luciferase-based cytotoxicity assays are used to compare ATP levels of control

cells and SH-SY5Y APP wt (APPwt) cells, which serve as a mild model of Alzheimer's disease. Using Western Blot we examine autophagic flux in control cells and APPwt. For *in vivo* investigation if knockdown of SVOP-1 alters mitochondrial morphology we created a genetically modified *C. elegans* strain expressing CFP tagged neuronal mitochondria. In conclusion clarifying the interaction of LEV and mitochondria via SV2a or via a different mode of action might represent an important step towards developing new therapeutic strategies to improve symptoms of Alzheimer's disease patients.

Disclosures: **J. Reichert:** A. Employment/Salary (full or part-time):; Johannes Gutenberg University Mainz. **M. Christ:** A. Employment/Salary (full or part-time):; University Medical Center Mainz of the Johannes Gutenberg University. **M. Jörg:** A. Employment/Salary (full or part-time):; Johannes Gutenberg University Mainz. **A. Kern:** A. Employment/Salary (full or part-time):; University Medical Center Mainz of the Johannes Gutenberg University. **C.W. Behl:** A. Employment/Salary (full or part-time):; University Medical Center Mainz of the Johannes Gutenberg University. **K. Friedland:** A. Employment/Salary (full or part-time):; Johannes Gutenberg University Mainzy.

Poster

651. Alzheimer's Disease: Energy Homeostasis

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 651.04/C76

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

Support: University of Arizona Center for Innovation in Brain Science startup fund to FY
NIA P01AG026572 to RDB (Project 1 to RDB & FY, Analytic Core to FY)
Arizona Alzheimer's Consortium Pilot Project grant to FY

Title: Apoe isoforms differentially regulate neuronal- and astrocytic mitochondrial bioenergetic capacity and fuel dependency

Authors: *G. QI[1], Y. MI[1], S. CHEN[1], R. D. BRINTON[1,2,3], F. YIN[1,2];
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Abstract: Late-onset Alzheimer's disease (LOAD) has a multifactorial nature and is associated with an early decline in brain glucose metabolism and mitochondrion dysfunction. As the greatest genetic risk factor for LOAD, APOE4 allele has been found to not only impair amyloid-β (Aβ) clearance and promote its aggregation, but also affect energy metabolism and mitochondrial function. While the exaggeration of age-related brain hypometabolism and mitochondrial inefficiency by APOE4 is well established in both AD patients and animal models of late stage AD, mixed results have thus far been reported regarding APOE4 effect on brain

bioenergetics in young animals or *in vitro* models. We propose that such a discrepancy is partially due to the heterogeneous cellular composition of the brain and the distinct capacity of these cells to metabolize various energy substrates. To distinguish the effect of APOE4 on regulating neuronal- and astrocytic mitochondrial function and their preference to fuels, primary neurons and astrocytes were isolated from the forebrain of humanized APOE4 and APOE3 mice (Jackson Laboratory). Mitochondrial bioenergetic profile and their dependency and capacity of metabolizing different substrates were characterized. As expected, both APOE3 and APOE4 embryonic neurons relied primarily on glucose than other fuels in terms of both dependency and capacity, whereas astrocytes could metabolize more fatty acids than neurons. Our results further revealed that APOE4 neurons and adult astrocytes exhibited lower spare respiration capacity ratio compared to APOE3 cells, although the basal respiration of APOE4 astrocytes was higher than that of APOE3 astrocytes. Across energy fuels, APOE4 astrocytes had higher maximum capacity metabolizing glucose than fatty acids while such a fuel preference was much less significant in APOE3 astrocytes. Consistently, the maximal capacity in metabolizing fatty acids was significantly lower in APOE4 astrocytes when compared to that of APOE3 astrocytes. Our findings indicated that the impact of APOE genotype on brain bioenergetics is not only cell type dependent but could also be age- and AD stage-dependent. It was suggested that the development of strategies to restore brain energy metabolism against AD should consider APOE genotype, age- and disease-stage, and the fuel preference of different cell types in the brain.

Disclosures: **G. Qi:** None. **Y. Mi:** None. **S. Chen:** None. **R.D. Brinton:** None. **F. Yin:** None.

Poster

651. Alzheimer's Disease: Energy Homeostasis

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 651.05/C77

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

Support: NIA Grant U01AG031115
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NIA Grant P01AG026572
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Alzheimer's Association Grant SAGA-17-419459

Title: APOE and chromosomal sex shows significant effect on the lipid pathways from multiple scale analysis of aged mice

Authors: *Y. SHANG[1], A. MISHRA[1], M. K. DESAI[2], T. WANG[1], R. D. BRINTON[1];
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Abstract: Late onset Alzheimer's disease (LOAD) is a complex neurodegenerative disease with four well-established risk factors: age, APOE*4 genotype, female sex, and maternal history of AD. Each risk factor impacts multiple systems biology pathways, making LOAD a complex systems challenge. To investigate interactions between LOAD risk factors, we utilized aged humanized hAPOE3 and hAPOE4 female and male mice. Multiple scale date sets including hippocampal bulk-RNAseq transcriptomics, AbsoluteIDQ-p180 metabolomics of cortical brain and plasma, brain diffusion-weighted magnetic resonance imaging (dMRI), and behavioral cognitive performance were derived from 16 months old female and male mice with targeted replacement of mouse Apoe with human APOE3 or APOE4 genes. Regression analysis indicated a significant positive correlation between cognitive test scores and brain structure changes indicated by the optic tract fractional anisotropy (FA) from dMRI imaging. hAPOE4 female and male mice exhibited significant cognitive deficits ($p<0.05$). Interestingly, in most brain regions, hAPOE4/4 females and males exhibited lower FA than their hAPOE3/3 counterparts, suggesting a lower level of white matter integrity in hAPOE4/4 mice. Because mitochondrial dysfunction and shifts in metabolic profile are among the earliest symptoms of AD, we analyzed metabolomic profiles of both cerebral cortex and plasma. Principal component analysis (PCA) of the plasma metabolites indicated that the clustering patterns were well separated by sex and by hAPOE isoform in females, suggesting a strong sex effect on peripheral metabolic profile and an APOE isoform effect primarily in females. Detailed analysis of metabolic changes in these mice indicated that amino acid concentrations were higher in hAPOE4/4 males while acylcarnitine concentrations were higher in females hAPOE4 carriers (hAPOE3/4 and hAPOE4/4). The AD signature accumulation of phospholipids, such as sphingomyelins and glycerophospholipids, was most prominent in hAPOE3/4 and hAPOE4/4 female mice. Consistently, the gene and pathway based RNAseq analysis indicated increased expression of fatty acid/lipid metabolism related genes and pathways in both hAPOE4 females and males, which was most apparent in the females. Collectively, these data provide therapeutic targets for sex-based precision medicine interventions during the prodromal phase of LOAD, when the potential to reverse, prevent and delay LOAD progression is greatest.

Disclosures: Y. Shang: None. **A. Mishra:** None. **M.K. Desai:** None. **T. Wang:** None. **R.D. Brinton:** None.

Poster

651. Alzheimer's Disease: Energy Homeostasis

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 651.06/C78

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

Support: NIH grant R01AG061038

Title: ApoE2-mediated neuroprotective mechanism through regulation of glycolysis

Authors: *X. ZHANG[1], L. WU[1], L. ZHAO[1,2];
[1]Pharmacol. and Toxicology, [2]Neurosci. Grad. Program, Univ. of Kansas, Lawrence, KS

Abstract: Continued clinical failures in the search for a successful treatment of Alzheimer's disease (AD) raise questions about the validity of currently-focused therapeutic targets, underscoring the importance of a novel concept that emphasizes less on the pathological manifestation of the disease but more on the neuroprotective mechanism that promotes brain resilience against the onset of AD. We have recently demonstrated that human ApoE genetic isoforms (ApoE2, ApoE3, ApoE4) differentially modulate brain energy metabolism with the ApoE2 brain exhibiting the most robust while the ApoE4 brain displays the most deficient profile. Using neuro-2a (N2a) cells stably expressing human ApoE isoforms (N2a-hApoE), all-trans-retinoic acid (RA)-induced differentiated N2a-hApoE cells (dN2a-hApoE) and dN2a cells transfected with hApoE, this follow-up study was sought to investigate in-depth the interrelationship between ApoE isoforms, glycolytic status and overall cellular health. Our data demonstrated that ApoE isoforms exerted a significant impact on both the expression and activity of hexokinase as well as glycolytic function. Specifically, ApoE2-expressing cells remained robust on glycolytic outcomes within the passages studied; in contrast, ApoE4-expressing cells exhibited gradual reduction with increasing passages indicating a chronic toxic effect. These ApoE-mediated glycolytic differences directly correlated to cellular overall health status, as indicated by both metabolic activity and morphological phenotype of the cells. Furthermore, our investigation of ApoE impact on other major enzymes involved in glycolysis revealed that, opposite to its regulation of HK, ApoE4 appeared to upregulate phosphofructokinase (PFKP), providing further evidence for the deficit energy state of the cells. Taken together, these data indicate that human ApoE isoforms differentially modulate neuronal glycolysis, in large part via regulation of hexokinase, which markedly influences neuronal metabolic activity and overall health. The ApoE2-mediated glycolytic robustness may serve as a mechanistic rationale for its neuroprotective role and consequently provides a novel therapeutic approach in the prevention and early intervention of AD.

Disclosures: X. Zhang: None. **L. Wu:** None. **L. Zhao:** None.

Poster

651. Alzheimer's Disease: Energy Homeostasis

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 651.07/C79

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

Title: Beta-amyloid monomers promote glucose uptake and aerobic glycolysis in neurons

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Abstract: We have previously demonstrated that monomers of β-amyloid protein (Aβ) selectively activate type-1 insulin-like growth factor receptors (IGF-IRs) both in recombinant and native cells. In neurons, Aβ monomers enhance glucose uptake by promoting the translocation of the Glut3 glucose transporter from the cytosol to the plasma membrane. Consistent with the evidence that Aβ is released from neurons in response to synaptic activity (Cirrito et al., Neuron 48, 2005), depolarization-induced glucose uptake is blunted after blocking endogenous Aβ production with gamma-secretase inhibitors, and re-established by exogenous Aβ monomers. Similarly, APP-null neurons fail to enhance depolarization-stimulated glucose uptake unless exogenous monomeric Aβ is added (Giuffrida et al., Front Cell Neurosci 9, 2015). Noteworthy, it is aerobic glycolysis rather than oxidative phosphorylation that covers neuronal demands during synaptic activation (Ivanov et al., J Cereb Blood Flow Metab 34, 2014), while increasing neuronal resilience to stressors (Newington et al., J Biol Chem 287, 2012). We wondered whether Aβ monomers are physiologically required to sustain brain aerobic glycolysis *via* IGF-IR activation. We found that pure neurons in culture relied on aerobic glycolysis (measured as lactate release in the bathing medium) when oxidative phosphorylation was blocked by the ATP synthase inhibitor, oligomycin. Interestingly, the endogenous release of Aβ was required for the occurrence of aerobic glycolysis with ensuing neuronal survival. Hexokinase-1 (HK-1) is the driving force for aerobic glycolysis when it is bound to the outer mitochondria membrane (OMM) of cells (Bustamante and Pedersen, Proc Natl Acad Sci USA 74, 1977). Accordingly, confocal microscopy showed an increased HK-1 signal at the mitochondria of neurons activated by Aβ monomers, which was prevented by the IGF-IR antagonist, picropodophyllin. Overall, our data suggest that Aβ monomers may promote aerobic glycolysis to face energy demand during synaptic activity or incoming stressors.

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Poster

651. Alzheimer's Disease: Energy Homeostasis

Location: Hall A

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Program #/Poster #: 651.08/C80

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

Support: Basal Center of Excellence in Aging and Regeneration (CONICYT-AFB 170005)
FONDECYT (no. 11160651) to PC

Sociedad Química y Minera de Chile (SQM) for the special grants “The role of K+ on Hypertension and Cognition” and “The role of Lithium in Human Health and Disease”.

Title: Wnt induced activation of glucose metabolism mediates the *in vivo* neuroprotective roles of Wnt signaling

Authors: *P. CISTERNAS[1], J. GUTIERREZ[1], C. GHERARDELLI[1], N. C. INESTROSA[2]; [1]Ctr. de Envejecimiento y Regeneración (CARE-UC), Dept. de Biología Celular y Molecular, Facultad de Ciencias Biológicas, Pontificia Univ. Católica de Chile, Santiago, Chile, Santiago, Chile; [2]Ctr. de Envejecimiento y Regeneración (CARE-UC), Dept. de Biología Celular y Molecular, Facultad de Ciencias Biológicas, Pontificia Univ. Católica de Chile, Santiago, Chile, Ñuñoa, Chile

Abstract: Dysregulated Wnt signaling is linked to major neurodegenerative diseases, including Alzheimer´s disease (AD). In mouse models of AD, activation of the canonical Wnt signaling pathway improves learning and memory, but the mechanism for this remains unclear. The decline in brain function in AD patients correlates with reduced glucose utilization by neurons. Here, we test whether improvements in glucose metabolism mediate the neuroprotective effects of Wnt in AD mouse model. APPswe/PS1dE9 transgenic mice were used to model AD, andrographolide or lithium was used to activate Wnt signaling, and cytochalasin B was used to block glucose uptake. Cognitive function was assessed by novel object recognition and memory flexibility tests. Glucose uptake and the glycolytic rate were determined using radiotracer glucose. The activities of key enzymes of glycolysis such as hexokinase (HK) and phosphofructokinase (PFK), ATP/ADP levels and the pentose phosphate pathway (glucose-6 phosphate dehydrogenase) were measured. Wnt activators significantly improved brain glucose utilization and cognitive performance in APPswe/PS1E9 transgenic mice. Wnt signaling enhanced glucose metabolism by increasing the expression and/or activity of HK, PFK and AMP-activated protein kinase (AMPK). Inhibiting glucose uptake partially abolished the beneficial effects of Wnt signaling on learning and memory. Wnt activation also enhanced glucose uptake and the glycolytic rate of cultured cortical and hippocampal neurons, as well as brain slices derived from APPswe/PS1E9 transgenic mice. In hippocampal neurons treated with amyloid-β, Wnt activation significantly reduced cell death; this protective effect was abrogated by inhibitors of glucose uptake or Wnt signaling. Combined, these data provide evidence that the neuroprotective effects of Wnt signaling in AD mouse models result, at least in part, from Wnt-mediated improvements in neuronal glucose metabolism.

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Poster

651. Alzheimer's Disease: Energy Homeostasis

Location: Hall A

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Program #/Poster #: 651.09/C81

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

Support: NIA P01AG012411
NCRR P20RR020146
Roy and Christine Sturgis Charitable and Educational Trust

Title: Alzheimer-related pathology impairs peripheral glucose tolerance by disrupting glucose transporter 1 localization and cerebral glucose delivery

Authors: *S. W. BARGER[1], R. D. HENDRIX[5], Y. OU[1], J. E. DAVIS[2], A. R. ALLEN[3], G. V. CHILDS[4];
[1]Geriatrics, [3]Pharmaceut. Sci., [4]Neurobio. and Developmental Sci., [2]Univ. of Arkansas for Med. Sci., Little Rock, AR; [5]Dept of Neurol., Washington Univ. Sch. of Med., Saint Louis, MO

Abstract: Alzheimer's disease (AD) is associated with disturbances in blood glucose regulation, and Type-2 diabetes elevates the risk for dementia. A role for amyloid β-peptide (Aβ) in linking these age-related conditions has been proposed, tested primarily in transgenic mouse lines that over-express mutated amyloid precursor protein. Because APP has its own impacts on glucose regulation, we examined the BRI-Aβ42 line ("$A\beta_{42}$-tg"), which secretes $A\beta_{1\text{-}42}$ in the CNS without elevation of APP. We also looked for interactions with diet-induced obesity (DIO) resulting from a high-fat, high-sucrose ("western") diet. While female $A\beta_{42}$-tg mice were unaffected, males were impaired in both spatial memory and glucose tolerance. The latter was only additive with that caused by DIO, and though the DIO induced insulin resistance, $A\beta_{1\text{-}42}$ accumulation did not. $A\beta_{42}$-tg mice exhibited no significant differences from wild-type in insulin production, body weight, lipidemia, appetite, physical activity, respiratory quotient, an-/orexigenic factors, or inflammatory factors. Similar to AD patients, $A\beta_{42}$-tg mice did have a reduced cerebral metabolic rate for glucose (CMR_{glc}), and this was associated with insufficient trafficking of glucose transporter 1 (GLUT1) to the plasma membrane in parenchymal brain cells; this effect on GLUT1 was also documented in cortical specimens from humans with AD. Together, the lower CMR_{glc} and diminished function of parenchymal GLUT1 indicate that aberrant regulation of blood glucose in AD likely reflects a central phenomenon, resulting from the effects of Aβ on cerebral parenchyma, rather than a generalized disruption of hypothalamic or peripheral endocrinology.

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Poster

651. Alzheimer's Disease: Energy Homeostasis

Location: Hall A

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

Support: National Institute on Aging UO1 AG047222

Title: Allopregnanolone prevent the loss of neuronal differentiative capacity in 3xTgAD mice

Authors: *S. CHEN, T. WANG, R. D. BRINTON;
Ctr. for Innovation in Brain Sci., Univ. of Arizona, Tucson, AZ

Abstract: Previous studies demonstrated that the endogenous steroid Allopregnanolone promotes proliferation of rodent and human neural progenitor/neural stem cells (NSCs) *in vitro*, reverses neurogenic and cognitive deficits in the triple transgenic mouse model of Alzheimer's disease (3xTgAD). In this study, we investigated the impact of Allopregnanoloneon neural differentiation. We first assessed the effect of aging and Alzheimer's-associated genotype on the differentiation capacity of adult NSCs in 3xTgAD mice. NSCs from 3-, 6- and 15-month 3xTgAD and non-transgenic mice were cultured and differentiation capacity was analyzed. We found an age- and Alzheimer's gene-dependent decrease in overall NSCs differentiation with a shift from neuronal to glial differentiation. Consistently, the number of immature doublecortin (DCX) positive neurons declined more significantly with aging in 3xTgAD mice compared to age-matched non-TG mice. To further determine the *in vivo* efficacy of Allopregnanolone to prevent or reverse the loss of neuronal differentiative capacity, we investigated the impact of neuronal differentiation in 5-month-old male 3xTgAD mice. Flow cytometry-based analysis indicated that Allopregnanolone treatment increased the number of newly generated neurons as indicated by the increase in the number of BrdU positive cells and BrdU/NeuN double positive cells. Immunostaining on brain sections confirmed that the number of DCX positive neurons was significantly increased following Allopregnanolone treatment *in vivo*, which was further supported by the enhanced level of DCX expression in hippocampal samples. Allopregnanolone treatment also increased the expression of Olig2, an oligodendrocyte precursor cell marker. Immunohistochemistry analyses showed that more Olig2 positive cells were distributed in corpus callosum area in the Allopregnanolone-treated brain. The increase of differentiation in neuronal cell and oligodendrocyte precursors was paralleled with an increase of expression in insulin-like growth factor-1 (IGF-1) and IGF-1 receptor (IGF-1R). To determine mechanisms of neural differentiation induced by Allopregnanolone, we are currently investigating expression of AKT and IGF-1/IGF-1R signaling pathway. Collectively these findings suggest that Allopregnanolone

is a regenerative therapeutic candidate to prevent or delay neurogenic deficits associated with age and Alzheimer's disease.

Disclosures: S. Chen: None. **T. Wang:** None. **R.D. Brinton:** None.

Poster

651. Alzheimer's Disease: Energy Homeostasis

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 651.11/C83

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

Support: NIH Grant AG053719
NIH Grant AG054937
NIH Grant AG 056862

Title: The role of diet and exosomes in the pathophysiology of Alzheimer's disease

Authors: *L. M. WISE[1], J. YANG[1], R. LALONDE[2], K.-I. FUKUCHI[1];
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Abstract: Obesity has become a worldwide epidemic with over 30% of the world's population being classified as obese. Obesity increases the risk of many adverse health conditions, including diabetes. Chronic consumption of energy dense foods, high in fats, is associated with obesity, insulin resistance, and diabetes. Obesity and diabetes are both high risk factors of cognitive decline, dementia, and Alzheimer's disease (AD). To investigate shared mechanisms, C57BL/6 mice were fed either a normal chow diet or a high-fat diet (60% kcal from fat) from 9-11 months of age. Starting at 11 months, blood exosomes were extracted twice a week from the serum from 11-15 months. The exosomes were injected into transgenic APP/PS1 AD mouse models from age 3 -7 months. Additionally, two separate groups of AD mouse models were either fed a normal chow diet or a high-fat diet from age 3-7 months. At 7 months, the AD mouse models completed behavioral tasks and glucose tolerance tests. Histological analyses of the hippocampus and cortex will be presented.
Supported in part by NIH AG053719, AG054937, and AG056862.
Keywords: Alzheimer's disease, obesity, diabetes, high-fat diet, glucose metabolism, cognition, behavior

Disclosures: L.M. Wise: None. **J. Yang:** None. **R. Lalonde:** None. **K. Fukuchi:** None.

Poster

651. Alzheimer's Disease: Energy Homeostasis

Location: Hall A

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Program #/Poster #: 651.12/C84

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

Support: NIH/NIA 1K01AG050719
NC Research Consortium Pilot Award

Title: Genetic and dietary iron overload in the pathogenesis of type-2-diabetes and Alzheimer's disease

Authors: *D. A. RUBINOW[1], S. SINK[2], A. ODELADE[4], C. GOLIAS[3], A. SNIPES[3], S. M. DAY[3], D. MCCLAIN[2], J. HAN[4], S. L. MACAULEY[3];
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Abstract: People with type-2-diabetes mellitus (T2DM) have an increased risk for developing Alzheimer’s disease (AD). However, the exact mechanisms for why this happens are currently unknown. Although iron is essential for many biological processes, it is also a potential contributing factor to disease since excess iron increases oxidative stress and cellular damage causing beta cell dysfunction and neurodegeneration. High fat diets (HFD) alter tissue iron levels and influence the regional distribution of iron in the brain; a pattern that could negatively impact cognition. Therefore, we investigated the relationship between T2DM, AD, and high iron using models of dietary and genetic iron overload in both wild type mice (WT) and mice overexpressing amyloid-beta (Aβ) and AD-related pathology (APP/PS1). Overall, a high fat diet is sufficient to drive the development of T2DM independent of iron levels. Mice on the control diet with normal dietary iron gained less weight and had lower blood glucose levels than the HFD groups. Although all experimental groups had comparable fasted blood glucose levels at baseline, HFD/normal iron and HFD/high iron groups had elevated fasted blood glucose levels after 3 months. The 1) APP/PS1/HFD/normal iron and 2) WT/HFD/high iron groups displayed the greatest glucose intolerance at 3 months post-intervention. HFE knockout mice, a genetic model of hereditary hemochromatosis and iron overload, bred to the APP/PS1 mice died prematurely, with a median survival of 105 days. Ongoing studies are characterizing the changes in pathology within the CNS and periphery, including the effects on iron distribution in the brain, plaque pathology, and neuroinflammation, as a result of T2DM, AD, and iron overload.

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Poster

651. Alzheimer's Disease: Energy Homeostasis

Location: Hall A

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

Support: CB2015-1/257849 from National council of Science and Technology (CONACYT)
grant support to graduate students from CONACYT with CVU number: 935046

Title: Determination of low density lipoprotein receptor-related protein 1 (LRP1) and receptor for advanced glycation end products (RAGE) in the hypocamp of rats subjected to the consumption of hypercaloric diets

Authors: *F. HERNANDEZ-LANDERO[1], E. MARTINEZ-ABUNDIS[2], E. N. DE LA CRUZ-HERNANDEZ[1], N. P. GOMEZ-CRISOSTOMO[2];
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Abstract: The consumption of hypercaloric diets is the main factor associated with the development of metabolic syndrome (MS), this pathology is a public health problem worldwide that is associated with cognitive impairment. Several investigations have shown that patients with MS develop lesions in the cerebral microvasculature promoting alterations in the permeability and transport through of the blood-brain barrier (BBB). The BBB is responsible for eliminating the B-amyloid peptide (AB) by binding to the advanced glycosylation end products receptor (RAGE) and the receptor related to low density lipoprotein 1 (LRP1). The decrease in AB clearance is associated with cognitive impairment. The objective of this study is to evaluate the effect of consumption of hypercaloric diets (high in sucrose -HSD- or high in fat -HFD-) on the expression of RAGE and LRP1 in hippocampus of rats. Newly weaned male Wistar rats exposed to the consumption of HSD or HFD diets were feed for 2, 4 and 6 months with the two diets. Body weight, plasma levels of glucose, cholesterol and triglycerides were determined. The hippocampus was obtained to determine the expression of RAGE, LRP1 and AB by western blot. The results show that rats did not develop SM at anytimes of consumption of the hypercaloric diets, however, it was noted an increase in body weight in the rats feed with both diets, as well as an increase in the plasma levels of triglycerides, but not in glucose and cholesterol. The expression of RAGE showed an increase after 2 months of diet consumption been more evident in the HSD group, while at 4 months a decrease was observed with both diets and after 6 months the expression was increased again with both diets. LRP1 showed a decreased expression at 2 months of diets with respect to the control, although it was not significant, whereas in the 6 months group shown an decrease in both diets, been more evident in the HFD. Although our

experimental groups did not develop SM, the results suggest that high levels of plasma triglycerides could alter the expression of RAGE and LRP1 receptors and therefore affect the clearance of AB through the BBB.

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Poster

651. Alzheimer's Disease: Energy Homeostasis

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Program #/Poster #: 651.14/C86

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

Support: 1R01AG062254-01
P01 AG012411-17A1
BX001655

Title: Endoplamic reticulum calcium pump is modulated by binding to phosphatidylinositol trisphosphate; disruption by Alzheimer- and diet-derived conditions

Authors: *S. AYYADEVARA[1,5], A. GANNE[6], R. HENDRIX[7], M. BALASUBRAMANIAM[2], S. T. GRIFFIN[1,5], R. J. SHMOOKLER REIS[3,5], S. W. BARGER[4,5];
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Abstract: Calcium-mediated signaling is critical to neuronal function and survival. Calcium homeostasis is dysregulated in neuropathies such as Alzheimer’s disease (AD), Parkinson’s disease (PD) and Huntington’s disease (HD). We here show that mice fed a diet rich in fat and sugar (diet-induced obesity, DIO) had half the levels of free SERCA2 (sarcoplasmic/endoplasmic reticulum calcium ATPase 2) found in control mice, associated with sequestration of the protein into detergent-insoluble aggregates. Similar sequestration of SERCA2 occurred in BRI-Aβ (AD-model) mice. SERCA2 was also enriched in aggregates from affected tissue of AD patients relative to age-matched controls. In mice fed either normal or DIO diets, >99% of the unaggregated fraction of cerebral SERCA2 is associated with membranes versus 86% in BRI-Aβ cerebra. In wild-type mice fed normal diet, ~20% of the membrane SERCA2 was bound to phosphatidylinositol (3,4,5)-triphosphate (PIP_3); this declined to ~5% in DIO mice and <1% in BRI-Aβ mice. Based on molecular-dynamic modeling of SERCA2, its PIP_3-binding region coincides with the binding site for thapsigargin, a non-competitive SERCA inhibitor. Threonine-230 is phosphorylated in DIO mice, which is predicted *in silico* to block

SERCA binding to PIP_3. In *C. elegans* models of neuropathic protein aggregation, SERCA knockdown led to an increase in total cellular protein aggregation. This was replicated after addition of palmitic acid, glucose, or both to the nematode diet; no further increase was seen in combinations with SERCA knockdown, whereas SERCA activation blocked the increase. *C. elegans* models of neurodegeneration implicated ER stress and depletion of ER calcium stores. These data show for the first time that SERCA2 binds to PIP_3 and that this is impaired by DIO and AD-like amyloidopathy, either of which disrupts calcium homeostasis and induces ER stress.

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Poster

651. Alzheimer's Disease: Energy Homeostasis

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 651.15/C87

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

Support: NIH AG059778
NIH AG057914
NIH AG054180
AARF-18-565506

Title: Midlife obesity and metabolic dysfunction in the AD-BXD mouse model of Alzheimer's disease

Authors: K. O'CONNELL, A. DUNN, N. HADAD, ***C. C. KACZOROWSKI**;
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Abstract: Age and genetic background are the greatest risk factors for Alzheimer’s disease, but it is increasing evident that mid-life obesity and metabolic syndrome further increase the risk of developing AD, as increased BMI is associated with an earlier age at onset. Furthermore, many AD patients also present with non-cognitive symptoms associated with metabolic dysfunction, such as weight loss, changes in appetite, and low circulating levels of the adipose-derived hormone leptin, suggesting that systemic metabolic function is an important factor in the etiology of AD in humans. However, the mechanisms underlying this dysfunction and their relationship to disease onset, progression, and severity are poorly understood. To address this gap, we assessed metabolic function in mice from our recently developed model of genetic variation in AD, the AD-BXD genetic reference panel (Neuner, et al 2019). A subset of AD-BXD and non-transgenic controls were fed a high-fat/high-sugar diet (HFD) starting at ~4 months of age to model mid-life obesity. Systemic metabolic function was measured using indirect calorimetry to

measure energy expenditure, V_{O2} and V_{CO2}, respiratory exchange rate (RER), locomotor activity, and food and water intake. A subset of mice were fed a high-fat/high-sugar diet (HFD) to model mid-life obesity. As previously reported, AD-BXD mice weigh less than their non-transgenic counterparts; assessment of body composition indicates this is due primarily to a loss of fat mass. AD-BXD strains also exhibited an increase in rearing behavior, which may indicate hypervigilance. Female AD-BXD strains exhibited increased energy expenditure and locomotor activity and failed to develop diet-induced obesity when fed HFD. Mice fed HFD generally displayed changes in RER consistent with a shift to fat metabolism; we further observed changes in patterns of food intake during the dark cycle, indicating possible circadian dysfunction in these mice. Taken together, these data indicate that AD-BXD mice exhibit some degree of metabolic dysfunction and that this is exacerbated by HFD. Ongoing work will quantify the impact of genetic background, diet, and complex geneXdiet interactions on these traits and determine causal relationships between metabolic and cognitive phenotypes using computational models.

Disclosures: C.C. Kaczorowski: None. **A. Dunn:** None. **K. O'Connell:** None. **N. Hadad:** None.

Poster

651. Alzheimer's Disease: Energy Homeostasis

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 651.16/C88

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

Support: NIA Grant 5P01AG026572

Title: Dynamic metabolic aging of the female brain during endocrinological and chronological aging

Authors: *Y. WANG[1], Y. SHANG[1], A. MISHRA[1], E. BACON[2], F. YIN[1], R. BRINTON[1]; [1]Univ. of Arizona, Tucson, AZ; [2]Sch. of Pharm., USC, Los Angeles, CA

Abstract: Natural aging and the perimenopausal transition are associated with brain glucose hypometabolism and mitochondrial dysfunction in females. The bioenergetic crisis is also a hallmark of late-onset Alzheimer’s disease (LOAD). Comprehensive understanding of the dynamic metabolic aging process in the female brain can shed light on potential prevention and interventions windows of opportunities to promote healthy aging. Using a rat model recapitulating fundamental characteristics of human menopausal transition, we observed systematic bioenergetic dysregulation in the aging female brain, as well as alternations in key metabolic regulators. Using an unbiased, discovery-based metabolomic and lipidomic approach, we characterized the dynamic adaptation of aging female brain from glucose centric to utilization

alternative fuel sources including amino acids, fatty acids, lipids, and ketone bodies, and finally to anaerobic glycolysis, during endocrinological and chronological aging. Transcriptomic profiling of bioenergetic gene networks were consistent with the metabolomic profiles. These data provide the first detailed metabolic profile of the female brain across both endocrinological and chronological aging transitions.
This study was supported by NIA 5P01AG026572 to RDB; Project 1 to RDB and FY.

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Poster

651. Alzheimer's Disease: Energy Homeostasis

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 651.17/C89

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

Support: NIA P01AG026572

Title: The immuno-metabolic crisis in the aging female brain: Implications for Alzheimer's disease

Authors: *A. MISHRA[1], Y. SHANG[3], Y. WANG[2], F. YIN[3], R. D. BRINTON[3];
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Abstract: Alzheimer’s disease (AD) is characterized by a long latent prodromal stage with recent discoveries pointing to the perimenopausal transition in women as a “tipping point” in the development of the AD phenotype (Brinton et al., 2015). The hallmark chronic low-grade inflammation in both aging and menopause has been implicated as a unifying factor that bridges across AD risk factors (Mishra and Brinton, 2018). Yet, the endocrine state specific effect of neuroinflammation on female aging has not been characterized. In this study, we characterize the neuroinflammatory profile across chronological and endocrine aging transitions. Relevance to AD and neurodegenerative inflammatory mechanisms.
Preliminary findings from the perimenopausal rat model, in which we can experimentally segregate the effects of chronological aging from endocrine aging, indicate that the inflammatory phenotype is quite dynamic throughout the endocrine transition in menopause. Our results show that type I and type II interferon (IFN) response genes, recently implicated in age related neurodegeneration (Mathys et al., 2017) are upregulated in the hippocampus the perimenopausal transition. Co-incident with the upregulation of the IFN response genes in the hippocampus, was the overexpression of major histocompatibility complex (MHC) -II genes in white matter tracts – corpus callosum and fimbria. Reproductive irregularity also affected phagocytic response and

redox status of microglial cells. Endocrine aging was associated with shifts in mitochondrial function in astrocytes and microglia. Estradiol regulation of the upregulation of interferon response genes was validated by ovariectomy and estradiol prevention paradigm. Clinical microarray data from the hippocampus was also analyzed to accomplish translational validity of the findings and, establish if the upregulation of MHC-II was preferentially observed in females The characterization of inflammation in the female aging brain and its role in transition to AD vulnerability has, thus far, been scarce. This pioneering study elucidates the dynamic immune profile in brain that occurs during chronological and endocrine aging which is coincident with decline in steroid hormones and brain glucose metabolism . Molecular characterization of the neuroinflammatory mechanisms during this neuro-endocrine transition state can inform therapeutic strategies to mitigate the risk of onset of Alzheimer's disease in women.

Disclosures: A. Mishra: None. **Y. Shang:** None. **Y. Wang:** None. **F. Yin:** None. **R.D. Brinton:** None.

Poster

651. Alzheimer's Disease: Energy Homeostasis

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 651.18/C90

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

Support: NIA P01AG026572 (Project 1 to RDB, Analytic Core to FY)
SAGA-17-419459

Title: Emergence of an Alzheimer's disease bioenergetic endophenotype in mid-life: Preclinical model

Authors: *Z. MAO[1], Y. SHANG[2], J. BERGHOUT[3], Y. LUSSIER[3], F. YIN[1], R. D. BRINTON[1]; [1]Ctr. for Innovation in Brain Sci., [2]Ctr. for Innovation in Brain Science, Ctr. for Biomed. Informatics and Biostatistics, [3]Ctr. for Biomed. Informatics and Biostatistics, Univ. of Arizona, Tucson, AZ

Abstract: Perimenopause is a female aging transition that proceeds- and leads to reproductive senescence and is associated with multiple neurological symptoms, including those associated with increased Alzheimer's risk. We previously demonstrated decline in bioenergetic function and long-term potentiation coincident with perimenopausal endocrine aging in brain that were consistent with an early prodromal stage AD phenotype. Using a pathway-centric bioinformatic approach, the present study aimed to systematically determine the underlying biological processes that drive the transformation of perimenopausal brain and their contribution to AD vulnerability. Hippocampal RNAs from six groups of female rats undergoing chronological and endocrine aging were sequenced followed by bioinformatic analyses. Outcomes indicated that

rats undergoing perimenopause exhibit substantially higher variances in overall hippocampal gene expression relative to other groups, supporting the perimenopausal brain being in an unstable transition state. Gene Set Enrichment Analysis (GSEA) further revealed alterations in bioenergetic-, inflammatory-, and cell proliferation pathways during the transition and characterized by decline in bioenergetic gene expression and low-grade activation of immune pathways. Moreover, nuclear- (nDNA) and mitochondrial DNA (mtDNA)-encoded bioenergetic genes were differentially regulated by chronological- and endocrine aging: mtDNA genes correlated closely with chronological aging while nDNA-encoded counterparts were largely endocrine dependent. Notably, the differential regulation of mtDNA and nDNA was also observed in our analysis of a human brain transcriptome dataset including young, old and AD groups. Lastly, the strong correlation between bioenergetic pathways with genes associated with AD and other neurodegenerative disorders linked bioenergetic deficits to neurodegeneration and elevated AD vulnerability. Our findings suggest that hippocampal gene expression during perimenopause is a mid-life transition state characterized by perturbations to bioenergetic- and inflammatory pathways, which could contribute to increased AD risk in women. This study provides novel mechanistic insights into the impact of perimenopausal transition on brain function, which could have implications for identifying phenotypes of AD risk for earliest detection in aging females.

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Poster

651. Alzheimer's Disease: Energy Homeostasis

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 651.19/C91

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

Support: NIH Grant HL106511

Title: Inhibition of adenylyl cyclase type 5, a novel model for protection against Alzheimer’s disease

Authors: D. BABICI[1], J. ZHANG[1], R. YAN[2], J. ZHANG[2], S. C. MADDILA[2], T. BERKMAN[1], D. E. VATNER[1], *M. M. MOURADIAN[2], S. V. VATNER[1];
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Abstract: The Adenylyl Cyclase Type 5 (AC5) knockout (KO) mouse is a model of healthful aging, as these mice live a third longer than their wild type littermates (AC5 KO WTL) and are protected against diabetes, obesity, exercise intolerance, heart disease and cancer. In contrast,

Alzheimer's Disease is a model of unhealthful aging, and many features protected in the AC5 KO mouse are found to be more severe in Alzheimer's Disease. Accordingly, we hypothesized that inhibiting AC5 may be a novel model for protection against Alzheimer's Disease. Although a number of studies have shown a relationship between Alzheimer's Disease and adenylyl cyclase, the results are inconsistent. The goal of this investigation was to compare the AC5 KO mouse model (n=20) with J20 mice (n=12) at 10-18 months of age, at a time when J20 mice exhibit features of Alzheimer's Disease, as amyloid plaques develop in the hippocampus, and the animals exhibit abnormal responses in behavior tests. Rigor: 1) all experiments were conducted blinded and by two investigators; 2) ANOVA was used to compare the 3 groups statistically; 3) both males and females were studied. Results: Abnormal behavior was confirmed in the J20 mice. For example, the water maze test, used to assess spatial learning and memory, demonstrated the expected deficit, $p<0.05$; the rotorod test demonstrated impaired locomotor activity $p<0.05$; and the open field test showed anxiety behavior. In contrast, AC5 KO mice demonstrated opposite findings with significantly better performance, $p<0.05$, in all these tests, not only in comparison with J20 mice, but also in comparison with AC5 KO WTL (n=16). In addition, J20 mice exhibited reduced exercise performance and impaired glucose tolerance, in direct opposition to AC5 KO mice, which demonstrated enhanced exercise performance and glucose tolerance. Thus, AC5 KO mice are protected against behavioral changes, neuropsychiatric symptoms and locomotor impairment associated with Alzheimer's disease, as well as impaired exercise performance and glucose tolerance, also characteristic of Alzheimer's Disease. These findings suggest that inhibition of AC5 may be a novel therapeutic approach for Alzheimer's Disease.

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Poster

651. Alzheimer's Disease: Energy Homeostasis

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 651.20/C92

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

Support: NIA Grant P01AG014930

Title: Increasing neuronal NAD(P)H pool protects Alzheimer's disease neurons from oxidative stress

Authors: *P. MARTIN-MAESTRO[1], Y. GANAT[2], A. SPROUL[3], D. PAQUET[4], S. NOGGLE[2], A. STARKOV[1];

[1]Weill Cornell Med., New York, NY; [2]New York Stem Cell Fndn., New York, NY; [3]Columbia Univ., New York, NY; [4]Inst. for Stroke and Dementia Res., Munich, Germany

Abstract: Background: The generation of reactive oxygen species (ROS) is a part of normal metabolism in a biological system. Oxidative stress is important in etiology of Alzheimer's disease (AD) and in age-related neurodegeneration and cognitive decline. The balance between the production and removal of ROS is essential to prevent adverse effects of oxidative stress. A failure of ROS scavenging can as well contribute to oxidative stress in brain cells. All cellular ROS scavenging systems are fueled by NADPH. Because of that, a decrease in glucose utilization, characteristic of AD brains, is expected to decrease the capacity of ROS scavenging systems and augment oxidative stress. Due to NADP is synthesized from NAD, controlling the cellular NAD pool by providing NAD precursors, or by inhibiting NAD degradation is essential for the cell.
Methods: In the present study, we have manipulated the level of NAD(P)H pool in a cellular AD model - human neurons derived from induced pluripotent stem cell (iPSC) harboring FAD-associated Presenilin 1 *M146L* mutation.
Results: We demonstrated that treating neurons with NAD precursors is a better way to increase the cellular NAD pool than preventing NAD degradation. This increase in the NAD pool clearly enhance tolerance of PSEN1-mutated AD neurons to oxidative stress.
Conclusions: Our findings indicate that increasing NAD(P) pool in AD-related cellular model (PSEN1-mutated neurons) is an efficient way to decrease the oxidative stress. Considering that our cellular model recapitulates many of the features previously described in other AD models, we think it is most suitable to evaluate AD-targeting pharmaceuticals. It also demonstrates that increasing NAD(P) pool alleviates neuronal oxidative stress, the effect which may be beneficial in other neurodegenerative diseases.

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Poster

651. Alzheimer's Disease: Energy Homeostasis

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 651.21/D1

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

Support: NSF grant

Title: Protein expression and activity levels of UCP2 in Alzheimer's disease brain tissue

Authors: *T. A. CLEMONS;
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Abstract: The traditional role of uncoupling proteins is to allow protons back across the mitochondrial membrane during the electron transport process, which negatively impacts ATP production at complex V. There are five uncoupling proteins that have been identified and each uncoupling protein has a very distinct role. Recently, uncoupling protein 2 (UCP2) has been suggested to have a cell signaling role. Furthermore, the expression of certain UCP's have been shown to be diminished in Alzheimer's disease brains, which suggests that certain UCP's may have a protective role in preventing the disease. The question as to what proteins contributes to the diminished levels of UCP in Alzheimer's disease brains has yet to be elucidated. This study analyzes the protein expression and activity levels of UCP2 on Alzheimer's disease brains in comparison to SH-SY5Y cells. In addition, although plaque formation in Alzheimer's disease brains has already been established, the proteins that contribute to plaque formation are not understood. Amylin is a protein that is known to cross the blood-brain barrier and possibly contribute to plaque formation. Is there a possibility that UCP2 could be involved with preventing plaque formation? This study attempts to answer this question by analyzing amylin protein expression and activity levels to determine if there is a correlation between UCP2 and amylin protein and activity levels in Alzheimer's disease brain tissue and/or SH-SY5Y cells. The overall goal is to determine if UCP2 could possibly be a key protein in preventing plaque formation.

Disclosures: T.A. Clemons: None.

Poster

651. Alzheimer's Disease: Energy Homeostasis

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 651.22/D2

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

Support: NIH grants R01-NS100447
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Title: Tissue plasminogen activator reduction mediates neurovascular dysfunction produced by amyloid-β peptides

Authors: *A. ANFRAY[1], J. ZHOU[1], P. ZHOU[2], J. SEO[3], J. ANRATHER[5], C. IADECOLA[3], L. PARK[4];
[1]BMRI, [2]Brain and Mind Res. Inst., [4]Feil Family Brain and Mind Res. Inst., [3]Weill Cornell Med., New York, NY; [5]Weill Med. Col. Cornell Univ., New York, NY

Abstract: The amyloid-β peptide (Aβ), a key pathogenic factor in Alzheimer's disease, markedly attenuates the increase in cerebral blood flow (CBF) evoked by neural activity

(functional hyperemia), a vital homeostatic response in which NMDA receptor plays a key role. The protease tissue plasminogen activator (tPA) regulates the NMDA receptor-dependent component of functional hyperemia (PNAS, 105:1073, 2008). Thus, we investigated whether tPA is involved in the deleterious neurovascular effects of Aβ. CBF was measured by laser-Doppler flowmetry in the somatosensory cortex of urethane-chloralose anesthetized male mice. In tg2576, the increase in CBF produced by neural activity (whisker stimulation; WS) or by topical application of the endothelium-dependent vasodilator acetylcholine (ACh) was attenuated compared to WT littermates (WS: -37%; ACh, -35%; $p<0.05$; mean±SE). Neocortical application of the NMDA receptor inhibitor MK-801 (10 μM) attenuated functional hyperemia in WT (-58%; $p<0.05$), but not tg2576 mice ($p>0.05$ from vehicle). Furthermore, the CBF increase elicited by neocortical application of NMDA (40 μM) was smaller in tg2576 mice (11±2%) than in WT littermates (36±3%; $p<0.05$), while responses to kainate (10 μM) or AMPA (10 μM) were comparable ($p>0.05$ from WT). The attenuation in the CBF increase produced by WS and NMDA in tg2576 mice was associated with reduced tPA activity, assessed by ELISA and *in situ* zymography (-47%; $p<0.05$ from WT mice), but not tPA mRNA and protein levels ($p>0.05$). Intranasal treatment of recombinant tPA (20 μg) in tg2576 mice rescued the attenuation in functional hyperemia ($p<0.05$ from vehicle-treated tg2576), but it has no effects on $A\beta_{1\text{-}40}$ or $A\beta_{1\text{-}42}$ level. Neocortical application of $A\beta_{1\text{-}40}$ (5 μM) failed to attenuate functional hyperemia in tPA-null mice and in mice lacking the tPA inhibitor PAI-1 ($p>0.05$). Furthermore, neocortical superfusion of the PAI-1 inhibitor PAI-039 (30 μM) prevented the Aβ-induced attenuation of functional hyperemia in WT mice and rescued neurovascular function in tg2576 mice, effects associated with increased PAI-1 activity ($p<0.05$), but not PAI-1 mRNA and protein levels ($p>0.05$). The data indicate that the neurovascular dysfunction produced by Aβ is mediated by a PAI-1-induced deficit in tPA activity, which, in turn, suppresses the NMDA-dependent component of functional hyperemia. Even though the mechanisms of PAI-1 upregulation require further investigation, targeted inhibition of PAI-1 activity may be a therapeutic strategy to counteract the detrimental effects of Aβ on cerebrovascular regulation.

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Poster

651. Alzheimer's Disease: Energy Homeostasis

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 651.23/D3

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

Support: NIH/NIA 1K01AG050719
Harold and Mary Eagle Fund for Alzheimer’s Research
New Vision Award through Donors Cure Foundation

Title: Aging and pathology cause sleep disruptions and altered metabolism in mouse models of Alzheimer's disease

Authors: *C. M. CARROLL[1], M. STANLEY[3], M. PAIT[1], D. A. RUBINOW[1], D. M. HOLTZMAN[4], S. L. MACAULEY[2];
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Abstract: The development of Alzheimer's disease (AD), the most common form of dementia, is multifaceted and influenced by a variety of genetic, environmental, and lifestyle components. Both Type 2 diabetes (T2D), a metabolic condition associated with aging, and sleep disorders are implicated in the pathogenesis of AD, but the exact role sleep and metabolism play remains unclear. Further, individuals with T2D are 2-4-fold more likely to develop AD, suggesting a common mechanism underlying these diseases. The goal of this study, therefore, is to determine if AD pathology and glycemic fluctuations synergize to cause sleep loss and peripheral glucose intolerance, thereby increasing the risk of both T2D and AD. We implanted biosensors detecting ISF glucose and lactate, measures of cerebral metabolism and neuronal activity, respectively, bilaterally into the hippocampi of two mouse models of AD: APP/PS1 mice, a model of Aβ pathology, and P301S mice, a model of tauopathy and neurodegeneration. We delivered hyper- and hypo-glycemic challenges to determine the effect of peripheral metabolic fluctuations on the brain as a function of both aging and pathology. Simultaneous cortical EEG/EMG recordings were utilized for sleep/wake analysis. Glycemic fluctuations resulted in a decoupling of the typical relationships between cerebral metabolism and neuronal activity while also causing increased arousal in 3-month old, wildtype mice. However, in an aged, 18 month old APP/PS1 model mouse, the metabolic response to glycemic challenges was muted and there was seemingly no impact on arousal state, likely due to an age and pathology-dependent increase in the overall amount of time spent awake. Further, in the aged, 11-month-old P301S mice, the metabolic response was lost with a similar ceiling effect on arousal state. Moreover, the 18-month-old PSAPP mice demonstrate decreased glucose sensitivity in glucose tolerance testing (GTT) as compared 9-month-old PSAPP mice that show glucose intolerance and insulin resistance. These results indicate a bidirectional, pathology-dependent shift in metabolic responsivity as AD progresses. This study represents a novel approach to defining the dynamic interplay between risk factors for AD and T2D and suggests feedforward loop of disease progression where sleep disruptions can modulate AD and T2D risk by altering the relationship between glucose tolerance, cerebral metabolism, neuronal activity, and Aβ/tau levels. Understanding the timing of these relationships is critical for offering potential strategies to mitigate the increased risk of AD among individuals with T2D.

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Poster

651. Alzheimer's Disease: Energy Homeostasis

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 651.24/D4

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

Support: T32-AG061897

Title: Comprehensive phenotyping of patient-derived fibroblasts from patients with sporadic Alzheimer's disease

Authors: *G. L. BRANIGAN[1,2,3], L. WHITMAN[1], M. J. CORENBLUM[1], L. MADHAVAN[1,4], R. D. BRINTON[1,2,4];
[1]Ctr. for Innovation in Brain Sci., [2]Pharmacol., [3]MD-PhD Training Program, [4]Neurol., Univ. of Arizona, Tucson, AZ

Abstract: Globally, neurological disorders rank as the leading cause of disability-adjusted life-years, and the second-leading cause of deaths. The high global prevalence and economic impact of Alzheimer’s disease presents a significant public health challenge while the identification of early biomarkers to diagnose Alzheimer’s disease (AD) remains a challenge. It has been shown that risk for late-onset AD is partially driven by genetics while studies using pathway analysis have implicated immunity, lipid metabolism, tau binding proteins, amyloid precursor protein (APP) metabolism and mitochondrial energetics as possible mechanisms of disease risk. Given the lack of successful mechanistic studies for AD biomarkers, the Center for Innovation in Brain Science (CIBS) at the University of Arizona has acquired and banked fibroblast lines from male and female patients with sporadic age-associated neurodegenerative diseases (n=12/disease) and age-matched healthy controls. Human dermal fibroblasts (hDF) from patients with Alzheimer’s disease (AD) were phenotypically profiled for both genetic (genetic sex, APOE genotype, mitochondrial haplotype) and molecular (transcriptomics, metabolomics, immunological profile, bioenergetic signature and mitochondrial respiration) characteristics to determine inherited, age- and sex-related mechanisms of neurodegeneration. To address morphological and cytochemical phenotypes, hDF lines were stained by IHC for known AD aggregation proteins amyloid-beta and hyperphosphorylated tau and profiled using live in-vivo imaging for mitochondrial tracking. Using this approach, we have begun to establish phenotypic profiles for neurodegeneration in Alzheimer’s disease using a patient-specific cell model. We will continue to generate and characterize reprogrammed patient-derived fibroblast and induced neural cells to determine the molecular pathways driving early age-associated AD vulnerability. Preliminary results of comprehensive phenotyping in the hDF show a variety of APOE genotypes present in the samples (APOE 2/3, 3/3, 3/4, 4/4) representing a roughly even distribution of genetic sex in each

genotype. Preliminary staining shows common markers of aggregations between CNS and peripheral fibroblast indicating opportunities novel biomarker development.

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Poster

652. Alzheimer's Disease Biomarkers

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 652.01/D5

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

Support: JSPS KAKENHI Grant Number 17K16381
JSPS KAKENHI Grant Number 18K07564

Title: TREM1 mRNA expression in leukocytes and cognitive function in patients with Alzheimer's disease

Authors: *J. IGA, T. SAO, Y. YOSHINO, K. YAMAZAKI, Y. OZAKI, Y. MORI, S. OCHI, T. YOSHIDA, T. MORI, S.-I. UENO;
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Abstract: Background: Triggering receptor expressed on myeloid cells 2 (TREM2) activates the innate immune system, promotes phagocytosis by microglia, and is associated with Alzheimer's disease (AD). The possible role of a related molecule, TREM1, in AD remains unknown. Objective: We investigated a possible role for TREM1 in AD by determining the gene expression and methylation levels of TREM1 in leukocytes from AD patients. Methods: Fifty patients with AD and 50 age-matched healthy controls were enrolled. AD patients underwent a battery of neuropsychiatric tests. Peripheral blood samples were obtained from each participant, RNA and DNA were extracted, and samples were assessed for TREM1 mRNA expression and methylation rates at three CpG sites in the TREM1 promoter. Results: TREM1 mRNA expression levels in AD patients were significantly higher than those in controls ($p = 0.008$). TREM1 mRNA expression levels were not correlated with sex, age, duration of illness, APOE genotype, donepezil treatment, or scores of most neuropsychiatric tests. TREM1 mRNA expression levels in AD patients were correlated with the total score of the Montgomery-Åsberg Depression Rating Scale ($p = 0.047$, $r = -0.344$). Methylation rates at the three CpG sites were significantly lower in AD patients than in controls. We also found a significant correlation between TREM1 mRNA expression and TREM1 DNA methylation rates ($p < 0.001$). Conclusion: TREM1 may be associated with the immune responses in AD, and along with hypomethylation at CpG sites in the TREM1 promoter, may become part of a biomarker panel for AD pathogenesis.

Disclosures: **J. Iga:** None. **T. Sao:** None. **Y. Yoshino:** None. **K. Yamazaki:** None. **Y. Ozaki:** None. **Y. Mori:** None. **S. Ochi:** None. **T. Yoshida:** None. **T. Mori:** None. **S. Ueno:** None.

Poster

652. Alzheimer's Disease Biomarkers

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 652.02/D6

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

Support: Davee Foundation

Title: Reduced expression of antioxidant enzymes in postmortem tissues of subjects with Alzheimer's disease and prior depression

Authors: *W. LUO[1], E. H. BIGIO[2], S. WEINTRAUB[2], M. MESULAM[2], E. E. REDEI[1]; [1]Dept. of Psychiatry and Behavioral Sci., [2]Mesulam Ctr. for Cognitive Neurol. and Alzheimer's Dis., Northwestern Univ. Feinberg Sch. of Med., Chicago, IL

Abstract: Earlier-life depression, defined as major depressive disorder (MDD) or depressive symptoms occurring before age 60, has consistently been associated with a more than two-fold increase in dementia risk including Alzheimer's Disease (AD). In an animal study, we measured hippocampus-based memory in females of a genetic rat model of depression, the Wistar Kyoto More Immobile (WMI) strain. At a young age, there was no difference in memory between the WMI and their genetically close control, the Wistar Kyoto Less Immobile (WLI), that does not show depression-like behavior. However, by middle age, memory decline had occurred in the WMI females. Hippocampal transcript levels of catalase (*Cat*) showed a pattern that paralleled memory decline, with decreases solely in the middle-aged WMI hippocampus. Enhanced oxidative stress has been implicated in AD, both as an active continuing process and as an early indicator of the disease. Although an oxidant/antioxidant imbalance has been found in postmortem AD brain regions, none of the antioxidants produced the expected benefits in clinical trials with AD patients. We hypothesized that the oxidative imbalance in the subpopulation of AD subjects with MDD might be more pronounced, and that if blood-based biomarkers for this process could be identified, it could lead to development of treatment in specific subgroups. We examined the differences in transcript levels of *CAT* and superoxide dismutase 1 (*SOD1*) in post-mortem brain samples from individuals with AD dementia and neuropathologic changes of AD, with (n=15) and without (n=19) prior depression. Hippocampal (Hip) and anterior cingulate cortex (ACC) tissues were received from the Brain Bank of the Northwestern Cognitive Neurology and Alzheimer Disease Center. Transcript levels were determined by quantitative RT-PCR. Both hippocampal and ACC expression of *CAT* were significantly lower in subjects with AD+MDD compared to those of AD. Although *SOD1* expression was significantly different by comorbidity with MDD, this difference came from decreased *SOD1* expression in females with

AD+MDD, specifically. Since excess *Cat* enhances cognition in animal studies, if the levels of these transcripts are further reduced in the brain of AD+MDD subjects, exploring their regulatory pathways could provide focused targets for drug discovery.

Disclosures: W. Luo: None. **E.H. Bigio:** None. **S. Weintraub:** None. **M. Mesulam:** None. **E.E. Redei:** None.

Poster

652. Alzheimer's Disease Biomarkers

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 652.03/D7

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

Support: UH3NS100606

Title: Identifying subsets of subjects with mild cognitive impairment and cardiovascular risk factors based on differential expression of angiogenic and inflammatory biomarkers

Authors: *Z. S. WINDER[1], T. L. SUDDUTH[2], D. FARDO[3], Q. CHENG[4], L. B. GOLDSTEIN[5], P. T. NELSON[2], F. A. SCHMITT[2], G. A. JICHA[2], D. M. WILCOCK[2]; [1]Physiol., [2]Sanders-Brown Ctr. on Aging, [3]Biostatistics, [4]Biomed. Informatics, [5]Neurol., Univ. of Kentucky, Lexington, KY

Abstract: Agglomerative hierarchical clustering analysis (HCA) is a commonly used unsupervised machine learning approach for identifying informative natural clusters of observations. HCA calculates a pairwise dissimilarity matrix, and then clusters similar observations until all observations are grouped within a cluster. We compared a novel HCA technique with one used in previous biomedical applications by applying both techniques to plasma angiogenic (FGF, FLT, PIGF, Tie-2, VEGF, VEGF-D) and inflammatory (MMP1, MMP3, MMP9, IL8, TNFα) protein data. Our HCA model is novel in two ways: 1, use of consensus clustering to combine multiple HCA algorithms to create a dissimilarity matrix between observations determined by the percentage of models in which two observations are found within the same cluster; 2, creation of each HCA algorithm using the Minkowski distance to calculate dissimilarity between observations. We varied the p value, necessary to compute the Minkowski distance, to obtain multiple HCA algorithms for the consensus clustering within our novel HCA model. Study subjects were clinically diagnosed with mild cognitive impairment (MCI) associated with cerebrovascular disease (CVD). By comparing the two HCA techniques using this dataset, we were able to identify subsets of individuals showing differences in VEGF ($p < 0.001$), MMP1 ($p < 0.001$), and IL8 ($p < 0.001$) expression. These profiles provide novel insights into angiogenic and inflammatory pathologies that may contribute to vascular cognitive impairment and dementia.

Disclosures: **Z.S. Winder:** None. **T.L. Sudduth:** None. **D. Fardo:** None. **Q. Cheng:** None. **L.B. Goldstein:** None. **P.T. Nelson:** None. **F.A. Schmitt:** None. **G.A. Jicha:** None. **D.M. Wilcock:** None.

Poster

652. Alzheimer's Disease Biomarkers

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 652.04/D8

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

Support: NRF-2016R1C1B2010206
Korea Centers for Disease Control and Prevention (#4845-303)

Title: Identification of cathepsin D as a plasma biomarker candidate for Alzheimer's disease

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Abstract: Alzheimer’s disease (AD) is the most common neurodegenerative disease, but there are still no drugs available to treat or prevent AD dramatically. However, efforts to develop early diagnostic ways should also be made along with the development of treatment of AD for appropriate medical intervention from the early stage of the disease. Here, we have examined the change in the level of selected proteins implicated in the pathogenesis of AD using the plasma of control subjects and patients with cognition impairment. To precisely categorize the diseases, all the patients were examined with amyloid PET scan and the white matter hyperintensity was scored by magnetic resonance imaging. By analyzing quantitative immunoblot and ELISA, we found the plasma level of cathepsin D which is a major lysosomal protease significantly decreased in the group with amyloid plaque deposition at the brain compared to the control group. These results suggest that the plasma cathepsin D level could be a candidate to be developed as a diagnostic biomarker of AD. This study also suggests that lysosomal degradation activity could be associated with the onset or the progression of AD.

Disclosures: **Y. Kim:** None. **S. Jung:** None. **S. Lee:** None. **J. Chang:** None.

Poster

652. Alzheimer's Disease Biomarkers

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 652.05/D9

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

Support: JSPS KAKENHI (JP26282026, JP17K19951, JP17H02188)

Title: Phosphorylation of specific serine sites on hippocampal insulin receptor substrate 1 is associated with Alzheimer's disease-unrelated memory deficit and -related pathology

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Abstract: Modification of Insulin receptor substrate 1 (IRS1) through the phosphorylation of serine (Ser) residues occurs in an insulin-dependent and -independent manners. In the central nervous system, increased phosphorylation of specific Ser residues on IRS1 is observed in patients and transgenic animal models with Alzheimer's disease (AD). To investigate whether the activation of AD-related Ser sites on neural IRS is incidental to any type of memory decline, we employed various memory impairment animal models, such as high fat diet (HFD)-induced type2 diabetes (T2DM) model mice, streptozotocin (STZ)-induced type 1 diabetes (T1DM) model mice, aged mice, and amyloid precursor protein (APP) knock-in (APPKI $^{NL-G-F}$) mice, a novel AD mouse model. The substantial phosphorylation of Ser307 and Ser1097 on hippocampal IRS1 occurred in T2DM and aging-associated memory deficits in mice, regardless of the presence/absence of the activities in canonical downstream factors, such as Akt and GSK3ß. By contrast, memory impairment in T1DM mice arose independently of IRS1 activities. Despite exhibiting normal memory formation, the phosphorylation of hippocampal IRS1 at multiple Ser residues increased on condition that amyloid β (Aβ) accumulation was already evident in young APPKI $^{NL-G-F}$ mice, whereas the phosphorylation level of Ser307 was unchanged in middle-aged APPKI $^{NL-G-F}$ mice exhibiting memory decline compared to age-matched wild-type mice. These data suggest that the phosphorylation of hippocampal IRS1 at specific Ser sites may be potential markers for non-AD-related memory deterioration caused by T2DM and aging; however, AD-associated activation of IRS1Ser residues may be induced in response to AD pathology but not to memory decline.

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Poster

652. Alzheimer's Disease Biomarkers

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 652.06/D10

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

Support: NIH/NIBIB 4R00EB017289-03
Seeding Grant KIHA-2019

Title: Down syndrome-Alzheimer's disease related increases in polyamines causes decreased mitochondrial motility

Authors: *D. FUDGE[1], S. MELGAR[1], C. HICKS[1], A. SANDBERG[2], S. HARVEY[3], D. PATTERSON[1], G. VACANO[2], A. LEDREUX[2], P. CAVIEDES[5,6], D. LINSEMAN[4], L. HERNANDEZ[7], L. GRANHOLM-BENTLEY[2], Y. QIN[1], D. PAREDES[2];
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Abstract: Down Syndrome (DS) is a genetic condition where there is an extra copy of chromosome 21 resulting in triplication of the amyloid precursor protein (APP) gene. Increased APP results in an increased incidence of Alzheimer’s disease (AD) pathology in individuals with DS. AD pathology in DS individuals is a superb platform to study the mechanisms of AD pathology due to the increased production of the Beta Amyloid (Aβ) peptide. AD is currently the most prevalent neurodegenerative disease affecting the human population. Many avenues have been explored to determine the mechanism of action or important biomarkers for AD with partial success. Some of these avenues suggest polyamines potentially underlying the mechanism leading to AD pathology. Polyamines are aliphatic amines at physiological pH associated with a positive charge. This positive charge allows polyamines to interact with negatively charged macromolecules such as DNA, RNA, and some amino acids. Polyamines have been found to modulate cell proliferation, gene expression, and immune response but little investigation into polyamines effects on AD has been performed. Increased polyamine concentrations have been found in AD brains. We have found the same pattern exists in DS related AD brains. We hypothesize that polyamine concentrations increase due to increased beta amyloid proteins which activate ornithine decarboxylase (ODC) to convert ornithine into polyamines. We found increased polyamine concentrations in mice DS cell lines, with simultaneously increased aggregation of amyloid beta (Aβ) proteins. Besides facilitating aggregation of Aβ we have shown the increased concentrations of polyamines decreased mitochondrial motility. This decrease in motility has been found in primary cultured rat neurons as well as in a DS mouse

neuron model. The production of polyamines can be blocked using an Difluoromethylornithine (DFMO). DFMO inhibits ODC preventing the production of polyamines. DFMO restores the mitochondrial motility and decreases Aβ aggregation in the DS mouse model. In the mouse neuron model a normosomic control cell line was used to establish a reference point for polyamines and Aβ aggregation. Mitochondrial motility in relation to polyamines has never been connected prior to these results indicating a novel mechanistic pathway for the underlying pathology of AD in DS brains. This could potentially set the grounds for targeting the polyamine pathway to halt the progression of AD pathology in DS individuals. Supported by: Knoebel Institute for Healthy Aging KIHA-84311-294811.

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Poster

652. Alzheimer's Disease Biomarkers

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 652.07/D11

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

Support: NIH RO1 AG058171

Title: Developing a method for detection of mitochondrial oxidative stress in a mouse model of amyloidogenesis

Authors: *L. J. OUILLETTE[1], S. J. MOORE[2], T. STEVENSON[2], V. A. CAZARES[2], R. PARENT[2], G. G. MURPHY[2];
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Abstract: Alzheimer’s disease (AD) is a neurodegenerative disease and is the most common form of dementia. It is characterized by hallmark neuropathological changes including intracellular neurofibrillary tangles (NFTs), which are composed primarily of aggregates of hyper-phosphorylated microtubule-associated tau proteins, and amyloid plaques which are aggregated extra-cellular amyloid beta (Aβ) protein. While the study of Aβ and Tau pathologies have provided crucial information about their role in AD, the exact mechanism regarding the onset of AD pathology remains unclear. Mitochondrial dysfunction has been thought to be a critical factor in AD because of its potential to produce oxidative stress in the form of superoxide (O_2-), which is a reactive oxygen species (ROS) and a byproduct of cellular respiration. Additionally, mitochondrial oxidative stress has been hypothesized to play a role in aging and AD onset, including the propagation of Aβ. Recent advancements have facilitated the detection

of global oxidative stress using in vivo imaging (Berkowitz, 2017), but this method lacks cellular and subcellular resolution. To interrogate the cell types and cellular compartments that may experience increased oxidative stress, we have developed a method that allows direct identification of oxidative stress markers. This method combines confocal imaging of brain slices acutely prepared from mice with a mitochondrial specific probe that when oxidized, emits a fluorescent signal. We are currently testing this method in a variety of mouse models including the 5XFAD model of amylogenesis. Development of this method has the potential to foster significant progress in determining cell specific interactions between the declining health of brain tissue and ROS in many disease models.

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Poster

652. Alzheimer's Disease Biomarkers

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 652.08/D12

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

Support: Anonymous Foundation Grant

Title: Levels of newly generated soluble amyloid precursor proteins in human cerebrospinal fluid

Authors: *J. A. DOBROWOLSKA ZAKARIA[1], R. J. BATEMAN[2], B. W. PATTERSON[3], R. J. VASSAR[1];
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Abstract: The amyloid hypothesis proposes that increased production and/or decreased clearance of amyloid-beta (Aβ) leads to higher order amyloid structures that initiate a cascade of events, culminating in neuronal death manifesting as Alzheimer's disease (AD). Sequential cleavage of Amyloid Precursor Protein (APP) generates Aβ. APP may be processed in one of at least two pathways, initially being cleaved by either α- or β-secretase (BACE1). BACE1 cleavage of APP releases soluble APP-β (sAPPβ) and subsequent cleavage by γ-secretase produces Aβ. Alternatively, α-secretase cleavage of APP precludes Aβ formation and produces soluble APP-α (sAPPα).
We hypothesize that a subgroup of the AD and non-demented Amyloid+ populations overproduce Aβ because of increased BACE1 activity. Our objective is to measure CSF sAPPβ and sAPPα kinetic rates, as surrogate markers of BACE1 activity, to determine if, and by how much, BACE1 activity is increased in these individuals.

Using stable isotope labeling kinetics/immunoprecipitation/liquid chromatography-tandem mass spectrometry methods, we quantified sAPPβ and sAPPα in CSF from human Amyloid+ (AD) and Amyloid- (control) subjects who had undergone [U-$^{13}C_6$]-leucine labeling and hourly CSF collection. The fraction of metabolite derived from *de novo* synthesis was measured by calculating normalized metabolites' hourly mole fraction labeled (MFL), over 36 hours. Normalized MFL was multiplied by the metabolites' absolute concentration to quantitate newly generated metabolites. Regression analyses were performed to determine extent of the relationship between these measures and brain amyloid load.
We have previously shown in a pilot study that both sAPPβ and sAPPα turnover rates were slower in Amyloid+ subjects than in Amyloid- subjects. Additionally, the rate of turnover of sAPPβ was marginally slower than the sAPPα turnover rate in both groups. This difference was more pronounced in the setting of amyloidosis. Newly generated sAPPβ, and the newly generated sAPPβ:sAPPα absolute ratio, were significantly elevated in Amyloid+. Newly generated sAPPα was not significantly different between groups. Brain amyloid load was positively correlated to sAPPβ:sAPPα. The pilot results strongly suggest increased APP processing by BACE1 in the subjects with brain amyloid deposition.
This study is ongoing and we will be presenting data from an increased sample size. The full study's results will allow for characterization of AD subpopulations most likely to benefit from BACE1 inhibitors.

Disclosures: J.A. Dobrowolska Zakaria: A. Employment/Salary (full or part-time):; Northwestern University Feinberg School of Medicine. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); antibodies from Merck & Co.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); royalties from a patent licensed to C2N Diagnostics by Washington University. **R.J. Bateman:** A. Employment/Salary (full or part-time):; Washington University in St. Louis. 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.; Tau SILK Consortium, DIAN Pharma Consortium. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); equity ownership interest in C2N Diagnostics and receives royalty income based on technology licensed by Washington University to C2N Diagnosti. F. Consulting Fees (e.g., advisory boards); C2N Diagnostics, scientific advisory board, Eisai consultant, Merck, advisory board member, Pfizer, advisory board member. Other; Honoraria from Janssen, Pfizer, and Roche as a speaker, Washington University, with RJB as co-inventor, has submitted the US nonprovisional patent application and a provisional patent application, Funding for clinical trials include Eli Lilly and Co, Hoffman La-Roche, Janssen, Avid Radiopharmaceuticals. **B.W. Patterson:** A. Employment/Salary (full or part-time):; Washington University in St. Louis. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Royalties on patents licensed to C2N Diagnostics by Washington University. F. Consulting Fees (e.g., advisory boards); C2N Diagnostics. **R.J. Vassar:** A. Employment/Salary (full or part-time):; Northwestern University Feinberg School of Medicine.

Poster

652. Alzheimer's Disease Biomarkers

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 652.09/D13

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

Support: AG005134
AG036694
AG061206
U01NS086659
MH100350

Title: Autoradiographic characterization of novel tau PET tracer [18F]-PI-2620 in human postmortem brain tissue

Authors: *M. DHAYNAUT[1,4,5], C. AGUERO[2,6], R. NEELAMEGAM[1,4], M. D. NORMANDIN[1,4], G. EL FAKHRI[1,4], M. P. FROSCH[3,6], T. GÓMEZ-ISLA[2,6];
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Abstract: Background: The development of tau targeted PET tracers has opened the opportunity of using them to improve diagnostic accuracy in Alzheimer’s disease (AD) and related tauopathies. We and others have previously demonstrated that [F-18]-Flortaucipir (AV-1451, T807) and [F-18]-MK-6240 bind with strong affinity to tau aggregates in AD but have relatively low affinity for tau deposits in non-AD tauopathies and exhibit off-target to neuromelanin- and melanin-contaning cells and hemorrhages. In the present work we examined region and substrate specific autoradiographic binding patterns and potential off-target of novel second generation tau PET tracer PI-2620 and compared the binding properties of the three tau tracers in some of same tissue specimens. Methods: We applied [F-18]-PI-2620 phosphor screen autoradiography to postmortem brain samples with a pathological diagnosis of Alzheimer disease, frontotemporal lobar degeneration-tau (Pick’s disease, progressive supranuclear palsy and corticobasal degeneration), frontotemporal lobar degeneration-TDP-43, dementia with Lewy bodies, cerebral amyloid angiopathy and controls free of pathology. High resolution nuclear emulsion autoradiography and immunohistochemistry experiments are currently ongoing. We examined potential nonspecific binding of the three tracers to monoamine oxidases (MAO) by using autoradiography in the presence of selective MAO-A and MAO-B inhibitors. Results: [F-18]-PI-2620 strongly binds to neurofibrillary tangles in AD. There is no evidence of tracer’s binding to

lesions containing beta-amyloid, alpha-synuclein or TDP-43. Like Flortacucipir and MK-6240, PI-2620 seems to have a relatively low affinity for tau aggregates in non-AD tauopathies. Autoradiography experiments avoiding ethanol in the washing conditions are currently ongoing to rule out the possibility that ethanol may have displaced some weaker signal in non-AD tauopathies. The three tracers exhibit identical off-target to neuromelanin and melanin-containing cells, and areas of hemorrhage. [F-18]-Flortaucipir, [F-18]-MK-6240 and [F-18]-PI-2620 autoradiographic binding signals are only weakly displaced by competing concentrations of selective MAO-B inhibitor deprenyl suggesting that MAO enzymes are not a significant binding target of these tracers. Conclusion : These novel findings provide relevant insights for the correct interpretation of *in vivo* [F-18]-PI-2620 PET imaging.

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Poster

652. Alzheimer's Disease Biomarkers

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 652.10/D14

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

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Alzheimer’s Association strategic 509279 grant
Foundation Leducq reference no. 16 CVD 05
NIH P50AG05681
NIH P01AG03991
NIH P01AG026276

Title: Blood-brain barrier breakdown predicts early cognitive dysfunction in APOE4 carriers independent of aβ and tau

Authors: ***M. D. SWEENEY**[1], A. MONTAGNE[1], D. A. NATION[1], A. CHAKHOYAN[1], A. P. SAGARE[1], M. PACHICANO[1], F. SEPEHRBAND[1], M. G. HARRINGTON[2], D. P. BUENNAGEL[2], J. M. RINGMAN[1], E. JOE[1], L. S. SCHNEIDER[1], J. PA[1], V. D. BUCKLES[3], T. L. S. BENZINGER[3], A. M. FAGAN[3], J. C. MORRIS[3], M. LAW[1], H. C. CHUI[1], A. W. TOGA[1], B. V. ZLOKOVIC[1];
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Abstract: Vascular dysfunction is increasingly recognized in the pathophysiology of Alzheimer’s disease (AD), and measures of vascular dysfunction can be evaluated using

cerebrospinal fluid (CSF) and imaging-based biomarker approaches. A clinical need exists to identify reliable biomarkers for early AD diagnosis, early intervention, and evaluating the efficacy of clinical trials. In this study, human participants were recruited from the University of Southern California (USC) Alzheimer's disease Research Center (ADRC) and the Washington University Knight ADRC. Here, we quantified novel CSF biomarkers of responses and injury to the neurovascular unit (NVU) - comprising vascular cells, glia, and neurons - using immunoassays, and evaluated regional K_{trans} measures of blood-brain barrier (BBB) permeability using dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI). CSF NVU biomarkers and DCE-MRI were analyzed in relation to participants' cognitive status (cognitively normal and early cognitive impairment) and the major genetic risk factor for sporadic AD, apolipoprotein E-ε4 (*APOE4*). We found that CSF measures of microvascular pericyte injury, namely soluble platelet-derived growth factor receptor-β (sPDGFRβ), was increased in *APOE4* carriers with cognitive impairment. Biomarkers of BBB breakdown including, for example, albumin quotient were similarly increased in *APOE4* carriers during cognitive impairment. Glial, inflammatory and neuronal injury markers were not altered with *APOE4* or cognitive impairment. The BBB and pericyte injury biomarkers increased independent of amyloid-β (Aβ) and tau. Consistently, we also found increased regional BBB permeability in the hippocampus and parahippocampal gyrus in *APOE4* carriers, independent of Aβ and tau. These suggest that CSF and MRI-based biomarkers of BBB and/or pericyte dysfunction are early detectable changes that are altered early in cognitive impairment and accelerated in *APOE4* carriers. Pilot data also indicate that high baseline levels of CSF sPDGFRβ predicts longitudinal decline in cognitive function in *APOE4* carriers, but not in *APOE4* noncarriers. Altogether, BBB breakdown is related to early cognitive dysfunction in *APOE4* carriers independent of Aβ and tau, and cerebrovascular biomarkers may be useful predictors of subtle cognitive dysfunction.

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Poster

652. Alzheimer's Disease Biomarkers

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 652.11/D15

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

Title: Treatment GSK3-beta inhibitor Tideglusib improves memory performance, regulate tau phosphorylation and amyloid beta peptide in a type 2 diabetics rats

Authors: *T. PONCE-LOPEZ, M. ABASCAL-DÍAZ;
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Abstract: Several studies have shown that patients with diabetes mellitus type 2 (DM2) are at increased risk of developing Alzheimer's disease (AD). Due to the profound socioeconomic impact of diabetes and AD, understanding the mechanisms that could link both diseases is essential. Oxidative stress, dysfunction of glucose and cholesterol metabolism, and mitochondrial activity, among others, have been shown to be associated with diabetes and AD. In fact, patients with diabetes have cognitive impairment, beta amyloid peptide deposits and hyperphosphorylated tau protein, neuropathological features of AD. It has been associated with disorders of signal transduction of the insulin receptor (IR), termed "cerebral insulin resistance". This is analogous to peripheral insulin resistance, represented by impaired neuronal insulin functions; such as glucose regulation, growth, neuronal survival and remodeling, and assembly of microtubules. Insulin is known to regulate tau phosphorylation through the PI3K-Akt-GSK3 pathway of insulin receptor (IR), disruption of this balance leads to abnormal phosphorylation of tau and amyloid deposits. As a consequence, GSK3 inhibitors have emerged as potential therapeutic tools for neural diseases dealing the tiadiazolidindione-derivative tideglusib ATP-noncompetitive GSK3 inhibitor has been shown to induce beneficial effects in some clinical trials for AD treatment with cognitive decline. This study aims to evaluate the effect intrahippocamcal admnsitration of tideglusib a memory impairments, disruption insulin receptor (IR), phosphatidylinositol-3-kinase/protein kinase B/GSK3 (PI3K-Akt/PKB-GSK3) signaling cascade, and abnormal phosphorylation of tau and beta amyloid peptide in a DM2 model. Wistar rats were given streptozotocin (STZ; 45 mg/kg) and a high-fat diet. The administration of tideglusib stereotactic surgery will be performed for the intrahippocampal administration of tideglusib (50 mg/kg). The spatial memory were assessed by Morris water maze. We are quantifying peripheral insulin and lipids by the ELISA test, the Akt, GSK3 and tau protein will be through western blot in hippocampus. Results showed that tideglusib improved spatial learning and memory. This evidence will provide insight about the role PI3K-Akt/PKB-GSK3 signaling cascade of IR and the therapeutic benefits of tideglusib on abnormal phosphorylation tau and memory dysfunction to prevent the development of the AD in patients with DM2.

Disclosures: T. Ponce-Lopez: None. **M. Abascal-Díaz:** None.

Poster

652. Alzheimer's Disease Biomarkers

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 652.12/D16

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

Title: Olfactory impairment is associated with *in vivo* tau and amyloid-β accumulation in Alzheimer's disease spectrum

Authors: *M. BAEK, C. LYOO, H. CHO;
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Abstract: Objective: To examine whether impaired olfaction is related to imaging biomarkesr of tau and amyloid-β (Aβ) accumulation in Alzheimer's disease spectrum disease **Methods:** From January 2015 to August 2017, we prospectively recruited 208 participants [67 healthy control(HC), 83 mild cognitive impairment(MCI) and 58 dementia(DEM)] at the Memory Disorder Clinic of Gangnam Severance Hospital. Participants completed clinical interviews, a neuropsychological test battery, Cross-Cultural Smell Identification Test (CCSIT), magnetic resonance imaging(MRI), PET scan studies including ^{18}F-flortaucipir for tau and ^{18}F-florbetaben for Aβ. After correcting for partial volume effect, standardized uptake value ratio (SUVR) images were created. Regional SUVRs were measured between normosmia and hyposmia groups, and we also investigated a correlation between olfactory function and *in vivo* tau and Aβ accumulation in Alzheimer's disease spectrum. **Results:** Mean CCIST score in DEM was lower than in MCI and in HC (9.0±2.3 in DEM, 7.1 ± 2.8 in MCI 9.0 ± 2.3 in HC, P<0.001), and the proportion of hyposmia was higher in DEM (46/58(79%) in DEM, 40/83(48%) in MCI, and 15/67(22%) in HC). While there was no difference in tau and Aβ accumulation between normosmia and hyposmia groups in HC, tau accumulation in multiple temporo-parietal regions were increased in hyposmia group in MCI. Aβ accumulation in cerebral white matter and, tau accumulation in sensorymotor cortex, and precuneous region were shown in DEM. After adjustment for sex, age, ApoE ε4 positivity, and education duration, olfactory impairment was correlated with tau accumulation in multiple regions in MCI [superior/middle temporal/inferior temporal (P<0.05, respectively), inferior parietal (P<0.05) and insular(P<0.05)], and in DEM groups [prefrontal (P<0.01), sensorimotor (P<0.01), superior/inferior parietal (P<0.01, repectively), precuneus (P<0.01), and entorhinal(P<0.01)]. Correlation between olfactory impairment and Aβ was relatively weak. CCSIT score also showed correlation with language(BNT), visual memory(RCFT_DR) and frontal/executive functions(COWAT).**Conclusions:** Olfactory impairment is correlated with *In vivo* tau accumulation in multiple brain regions. Olfactory impairment may precede the tau accumulation and cognitive impairment, so left possibility for early biomarker for Alzheimer's disease spectrum disease

Disclosures: M. Baek: None. **C. Lyoo:** None. **H. Cho:** None.

Poster

652. Alzheimer's Disease Biomarkers

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 652.13/D17

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

Support: NIA K01 AG050719
Harold and Mary Eagle Fund for Alzheimer's Research
UL1TR001420
P40OD010965
NC Diabetes Research Center

Title: Type 2 diabetes alters CSF but not plasma metabolomic and AD risk profiles in vervet monkeys

Authors: *S. M. DAY[1], M. PAIT[1], W. MORTIZ[4], C. NEWGARD[5], O. ILKAYEVA[5], D. MCCLAIN[2], K. KAVANAGH[3,6], S. L. MACAULEY[2];
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Abstract: Epidemiological studies have shown that individuals with type 2 diabetes (T2D) have a 2-4 fold increased risk for developing Alzheimer's disease (AD), however the exact mechanisms linking the two conditions remains unknown. In T2D and AD the majority of pathological changes (such as elevated glucose, elevated insulin, and insulin resistance in T2D, and amyloid β (Aβ) and tau aggregation in AD) occurs many years before the onset of clinical symptoms and diagnosis. In this study we sampled CSF and plasma from healthy, insulin resistant (IR), and T2D age-matched female vervet monkeys (*Chlorocebus aethiops sabeus*) and compared Aβ and metabolic biomarkers by metabolic status. T2D and insulin resistance were diagnosed by veterinary staff according to repeated fasting glucose measurements and American Diabetes Association criteria. We found that T2D vervet monkeys have decreased CSF acylcarnitine, CSF amino acid, and plasma lactate levels, which suggests a metabolic perturbation in the brains. Furthermore T2D monkeys also have decreased CSF Aβ40 and Aβ42 levels, which is indicative of increased amyloid deposition within the brain. In agreement with our previous rodent studies CSF Aβ40 and Aβ42 were highly correlated with CSF glucose levels, suggesting glucose drives Aβ production and aggregation within the brain. CSF Aβ40 and Aβ42 levels were also highly correlated with plasma lactate, but not CSF lactate. We also found that CSF glucose and plasma lactate were significantly correlated with amino acid and acylcarnitine levels. Together these data indicate that the brain begins to consume more amino acids and acylcarnitines as fuel while simultaneously accumulating Aβ as T2D progresses. Based on these

findings we hypothesize that the progression of T2D drives a state of hypermetabolic overconsumption in the brain that promotes Aβ aggregation; a finding that may explain the relationship between T2D and AD. Thus, AD and T2D exacerbate one another and contribute to increased AD risk factors, including altered brain metabolism and oxidative stress.

Disclosures: S.M. Day: None. **M. Pait:** None. **W. Mortiz:** None. **C. Newgard:** None. **O. Ilkayeva:** None. **K. Kavanagh:** None. **D. McClain:** None. **S.L. Macauley:** None.

Poster

652. Alzheimer's Disease Biomarkers

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 652.14/D18

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

Support: UNIPD Fund BIRD 2016-2017
CARIPARO foundation PhD Fellowship
PRAT 2015 CPDA157003

Title: Multi site electrode recordings in an Alzheimer's disease mouse model based on presenilin 2

Authors: A. LEPARULO[1], ***M. MAHMUD**[2], E. SCREMIN[1], S. VASSANELLI[1], C. FASOLATO[1];
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Abstract: Alzheimer's disease (AD) is one of the most devastating disease conditions in today's aging population worldwide. It is now imperative to detect any initial sign of the disease leading towards an early diagnosis which then might facilitate the long-term treatment plan (1). One such detection approach could be to identify early network dysfunctions occurring well before plaque deposition and inflammation. Since last decade, network activities measured as local field potentials (LFPs) have been utilised in investigating higher level cognitive functions in mammals including rodents, primates and humans (2). Apposite frequency bands extracted from the LFPs, such as slow and fast oscillations, using sophisticated time-frequency based analysis, have been found to be appropriate in studying network functions. Therefore, relevant biomarkers can be derived from these slow and fast oscillations in the network which is the basis for memory consolidation and information transfer between the cortex and the hippocampus (3,4).
Towards the detection of an early biomarker based on network dysfunction, we recorded LFPs *in vivo* with a multi-electrode linear probe spanning the posterior parietal cortex (PPC) and the dorsal hippocampal formation (HPF) to investigate the spontaneous brain oscillatory activities of AD mice under anaesthesia. Recordings were performed in two groups of PS2APP (B6.152H) mice, at 3 and 6 months of age, i.e. before and after plaque deposition, and in age-matched WT

(C57Bl6/J) mice (5,6). Seven distinct channels were selected for the frequency-based analyses: 3 in the PPC, 2 in the Cornu Ammonis (CA1) and 2 in the Dentate Gyrus (DG). Analysis of power distribution in the different frequency bands showed that, with respect to WT, at 3 months of age, i.e. at the very onset of amyloid-beta accumulation, B6.152H mice have altered power ratios between slow oscillations (SO) [0.1-1.7 Hz] and Delta waves [1.7-4.7 Hz] at CA1 close to the hippocampal fissure. The phase-amplitude coupling between SO and higher frequency bands also appears dramatically impaired in CA1 as early as 3 months of age. With plaque deposition these defects worsen and reach the PPC.

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6. Fontana R. et al., Neurobiol. Aging. 50:64-76 (2017).

Disclosures: **A. Leparulo:** None. **M. Mahmud:** None. **E. Scremin:** None. **S. Vassanelli:** None. **C. Fasolato:** None.

Poster

652. Alzheimer's Disease Biomarkers

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 652.15/D19

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

Support: POR FESR LAZIO Grant 2014-2020, Public Notice "LIFE 2020" - “MoDiag”.
EU Horizon H2020-ICT Grant-2016 n.1732678 - “MADIA”.

Title: Improving diagnostic accuracy and patients stratification in neurodegenerative diseases by machine learning: Mining clinical and laboratory data

Authors: ***M. D'ONOFRIO**[1,2], I. ARISI[3,2], R. BRANDI[1], M. SONNESSA[4], F. MALERBA[5], R. FLORIO[5], R. MACCIONI[6], G. CONFESSORE[6,7], P. BERTOLAZZI[8], M. TORTI[9], M. CANEVELLI[10], L. VACCA[9], M. TSOLAKI[11], P. MECOCCI[12], G. BRUNO[10], F. STOCCHI[9], A. CATTANEO[5,13];
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Med. Care, Dept. of Neurology, IRCCS San Raffaele La Pisana, Roma, Italy; [10]Dept. of Human Neuroscience, Sapienza Univ. of Roma, Roma, Italy; [11]3rd Dept. of Neurology- Memory and Dementia Unit, Aristotle Univ. of Thessaloniki, Thessaloniki, Greece; [12]Inst. of Gerontology and Geriatrics, Univ. of Perugia, Perugia, Italy; [13]Bio@SNS Laboratory, Scuola Normale Superiore, Pisa, Italy

Abstract: The diagnostic accuracy and therapeutic efficacy for neurodegenerative diseases can be improved by the combined evaluation of multiple central and peripheral biomarkers to differentiate among patients with different clinical-neuropathological phenotypes. Low sensitivity and specificity of current diagnostic methodologies lead to frequent misdiagnosis. This raises the need of more efficient integration of biomarkers with multidimensional clinical data. Through an interdisciplinary approach, to extract new models for more accurate diagnosis, we aim to compare real-word data of Alzheimer's (AD), Parkinson's disease (PD) and progressive supranuclear palsy (PSP, atypical parkinsonism) with public databases, such as ANM (AddNeuroMed) for AD, PPMI (PD Progressive Markers Initiative) for PD and PRIAMO (PaRkinsondIseAse non-MOtor symptoms) for PSP, by Machine Learning methods (ML). The platform will integrate and analyze clinical and instrumental parameters with transcriptomics from patients with the most severe neurodegenerative diseases, including PSP, less common and usually more severe than PD, characterized by rapid progression and atypical features. Its correct diagnosis is critical, as prognosis and symptomatic treatment of PSP is different from PD. Transcriptomics from ANM (multi-center initiative for AD clinical, transcriptomic and proteomic data), analyzed by ML, allowed identification of 268 (AD-CTL), 361 (AD-MCI) and 272 (MCI-CTL) genes unique to each gene-based classifier: 104 highly ranked genes shared between AD-CTL & MCI-CTL, 15 genes between AD-CTL & AD-MCI and 11 genes between AD-MCI & MCI-CTL classifiers. These genes represent potential transcriptomic biomarkers, highlighting the cellular processes involved. For gene-based classification, models provide excellent discrimination between AD vs CTL (AUC=0.94) and MCI vs CTL (AUC=0.90); good between AD vs MCI (AUC=0.81). Regarding PSP, RNASeq was performed on blood of 18 PSP patients and 12 matched CTLs, after approval of Ethical Committee and in accordance with current regulation. By ML, hundreds of clinical variables were correlated with real-world data, collected by excellence Italian AD, PD and movement disorders Centers. The integration of Statistics and ML in MCI and AD subjects allowed an efficient and significant selection of new sets of pathways and variables with the highest predictive power. We intend to realize a technological platform to support more precocious and accurate diagnosis of neurodegenerative diseases, towards more targeted and effective therapeutic intervention in terms of patient wellbeing and optimization of health costs.

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Poster

652. Alzheimer's Disease Biomarkers

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 652.16/D20

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

Support: NIA RF1AG041915, R56AG058854 and U01AG024904.

Title: Inflammatory markers related to liver function predict longitudinal brain atrophy

Authors: *C. P. BOYLE[1], C. CHING[2], S. THOMOPOULOS[3], A. ZAVALIANGOS-PETROPULU[4], A. MEZHER[4], P. M. THOMPSON[5];
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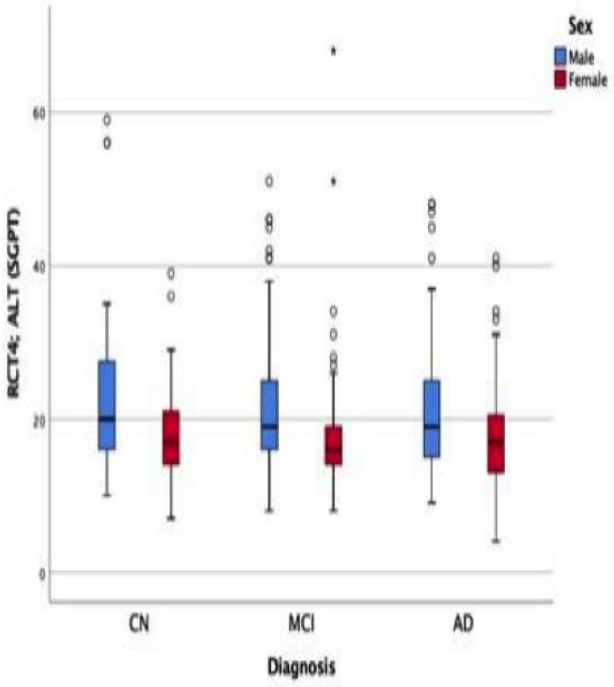
Abstract: Objective and Rationale:
Dementia risk is associated with cardiovascular, metabolic, and inflammatory markers related to liver function. Here we analyzed the relationship between longitudinal brain atrophy and two markers of liver inflammation: aspartate aminotransferase (AST) and alanine aminotransferase (ALT).
Several processes in the brain and body have been linked to the risk of dementia, including cardiovascular, metabolic and inflammatory markers, which include enzymes related to liver function. Here we aimed to define the relationship between rates of brain atrophy in old age and two markers of liver inflammation: AST (aspartate aminotransferase) and ALT (alanine aminotransferase).
Methods:
We analyzed 1.5-Tesla T1-weighted brain MRI scans from 620 older adults from the Alzheimer's disease neuroimaging initiative (ADNI) [1] (142 with Alzheimer's disease (AD), 283 with mild cognitive impairment (MCI), 195 healthy elderly; mean age: 75.2 ± 6.7 years; 42.3% female). Baseline liver enzyme levels were measured from blood serum samples collected following an overnight fast. Both ALT and AST were generally within the normal range, i.e., 8 to 48 (U/L) for AST and 7 to 55 (U/L) for ALT [2].
We measured annualized rates of brain atrophy using unbiased tensor-based morphometry. Average expansion or contraction rates (Jacobian determinant) were derived for whole temporal lobe and statistically defined temporal ROIs [3].
Using multiple linear regression, we tested whether liver function markers differed by age, sex or diagnosis; we then tested associations of brain atrophy rates with ALT and AST (See Figure 1).
Results and Conclusion:

Higher baseline AST was associated with greater rates of brain atrophy and ALT and AST differed with respect to age and sex. AST and ALT measures are known to be related to atrophy in patients with alcohol dependence [7]. Continued analysis of ADNI phase 2/3 scans and the identification of additional markers will offer more insight into the effects of liver function and influencing factors (e.g., primary liver disease) on atrophy rates.

Figure 1: Both AST and ALT were negatively correlated with age and higher in men, in line with current literature suggesting that liver function measures decline with age and that men have, on average, higher measures than women [4,5,6]. After adjusting for age and sex, we examined the relationship between AST and ALT levels and diagnosis but found no detectable difference in average measures with varying diagnosis.



* These cases represent extreme outliers for ALT which we confirmed did not affect our results.

Along with covariates such as age, sex and diagnosis, AST (but not ALT) significantly predicted rates of brain atrophy, passing FDR correction at <.05 across the whole brain. People with higher AST levels had significantly higher brain atrophy rates measured using both ROI methods.

ROI	beta value	std. error	t-value	p-value
Statistical	-0.173	0.009	-3.7	0.000
Anatomical	-0.146	0.006	-2.911	0.004

Disclosures: C.P. Boyle: None. **C. Ching:** None. **S. Thomopoulos:** None. **A. Zavaliangos-Petropulu:** None. **A. Mezher:** None. **P.M. Thompson:** None.

Poster

652. Alzheimer's Disease Biomarkers

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 652.17/D21

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

Support: VA Grant I01 BX003527
VA Grant I21 BX003807
Cure Alzheimer's Fund

Title: Profiles of amyloid, tau and neurofilament light chain in plasma from Alzheimer's patients

Authors: M. CHEN[1], L. MOO[1], ***W. XIA**[2];
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Abstract: Amyloid-containing neuritic plaques and hyper-phosphorylated tau-containing neurofibrillary tangles are pathological hallmarks in brains of Alzheimer's disease (AD) patients. Whether these pathological proteins are similarly increased in peripheral system remains to be an unresolved question. In addition, neurofilament light chain and neuroinflammation markers have been investigated in biofluid samples from patients with AD. Increased inflammatory profile in blood reflects vulnerabilities in AD patients caused by an aging immune system. Since the relatively invasive nature of cerebrospinal fluid (CSF) sampling limits the use of the current biomarkers of tau and amyloid β proteins (Aβ) for AD, we aim to use mass spectrometry (MS)- and ELISA-based analysis to study several classic pathological proteins and find the connection between the peripheral and central nervous system in AD pathogenesis. We collected blood from >100 AD patients and healthy controls, and at autopsy, post-mortem brain tissue (superior frontal cortex, inferior cortex and cerebellum area) from several subjects. Liquid chromatography/MS was used to analyze plasma proteins and proteins in brain tissues labelled with isobaric mass tags (TMT) for relative protein quantification. We examined protein-protein interaction networks through a bioinformatics approach and revealed a group of differentially expressed plasma proteins that are associated with AD. ELISA-based comparative analysis of the plasma proteins between the AD patients and healthy control subjects revealed increased pathological proteins in those from AD patients. While no significant difference in levels of plasma Aβ42 was observed, AD patients exhibited significantly higher levels of plasma tau and phosphorylated tau (ptau 181). Accordingly, levels of neurofilament light chain were also increased in the same group of AD patients, compared to those from control subjects. In conclusion, a group of pathological proteins associated with AD was found to be increased in blood, supporting our future effort to validate these proteins in peripheral compartment as valid biomarkers for AD.

Disclosures: **M. Chen:** None. **W. Xia:** None. **L. Moo:** None.

Poster

652. Alzheimer's Disease Biomarkers

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 652.18/D22

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

Support: NIH R01 AG 059874 (Jahanshad)
RF1 Grant 5351832013 (Thompson)

Title: Classification of Alzheimer's disease patients using MRI-based cortical phenotyping 1 to 2 years before dementia onset

Authors: *F. PIZZAGALLI[1], S. P. GADEWAR[1], S. I. THOMOPOULOS[1], Q. YANG[1], P. KOCHUNOV[3], P. M. THOMPSON[4], N. JAHANSHAD[2];
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Abstract: MRI has a potential for early diagnosis of individuals at risk for developing Alzheimer's disease (AD). Cognitive performance in elderly patients with AD has been associated with measures of cortical gyrification (Cai et al. 2017) and thickness (CT) (Lee et al. 2018), yet the extent to which sulcal measures can help to predict AD conversion above and beyond CT measures is not known. Here, we analyzed 721 participants with MCI (mild cognitive impairment) from phases 1 and 2 of the Alzheimer's disease Neuroimaging Initiative. By their 24-month follow up, 188 individuals had converted from MCI to AD (76 females; mean age: 73.55 ± 7.29 years) and 533 remained MCI (214 females; mean age: 73.01 ± 7.51). Freesurfer 5.3 was used to extract 68 regional CT estimates; BrainVISA was used for identification and estimation of sulcal width (Pizzagalli et al. 2016) for 63 sulci. We used machine learning to classify individuals who converted from MCI to AD from the stable MCI group using the following features from their baseline assessments: sulcal width, CT, age, sex, Mini-Mental State Examination (MMSE) and the Clinical Dementia Rating Sum of Boxes (CDR-SB) scores. We compared classification performances of four classifiers (gradient boosting, extra trees, decision tree, random forests) when 1) using only clinical data, 2) with CT, 3) with sulcal-based width, and 4) all sets of measures. 75% of the dataset was selected as the training set (10 folds). We evaluated performance by assessing accuracy, ROC-AUC score, sensitivity and specificity. The width of the right inferior occipito-lateral sulci and the CT of the right inferior temporal gyrus were among the top 10 brain measures selected for classification. Classification performance was similar for classifiers that used only clinical/demographic data (accuracy=0.73 ± 0.05), sulcal width (accuracy=0.73 ± 0.05), or CT (accuracy=0.73 ± 0.02), although including all features

slightly improved accuracy (0.74 ± 0.01). In conclusion, sulcal width and CT may be useful as complementary features to help early detection of AD.

Disclosures: F. Pizzagalli: None. **S.P. Gadewar:** None. **S.I. Thomopoulos:** None. **Q. Yang:** None. **P. Kochunov:** None. **P.M. Thompson:** None. **N. Jahanshad:** None.

Poster

652. Alzheimer's Disease Biomarkers

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 652.19/D23

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

Support: CIHR

Title: Alzheimer’s disease biomarkers in exosomes isolated from the cerebrospinal fluid of rhesus monkeys injected with amyloid-β oligomers

Authors: *N. M. LYRA E SILVA[1], S. E. BOEHNKE[2], E. L. ROBERTSON[1], B. HYDUK[1], R. G. WITHER[2], A. WINTERBORN[1], V. BODART-SANTOS, SR[3], P. FRASER[4], F. G. DE FELICE[5], D. P. MUNOZ[6];
[2]Ctr. for Neurosci. Studies, [1]Queen's Univ., Kingston, ON, Canada; [3]Inst. de Bioquímica Médica, Univ. Federal Do Rio De Janeiro, Rio de Janeiro, Brazil; [4]Univ. of Toronto, Toronto, ON, Canada; [5]Fed Univ. Rio De Janeiro, Rio de Janeiro, Brazil; [6]Ctr. for Neurosci. Studies, Queens Univ., Kingston, ON, Canada

Abstract: Alzheimer’s disease (AD) is the most prevalent type of dementia affecting the elderly population. Exosomes are small extracellular vesicles that can transport cargoes of nucleic acids and proteins, including amyloid-β (Aβ) and tau. Exosomes isolated from AD brains have elevated levels of Aβ oligomers and AD is proposed to be propagated by exosomes. Currently, there is no effective treatment for AD and the pursuit of novel disease-modifying therapeutics is the object of intense investigation. Drugs that showed promise in preclinical studies and early clinical trials, have failed to work in AD patients suggestive of problems translating from rodent model species to humans. To understand higher cognitive functions in the human brain, and how brain dysfunction develops in AD, experimental animals that are more similar to humans are essential. One way to overcome this critical hurdle is to generate viable models of AD in non-human primates (NHPs). Our lab has developed a NHP model of AD that consists of a series of injections of amyloid-β oligomers (AβOs) into the lateral ventricle of Rhesus macaque monkeys. This animal model develops cardinal pathological features similar to those observed in AD brains, and currently this model is being validated longitudinally across multiple platforms including cerebrospinal fluid (CSF) and blood biomarkers, functional and structural brain imaging, cognitive and behavioral testing, and pathophysiology. Here, we evaluated if

exogenous AβOs would trigger an alteration on AD biomarkers present in exosome preparations from the CSF of NHPs. CSF samples were collected before and after the injection sequence and exosomes were isolated with the Exosome Isolation kit from System Biosciences. Isolated exosomes were characterized by Light Scattering and Western Blot techniques. We used a multiplex panel from Millipore on a luminex platform to access the AD biomarkers **Aβ**1-40, **Aβ**1-42, total tau, and phosphorylated tau at threonine 181. We observed an increase in total tau level in the exosome fraction isolated from AβO-injected NHPs. **Aβ**1-42 level was also elevated in the exosomes of AβO-injected NHPs, but a similar effect was observed in the vehicle-injected NHP. This data indicates that AβOs promote tau propagation within CSF exosomes in Rhesus monkeys, which may contribute to disease progression.

Disclosures: **N.M. Lyra e Silva:** None. **S.E. Boehnke:** None. **E.L. Robertson:** None. **B. Hyduk:** None. **R.G. Wither:** None. **A. Winterborn:** None. **V. Bodart-Santos:** None. **P. Fraser:** None. **F.G. De Felice:** None. **D.P. Munoz:** None.

Poster

652. Alzheimer's Disease Biomarkers

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 652.20/D24

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

Title: Convergence of miRNAs involved in gene expression regulation of biological pathways associated with Alzheimer's and diabetes diseases

Authors: K. CONTRERAS-RÁMIREZ[1], V. SERRATOS-LARIOS[2], D. DRAGO-GARCÍA[3], A. VARELA-ECHAVARRIA[4], C. ANGULO-ROJO[6], ***K. AVIÑA-PADILLA**[5];
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Abstract: Alzheimer's disease (AD) is caused by nerve cell death, leading to progressive decrease in memory and changes in behavior. The 95% of dementia patients show late-onset of AD. The pathophysiology of AD appears to be multifactorial involving many intrinsic and extrinsic factors. Recently, type 2 diabetes (T2D) has been shown to linked with AD pathophysiology. T2D is caused by impaired insulin metabolism due to the lack of functional pancreatic β cells, which use it. T2D is generally attributed to the sedentary lifestyle and the consumption of higher amount of fat in the diet, which together result in obesity. Interestingly, T2D is usually accompanied by many pathophysiological conditions, including death of neuronal cells. Although Alzheimer and T2D diseases appear to be very different, they many shared phenotypes. Understanding the shared and unique mechanisms underlying these diseases would be helpful for the prevention and treatment strategies. We performed meta-analysis of available

gene expression datasets to determine the role of miRNAs/target genes regulating conserved pathways in both diseases, in specific populations with high prevalence of T2D, such as Hispanic Americans, a highly affected group. We observed that the miRNAs such as hsa-miR-206, hsa-miR-1-3p, and hsa-miR-511-3p, regulates conserved biological pathways in AD and T2D.

Disclosures: K. Contreras-Rámirez: None. **V. Serratos-Larios:** None. **D. Drago-García:** None. **C. Angulo-Rojo:** None. **K. Aviña-Padilla:** None.

Poster

652. Alzheimer's Disease Biomarkers

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 652.21/D25

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

Support: CONICYT, Beca de Doctorado en Chile # 21171156

Title: The physiological activity and expression of neurotransmitters in the retinal ganglion cell of the 5xFAD Alzheimer’s disease mouse

Authors: *J. ARAYA[1,2], C. DURAN-ANIOTZ[3], M. ACOSTA[4], C. HETZ[3], M. CHACÓN[5], A. PALACIOS[2];
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Abstract: Purpose: To determine whether the 5xFAD mouse, a model of Alzheimer’s disease (AD), shows changes in the expression of glutamate (Glu) and gamma-aminobutyric acid (GABA) neurotransmitters and in the physiology of the retinal ganglion cells (RGCs) during the temporal course of AD.
Methods: Retinas from youngs (2-3 months, n=20) and adults (6-7 months, n=20) 5xFAD and WT mice were employed. For each animal, one eye was collected and fixed for immunogold-silver staining to detect Glu and GABA in the retina. RGCs activity were recorded using a multielectrode array under scotopic and photopic conditions from the contralateral eye. All methods use here are in compliance with bioethical certification.
Results: Glu was predominantly visualized in the RGC layer in youngs and adults 5xFAD mice, but not in the youngs or adults WT. GABA was predominantly found in the inner retina in youngs and adults WT and the RGC layer of youngs 5xFAD but not in the adults 5xFAD. In scotopic conditions the firing rate of RGCs was higher in youngs 5xFAD compared to youngs WT (all numeric results are presented as 25% percentile, median, 75% percentile in Hz. 5xFAD

= 0.559, 3.025, 8.44. WT = 0.31, 1.819, 7.02. Significative difference (SD), Mann Whitney test (MW test), $p<0.05$), while adults 5xFAD shows lower firing rate compared to the adults WT (5xFAD= 0.223, 1.081, 3.82. WT= 0.415, 2.04, 5.85. SD, MW test, $p<0.05$). In photopic conditions was a high firing rate for the youngs 5xFAD compared to youngs WT (5xFAD= 0.5, 2.918, 9.96. WT= 0.30, 1.858, 6.83. SD, MW test, $p<0.05$). However, no difference was found between the adults 5xFAD and the adults WT.
Conclusions: We report sensitive changes in the levels of Glu and GABA in the RGC layer for 5xFAD mice retinas and a concomitant upregulation of the RGCs physiology for spontaneous scotopic and photopic activity in the youngs 5xFAD. In the scotopic conditions the spontaneous RGCs firing activity of the adults 5xFAD is downregulated, but not in photopic conditions. Our results supports the idea that the integrated homeostatic network, that enables functional stability of central circuits, it is disrupted too in the retina in the AD, depending on illuminated condition.

Disclosures: **J. Araya:** None. **C. Duran-Aniotz:** None. **M. Acosta:** None. **C. Hetz:** None. **M. Chacón:** None. **A. Palacios:** None.

Poster

652. Alzheimer's Disease Biomarkers

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 652.22/D26

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

Support: ADNI NIA U01 AG024904
NIA AG019610
McKnight Brain Research Foundation
State of Arizona and Arizona DHS

Title: Alzheimer's disease fluid biomarkers related gray matter covariance patterns in healthy older adults

Authors: *P. K. BHARADWAJ[1,7], J. R. ANDREWS-HANNA[1,2], P. H. KUO[3,8,9], G. E. ALEXANDER[1,4,5,6,10];
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Abstract: Biomarkers of Alzheimer’s disease (AD) pathology in cerebrospinal fluid (CSF), including $A\beta_{42}$, $pTau_{181}$, and the ratio of $pTau_{181}/A\beta_{42}$, can help identify those with increased risk for dementia, before the onset of clinical symptoms. How these CSF biomarkers relate to

regional patterns of gray matter (GM) atrophy in cognitively unimpaired older adults has yet to be fully investigated. Here, we applied a multivariate network analysis technique, the scaled subprofile model (SSM; Alexander & Moeller, 1994) to identify gray matter covariance patterns related to CSF measures of $A\beta_{42}$, $pTau_{181}$, and the ratio of $pTau_{181}/A\beta_{42}$, in a sample of healthy older adults drawn from the Alzheimer's disease Neuroimaging Initiative (ADNI2; N=146; Age=73.5 ± 6.4 years, range=56-89 years; sex (F/M)=76/70; Education= 16.5 ± 2.5 years; MMSE=29.1 ± 1.2; CDR = 0; APOE-ε4 (N/Y)=108/38). GM maps were segmented from 3T T1-weighted volumetric magnetic resonance imaging (MRI) scans with SPM12, spatially normalized using diffeomorphic registration (DARTEL), and smoothed with a Gaussian kernel of 10mm. Regional SSM network analysis was performed on these GM maps using Akaike Information Criteria with 2000 Bootstrap iterations to identify linear combinations of GM patterns associated with each of the three fluid biomarker measures. The $pTau_{181}/A\beta_{42}$ - related GM SSM pattern (R^2=0.10, p≤ 4.4E-05) was characterized by bilateral reductions in the vicinity of the superior temporal gyrus (STG), and extensive bilateral GM reductions in cerebellar lobules. The $pTau_{181}$ related GM SSM pattern (R^2=0.06, p≤ 2.75E-03) showed extensive bilateral reductions in the cerebellum extending into the anterior cerebellar lobule. In contrast, CSF $A\beta_{42}$ did not exhibit an SSM pattern with robust regional GM contributions in this cohort. Additionally, the $pTau_{181}/A\beta_{42}$ (R^2 change = 0.042, p ≤ 0.007) and $pTau_{181}$ (R^2 change = 0.042, p ≤ 0.008) related GM patterns each remained significantly associated with their respective CSF biomarker, after adjusting for age, sex, years of education, APOE genotype, hypertension status, and intracranial volume. These results demonstrate that AD-related CSF biomarkers including $pTau_{181}$ and its ratio to $A\beta_{42}$ may be associated with individual differences in regional topographies of GM volume, involving temporal and cerebellar brain regions, in healthy cognitively unimpaired older adults. Together, these findings provide further support for the use of CSF fluid biomarkers in evaluating the earliest preclinical effects of AD and their relation to the effects of brain aging.

Disclosures: P.K. Bharadwaj: None. **J.R. Andrews-Hanna:** None. **P.H. Kuo:** None. **G.E. Alexander:** None.

Poster

652. Alzheimer's Disease Biomarkers

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 652.23/D27

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

Title: Quantitative analysis of calbindin-D28K immunoreactivity in locus coeruleus neurons of young and aged human brains

Authors: *S. LAMERAND[1], R. SHAHIDEHPOUR[1], I. AYALA[1], M.-M. MESULAM[1], E. BIGIO[2], C. GEULA[1];
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Abstract: We have previously shown that calbindin is present in some noradrenergic locus coeruleus (LC) neurons, while other calcium binding proteins such as parvalbumin and calretinin are absent. The LC is vulnerable to early degeneration in Alzheimer's disease (AD) with tangles present as early as the third decade of life. The cholinergic neurons of the basal forebrain (BFCN) are also vulnerable to early degeneration. BFCN are rich in the calcium binding protein, calbindin-D28K (CB) which displays significant loss over the course of aging. In AD, CB loss is associated with tangle pathology and BFCN loss. The purpose of the present study was to quantitatively determine the density of CB immunoreactive LC neurons in the human brain, and to assess potential age-related changes in the density of these neurons. Blocks of brainstem containing the LC from five young (20-63 years old) and five aged (70-77 years old) cognitively normal human brains were fixed in 4% paraformaldehyde for 30-36 hours at 4º C and taken through sucrose gradients for cryoprotection. Blocks were sectioned at a thickness of 40 µm on a freezing microtome and 1 in 24 series of sections were stored in 0.1 M phosphate buffer until use. One series of sections from each brainstem were immunohistochemically stained using a double chromogen procedure for the monoaminergic synthetic enzyme tyrosine hydroxylase (TH) and CB, using diaminobenzidine (brown reaction product) and benzidine dihydrochloride (blue / black granular reaction product) as chromogens respectively. Quantitative analysis was performed on digitized images to determine the total number of TH- and CB-positive LC neurons in each case. Overall, a relatively small proportion of TH-positive LC neurons contained CB. There was no significant difference ($p>0.05$) in the percentage of CB-positive LC neurons when young individuals (5.28% - 14.01%) were compared with the aged (8.33% -20.75%). Similarly, there was no significant difference ($p>.05$) between the young and aged groups in the average number of TH-positive (young=435, old=305) or the average number of CB-positive LC neurons (young=49, old=37). While CB immunoreactivity is present is a proportion of LC neurons, there does not appear to be any age-related changes in the number or proportion of CB-positive LC neurons. Therefore, unlike the BFCN, CB immunoreactivity in LC neurons is unlikely to contribute significantly to the vulnerability of these neurons to neurodegeneration.

Disclosures: S. Lamerand: None. **R. Shahidehpour:** None. **I. Ayala:** None. **M. Mesulam:** None. **E. Bigio:** None. **C. Geula:** None.

Poster

652. Alzheimer's Disease Biomarkers

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 652.24/D28

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

Support: TARCC
NIH
MJFF

Title: High sensitivity detection of misfolded protein aggregates implicated in Alzheimer's and Parkinson's disease by prion-like seeding assays

Authors: *S. PRITZKOW, M. SHAHNAWAZ, M. PINHO, N. MENDEZ, C. SOTO; UTHealth Sci. Ctr., Houston, TX

Abstract: A hallmark event in several neurodegenerative diseases is the cerebral accumulation of misfolded protein aggregates. Recent evidences indicate that soluble misfolded oligomeric versions of these proteins circulate in biological fluids and may serve as a specific biomarker for sensitive diagnosis. Recently, we have developed a technology for ultra-sensitive detection of soluble misfolded oligomers implicated in Alzheimer's (AD), Parkinson's (PD) diseases and related synucleinopathies and tauopathies. The technique, termed PMCA and also referred as RT-QuIC, is based on the cyclic amplification of protein misfolding, and mimics the seeding/nucleation model of aggregation in a highly efficient manner by combining phases of polymer growing with their fragmentation to multiply the number of seeds for the exponential amplification of the reaction. PMCA was first adapted and optimized for amplification of prion protein (PrP^{Sc}) implicated in prion diseases and more recently has been extended to detect amyloid-beta (Aβ), Tau, and α-synuclein (α-syn) misfolded oligomers. After the technology was optimized for reproducibility and sensitivity using synthetic protein aggregates, we tested the utility of PMCA to detect misfolded oligomers composed by each of these proteins coming from CSF of patients affected by AD, PD and other neurodegenerative disorders, using as controls people affected by other neurological disorders or healthy subjects. Our results showed that PMCA enables highly sensitive and specific detection of misfolded Aβ, Tau, and α-syn oligomers and can be used to detect these biomarkers in CSF of patients with >90% overall sensitivity and specificity. The simultaneous application of the various PMCA assays may enable to differentiate distinct types of mixed pathologies and perhaps to detect the disease process before the onset of clinical symptoms. Ongoing studies re aiming to optimize the technology for detection of protein aggregates in blood samples. Our findings suggest that PMCA represents a platform technology for the detection of misfolded oligomeric proteins implicated in various neurodegenerative diseases and offer a great promise for a much needed non-invasive, early biochemical diagnosis of these diseases.

Disclosures: S. Pritzkow: None. **M. Shahnawaz:** None. **M. Pinho:** None. **N. Mendez:** None. **C. Soto:** A. Employment/Salary (full or part-time):; Amprion.

Poster

652. Alzheimer's Disease Biomarkers

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 652.25/D29

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

Title: Detection and quantification of free brain levels of cholesterol in freely moving mice utilizing i*n vivo* microdialysis

Authors: *J. ROESER, C. CIARDIELLO, E. WEBER, M. VAN DER HART, H. B. JANSSENS, A. RASSOULPOUR;
Charles River Labs., South San Francisco, CA

Abstract: Cholesterol is an essential component for neuronal physiology not only during development stage but also in the adult life. Cholesterol metabolism in brain is independent from that in peripheral tissues due to blood-brain barrier. Defects in brain cholesterol metabolism has been shown to be implicated in neurodegenerative diseases, such as Alzheimer's disease (AD), Huntington's disease (HD), Parkinson's disease (PD), and some cognitive deficits typical of the old age. The brain contains large amount of cholesterol, but the cholesterol metabolism and its complex homeostasis regulation are currently poorly understood. The aim of the present study was to detect free cholesterol levels by microdialysis sampling in murine brain.
Water insoluble cholesterol was successfully sampled *In Vitro* by addition of hydroxypropyl-β-cyclodextrin which promotes solubility of lipophilic compounds in the aqueous microdialysis perfusion fluids. Next, *In Vivo* experiments combined with a sensitive, in-house developed, LC-MS/MS assay allowed for the quantification of cholesterol in microdialysate extracts of freely moving mice.
This is to the best of our knowledge the first occurrence of microdialysis sampling and detection of free brain cholesterol levels. These data demonstrate the feasibility of monitoring free brain cholesterol levels and has the potential to be extended to similar class of compound such as steroid hormones and/or sphingolipids. Our efforts have the potential to bring new insights in the CNS space and help the discovery of therapies for neurodegenerative diseases.

Disclosures: J. Roeser: None. **C. Ciardiello:** None. **E. Weber:** None. **M. van der Hart:** None. **H.B. Janssens:** None. **A. Rassoulpour:** None.

Poster

652. Alzheimer's Disease Biomarkers

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 652.26/D30

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

Title: Methods for diagnosing Alzheimer’s disease based on cell growth rate, size and protein amount

Authors: *F. V. CHIRILA, D. L. ALKON;
NeuroDiagnostics LLC, Rockville, MD

Abstract: Drugs to treat Alzheimer’s disease (AD) have been unsuccessful in preventing its devastating cognitive deficits and progressive neurodegeneration. The lack of a definitive diagnostic for AD has been a major obstacle to AD drug discovery. Our novel approach to AD screening based on a collection of markers rather than just one has a greater chance to capture the complexity of this disease. Here we show novel methods for diagnosing Alzheimer’s disease in a symptomatic human subject. These methods comprise of measuring the growth rate, size and/or protein amount of a subject’s skin fibroblasts and/or lymphocytes, and determining whether these values differ in certain ways from those of corresponding non-Alzheimer’s disease dementia cells. We also provide potential methods for determining whether an asymptomatic human subject is at risk from becoming afflicted with Alzheimer’s disease.

Disclosures: F.V. Chirila: None. **D.L. Alkon:** None.

Poster

652. Alzheimer's Disease Biomarkers

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 652.27/D31

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

Title: Transcranial magnetic stimulation neurophysiology in patients with Alzheimer’s disease: A systematic review and meta-analysis

Authors: *Y. MIMURA[1], H. NISHIDA[1], S. TSUGAWA[1], S. MORITA[1], K. YOSHIDA[2,1], F. MASUDA[1], K. OGYU[1], M. WADA[1], T. MIYAZAKI[1], S. L. NAKAJIMA[1,3], M. MIMURA[1], Y. NODA[1];

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Abstract: Background: Transcranial magnetic stimulation (TMS) is a non-invasive neurophysiological tool which allows us to investigate motor cortical excitability in the human brain. Paired-pulse TMS paradigms such as short- and long-interval intracortical inhibition (SICI/LICI), intracortical facilitation (ICF) and short-latency afferent inhibition (SAI) can assess and quantify neurophysiological functions of GABA, glutamate, and choline associated circuits, respectively. Accumulating evidence suggest that TMS neurophysiology can be novel biomarkers for the diagnosis of Alzheimer's disease (AD). In this study, we conducted meta-analyses to compare neurophysiological functions associated with monoaminergic neurotransmissions between patients with AD and healthy controls (HC). Methods: A systematic literature research was conducted using Embase, Medline, PsycINFO, and Pubmed up to September 2018. Original studies that examined resting motor threshold (RMT), SICI, ICF, LICI, SAI in patients with AD and HC, were included. Standardized mean differences (SMDs) were calculated to determine the difference in these neurophysiological markers in both groups. Results: Out of 695 initial records, 80 articles were identified the included studies, and dataset from 34, 20, 16 and 13 articles were available for further analyses for RMT, SAI, SICI, and ICF, respectively. RMT and SICI were significantly lower in patients with AD than in HC (SDM=-1.574, CI=-2.22 to -0.930, $p<0.001$ for RMT, SDM=0.394, CI=0.13 to 0.66, $p=0.004$ for SICI). SAI was significantly higher in patients with AD than in HC (SDM=1.54, CI=1.08 to 2.00, $p<0.001$ for SAI), whereas ICF was not significantly different in both groups.
Conclusions: The meta-analyses demonstrated that patients with AD had decreased RMT and SICI but increased SAI. These findings suggest that motor cortical excitability, GABAergic and cholinergic function were altered in patients with AD. Our results warrant further study with larger samples to replicate the current findings and identify the excitatory and inhibitory balance in AD for an appropriate assessment of the pathophysiology in this disorder.

Disclosures: **Y. Mimura:** None. **H. Nishida:** None. **S. Tsugawa:** None. **S. Morita:** None. **K. Yoshida:** None. **F. Masuda:** None. **K. Ogyu:** None. **M. Wada:** None. **T. Miyazaki:** None. **S.L. Nakajima:** None. **M. Mimura:** None. **Y. Noda:** None.

Poster

652. Alzheimer's Disease Biomarkers

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 652.28/D32

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

Support: MLIV Foundation

Title: Identification of plasma cytokine biomarkers of disease severity for the lysosomal storage disorder mucolipidosis IV

Authors: *L. WOOD[1], L. WEINSTOCK[2], A. FURNESS[3], A. MISKO[3], Y. GRISHCHUK[4]; [2]Dept. of Biomed. Engin. and Inst. for Bioengineering and Biosci, [1]Georgia Inst. of Technol., Atlanta, GA; [3]Massachusetts Gen. Hosp., Boston, MA; [4]Ctr. for Human Genet. Res., Massachusetts Gen. Hospital/Harvard Med. Sch., Boston, MA

Abstract: Problem Statement: Mucolipidosis IV (MLIV) is an orphan disease that causes severe motor and cognitive dysfunction and loss of vision. It is caused by loss of function of the lysosomal channel mucolipin-1, also known as TRPML1. Knockout of the *Mcoln1* gene in mice mirrors clinical and neuropathological signs in humans and shows robust activation of microglia and astrocytes in early symptomatic stages of disease. Although there is currently no therapy for MLIV, the research community is rapidly advancing treatment strategies. Therefore, identification of peripheral biomarkers of disease severity will be essential for rapidly quantifying the effects of treatment in advance of cognitive or motor changes. **Objectives:** Since neuroinflammation is a central feature of MLIV in humans and mice, we hypothesized that cytokines quantified from blood plasma would serve as biomarkers of pathology and neurologic function. **Methods:** Plasma was collected from *Mcoln1*$^{-/-}$ or CTRL mice and from human patients under an IRB approved protocol. We used multiplexed immunoassays to quantify 32 cytokines from mice and 41 cytokines from human samples. Motor function scores were assessed by a neurologist. Cytokine data were correlated against genotype in mice using a discriminant partial least squares regression (D-PLSR) and against motor function in humans using PLSR. **Results:** *Mcoln1*$^{-/-}$ mice possessed a plasma cytokine signature that correlates with disease severity by age. The profile includes IP-10 and IL-17 in the early symptomatic phase (1-2mo), and IL-12p40 and M-CSF in the late phase (6mo). In humans, we identified profiles of cytokines that significantly correlated with reduced motor function, including IL-1b, IFN-g, IFN-a2, IL-17and cytokine signature correlations with motor function scores were R= 0.65, p= 0.002 for deglutition, R=0.58, p=0.009 for articulation, R=0.73, p<0.009 for fine motor. **Conclusion:** Our data suggest that cytokines/chemokines quantified from blood plasma reflect disease severity in mice and in MLIV patients. The strength of the correlations between cytokine profiles and motor function suggests that cytokines/chemokines will serve as an effective biomarker for MLIV. Moreover, we have previously identified the interferon pro-inflammatory axis to be up-regulated in brains of *Mcoln1*$^{-/-}$ mice, suggesting the peripheral signature reflects the brain microenvironment.

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Poster

652. Alzheimer's Disease Biomarkers

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 652.29/D33

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

Support: NIH/NIA RO1 AGO56478
NIH/NIA RO1 AGO55865
Saban Family Foundation
Maurice Marciano Family Foundation

Title: Retinal pathology correlates with brain pathology in MCI and AD patients

Authors: *Y. KORONYO[1], A. RENTSENDORJ[1], D.-T. FUCHS[1], J. SHEYN[1], G. C. REGIS[1], H. SHI[1], N. MIRZAEI[1], E. BARRON[3], K. L. BLACK[1], D. R. HINTON[4], C. A. MILLER[5], M. KORONYO-HAMAOUI[1,2];
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Abstract: The retinae of patients with Alzheimer’s disease (AD) display several abnormalities, including the presence of Aβ deposits, tauopathy, and retinal ganglion cell (RGC) degeneration. Although inflammatory responses are tightly correlated with AD brain pathology, the processes in the retina are underexplored. Here, we study retinal pathology including amyloidosis, gliosis, RGCs, and vascular cell integrity in mild cognitively impaired (MCI) and confirmed AD patients as compared to age- and sex-matched cognitively normal controls (CN). We quantified extra- and intra-cellular amyloid beta (Aβ) load as well as macro- and micro-gliosis (Müller glia, GFAP, s100β, Iba1) in defined retinal layers and sub-geometrical regions in MCI and AD patients versus CN and compared to brain pathology. We further used an analytical biochemistry assay (ELISA) to quantify $A\beta_{42}$ in the retina of patients and CN. We found a wide range of pathological changes in retinal tissues isolated from MCI and AD patients. Aβ deposits were more abundant in inner retinal layers with substantial 4- to 10-fold increases in total Aβ and especially $A\beta_{42}$-specific burden in peripheral regions in AD patients as compared to CN. Retinal $A\beta_{42}$-containing plaques strongly correlated with brain Aβ plaques and predicted plaques in the entorhinal and primary visual cortices. Retinal $A\beta_{42}$ immunoreactive area significantly correlated with cerebral diffuse, immature, and mature plaques, as well as with NFTs and neurophil threads. Retinal $A\beta_{42}$ immunoreactive area predicted cognitive status (MMSE). Intracellular Aβ oligomer (AβO) burden in the innermost retinal layers of MCI and AD patients was 2-fold higher than CN, and strongly correlated with levels of $A\beta_{42}$ in the temporal hemiretina. Intriguingly, a strong

inverse correlation was found between retinal AβO burden and pre-mortem cognitive performance. Increasing retinal Aβ burden was tightly associated with gliosis, including reactive astrocytes and activated microglia. The greatest observed change was in astrogliosis in far peripheral regions with a 3.3-fold change in AD compared to CN. Retinal astrocytosis tightly associated with retinal $A\beta_{42}$ and predicted cognitive loss**.** Müller glias were also activated by 1.7-fold in AD retina compared to CN. Studying retinal vascular cell integrity showed that retinal pericyte loss inversely correlated with brain CAA. Our findings suggest that early and progressive accumulation of retinal Aβ and retinal inflammation such as astrocytosis are tightly associated with brain pathology in MCI and AD patients. These studies support non-invasive retinal imaging as a biomarker for early detection and monitoring of AD.

Disclosures: Y. Koronyo: None. **A. Rentsendorj:** None. **D. Fuchs:** None. **J. Sheyn:** None. **G.C. Regis:** None. **H. Shi:** None. **N. Mirzaei:** None. **E. Barron:** None. **K.L. Black:** None. **D.R. Hinton:** None. **C.A. Miller:** None. **M. Koronyo-Hamaoui:** None.

Poster

652. Alzheimer's Disease Biomarkers

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 652.30/D34

Topic: I.06. Computation/ Modeling/ and Simulation

Support: Boswell Fellowship
FWO Fellowship

Title: Dynamic bayesian model to study the sequential belief updates in early Alzheimer's disease

Authors: *Q. LIU[1], H. WU[2], D. PUNIA[3], X. ARAKAKI[3], A. N. FONTEH[3], M. G. HARRINGTON[3];
[1]Caltech, Pasadena, CA; [2]Inst. of Psychology Chinese Acad. of Sci., Beijing City, China; [3]Huntington Med. Res. Inst., Pasadena, CA

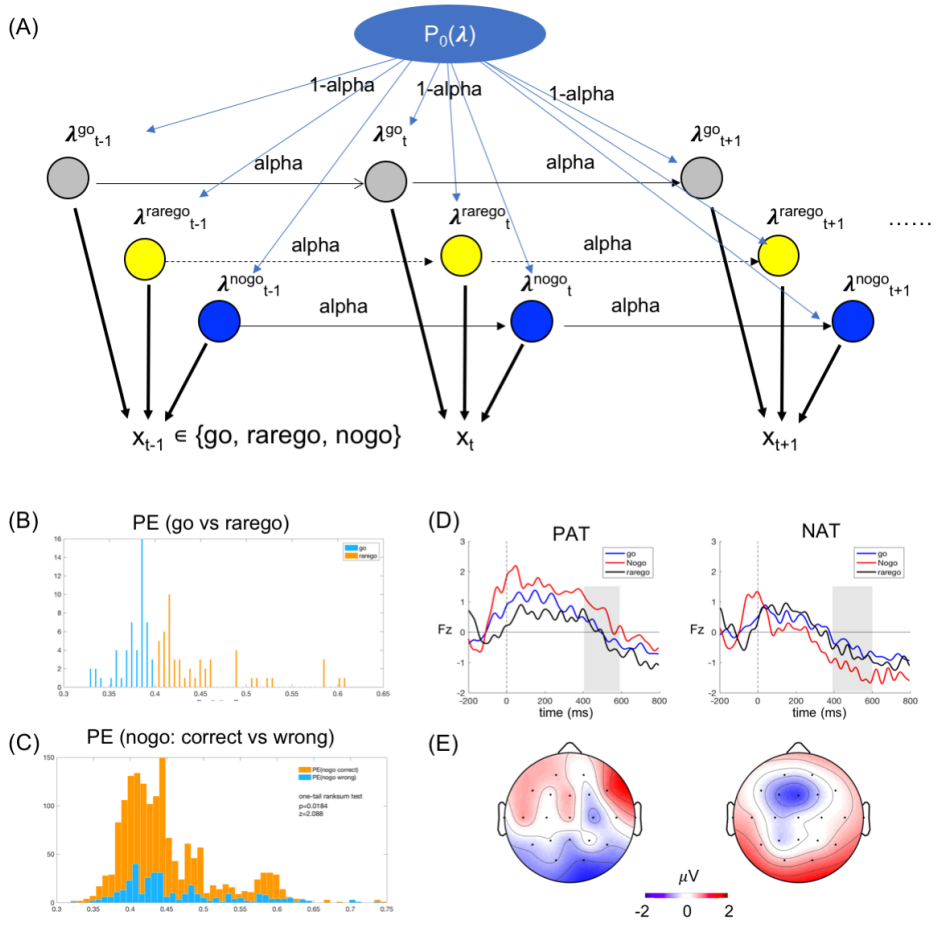
Abstract: Introduction Participants respond more rapidly and accurately to a stimulus if it reinforces a local pattern in stimulus history. A Bayesian perspective provides optimal prediction for control processes, to reveal hidden neurocomputational processes. Here, we used a Go-nogo-rarego paradigm to study cognitive processes of elderly participants for probability prediction, probability updates, and proactive control in early Alzheimer's disease (AD) pathology. **Experiment Participants:** 52 elderly participants diagnosed as cognitive healthy with the Uniform Data Set (UDS-3) assessment, and sub-classified into two CSF biochemical groups: normal amyloid/tau (NAT), or pathological amyloid/tau (PAT) ratios. **Task:** Go-Nogo-rarego task contains 60% ‘go’ trials, 20% ‘rarego’ and 20% ‘nogo’ trials. In each trial, a cue is

presented for 400ms, and fixation for 1000ms. Participants respond to ‘go’ and ‘rarego’ cues as quickly as possible, while withholding responses to ‘nogo’ cues. No feedback is provided. EEG was collected using the DSI-24 dry electrode EEG.

Method

Model: We propose a three-category Dynamic Bayesian Model (DBM) for a standard go-nogo-rarego task (Fig1A). We use Dirichlet distribution for the prior belief. We update the belief distribution from trial t-1 to trial t, $P=\alpha*P(\boldsymbol{\lambda};;;^{i}_{t-1}=\boldsymbol{\lambda};;;^{i}|x_{t-1})+(1-\alpha)*P_0(\boldsymbol{\lambda};;;^{i})$ The Bayesian estimate of probability is a categorical process. After evidence is presented, prediction error (PE) can be computed, and posterior belief distribution in trial t is updated. We fit behavioral data to estimate model parameters. **Results** CSF amyloid positively correlated with accuracy (for go, r=0.41, p<0.01; for rarego, r=0.27, p<0.05), and negatively correlated with RT (for go, r=-0.29, p<0.05). Tau did not correlate significantly with accuracy or RT, but correlated with the model parameter α (r=0.34, p<0.05), Fig B-C. The nogo ERP (N400) significantly differed between PAT and NAT (FigD-E).

Conclusion: Neural activity and the DBM parameter α predict early AD pathology (PAT).



Disclosures: **Q. Liu:** None. **H. Wu:** None. **D. Punia:** None. **X. Arakaki:** None. **A.N. Fonteh:** None. **M.G. Harrington:** None.

Poster

653. Genetic Models of Parkinson's Disease

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 653.01/D35

Topic: C.03. Parkinson’s Disease

Support: Michael J Fox Foundation

Title: μ Opioid receptor agonism, not antagonism, for the treatment of L-DOPA-induced dyskinesia in Parkinson’s disease

Authors: *E. Y. PIOLI[1], Q. LI[1], H. HULME[2], E. FRIDJONSDOTTIR[2], A. NILSSON[2], P. ANDREN[2], A. CROSSMAN[1], E. BEZARD[3];
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Abstract: Parkinson’s disease (PD) is characterized by severe locomotor deficits and is commonly treated with the dopamine (DA) precursor L-DOPA, but its prolonged usage causes dyskinesias referred to as L-DOPA induced dyskinesia (LID). Several studies in animal models of PD have suggested that dyskinesias are associated with a heightened opioid co-transmitters tone, observations that have led to the notion of a LID-related hyperactive opioid transmission that should be corrected by μ opioid receptor antagonists. Reports that both antagonists and agonist of μ opioid receptor may alleviate LID severity in primate models of PD and LID associated to the failure of non-specific antagonist in pilot clinical trials to improve LID in patients raised concerns about the reliability of the available data on the opioid system in PD and LID. After in vitro characterization of the functional activity upon μ opioid receptor, we selected prototypical agonist, antagonist and partial agonist at μ opioid receptor. We then show that both oral and discrete intracerebral administration of a μ receptor agonist, but not of an antagonist as long thought, ameliorate LIDs in the gold-standard bilateral MPTP-lesioned macaque model of PD and LID, calling for a re-appraisal of the opioid pharmacology as well as for the development of brain nucleus-targeted μ opioid agonists.

Disclosures: **E.Y. Pioli:** A. Employment/Salary (full or part-time):; Motac neuroscience. **Q. Li:** A. Employment/Salary (full or part-time):; Motac neuroscience. **H. Hulme:** None. **E. Fridjonsdottir:** None. **A. Nilsson:** None. **P. Andren:** None. **A. Crossman:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Motac Holding. F. Consulting Fees (e.g., advisory boards); Motac neuroscience. **E. Bezard:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Motac Holding. F. Consulting Fees (e.g., advisory boards); Motac neuroscience.

Poster

653. Genetic Models of Parkinson's Disease

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 653.02/D36

Topic: C.03. Parkinson's Disease

Support: Beckman Scholars Program

Title: Beta-synuclein as treatment for Parkinson's disease in *drosophila*

Authors: *G. D. PAUL[1], D. FLORES[2], M. CUNNINGHAM[2], S. KHOO[2];
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Abstract: Parkinson's disease (PD) is the second most common neurodegenerative disorder that impacts 1-2% of the elderly population. PD is characterized by the loss of midbrain dopaminergic neurons, leading primarily to motor impairment with the four cardinal signs being rigidity, tremors, postural instability, and bradykinesia. Another hallmark of PD is alpha-synuclein (aSyn) protein aggregates, also known as Lewy bodies. Lewy bodies can be targeted by beta-synuclein (bSyn), a protein homolog of aSyn that has been shown to reduce aSyn aggregation in SH-SY5Y cell lines and mouse models. In *Drosophila melanogaster*, aSyn can be expressed within its central nervous system (CNS) by inserting human aSyn gene into its 3rd chromosome. In this study, aSyn transgenic flies are fed bSyn peptide in a dose dependent, controlled environment to determine the effects of bSyn on PD symptoms. Assessment of motor function will be evaluated by locomotion assays while Lewy bodies inhibition will be observed using immunofluorescence microscopy within the flies CNS. The use of bSyn to treat motor impairment and protein aggregation in fly can potentially lead to more effective and noninvasive treatments for patients with PD.

Disclosures: G.D. Paul: None. **D. Flores:** None. **M. Cunningham:** None. **S. Khoo:** None.

Poster

653. Genetic Models of Parkinson's Disease

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 653.03/D37

Topic: C.03. Parkinson's Disease

Title: Single intrathecal administration of Resiniferatoxin, TRPV1 agonist, rescue motor deficits in AAV-A53T-induced mouse model of Parkinson's disease

Authors: A. NAHAMA[1], R. RAMACHANDRAN[1], J. TOIVANEN[2], T. BRAGGE[2], J. RYTKÖNEN[2], A. SUHONEN[2], ***T. T. AHTONIEMI**[2], D. MISZCZUK[2];
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Abstract: Transient receptor potential vanilloid 1 (TRPV1) activity in the brain plays a role in regulating glial activation resulting in the modulation of neuronal function such as control of motor behavior. Evaluation of post-mortem brain samples of PD patients and animal models has revealed astrocytic TRPV1 overexpression in substantia nigra (SNc). Moreover, TRPV1 activation by systemic administration of its agonist, capsaicin, protects nigrostriatal dopaminergic neurons via inhibition of glial activation-mediated oxidative stress and neuroinflammation in the MPTP and AAV-A53T human α-synuclein mouse model of PD (Chung et al., 2017, Nam et al., 2015).
We have assessed the efficacy of resiniferatoxin (RTX), an ultrapotent agonist of TRPV1, in AAV-A53T mouse model of PD. C57Bl/6J mice (n=110) were unilaterally infused with AAV-A53T or AAV-Null vector (5.1x1012vg/mL) into the SNc. Following AAV infusion, the mice were treated with a single intrathecal infusion of RTX (0.04 or 0.125 µg/mouse) at week 1 and week 2. At 7 weeks post AAV infusion, motor functions and gait were assessed using fine motor kinematic gait analysis system. Two principal component analysis (PCA) based overall scores were assessed - one focusing on gait changes manifested bilaterally and the other with emphasis to unilateral changes, i.e. left-right asymmetry of gait. Eight weeks after AAV infusion, dopamine and its metabolites levels were analyzed from ipsilateral and contralateral striata by HPLC.
As expected, AAV-A53T infusion significantly impaired the motor performance and gait accompanied by depletion of ipsilateral striatal dopamine and its metabolites levels as compared to contralateral striatum and AAV-Null treated group. No adverse effects, including no significant effect on body weight, were observed at any of the used RTX doses or dosing paradigm. Intrathecal administration of RTX at low and high dose at wk 1, but not at wk 2 after AAV-A53T infusion, significantly improved the motor function and the unilaterally differential overall gait score (gait asymmetries recovered in both low and high RTX dosed groups), and in bilateral overall score in high dose RTX group. However, RTX treatment did not have a significant rescuing effect against dopamine degradation in striatum.
The findings demonstrated efficacy of intrathecal administration of RTX at the early intervention paradigm to rescue motor deficits in AAV-A53T model. The lack of effect on dopamine levels suggest that behavioral recovery is driven by mechanisms other than direct protection of nigrostriatal dopaminergic neurons, including modulation of neuroinflammation and/or analgesic effect of RTX after IT delivery.

Disclosures: A. Nahama: None. **R. Ramachandran:** None. **J. Toivanen:** None. **T. Bragge:** None. **J. Rytkönen:** None. **A. Suhonen:** None. **T.T. Ahtoniemi:** None. **D. Miszczuk:** None.

Poster

653. Genetic Models of Parkinson's Disease

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 653.04/D38

Topic: C.03. Parkinson’s Disease

Support: Austrian Science Fund (FWF): W1206-08, I2102, and F4414

Title: Combined anti-alpha-synuclein therapy for disease modification in multiple system atrophy

Authors: *M. LEMOS[1], V. REFOLO[1], D. WECKBECKER[2], A. HERAS-GARVIN[1], P. GRUBER[3], G. STAFFLER[3], C. GRIESINGER[4], A. GIESE[5], G. K. WENNING[1], N. STEFANOVA[1];
[1]Neurol., Med. Univ. of Innsbruck, Innsbruck, Austria; [2]MODAG GmbH, Wendelsheim, Germany; [3]AFFiRiS AG, Vienna, Austria; [4]Max Planck Inst. for Biophysical Chem., Göttingen, Germany; [5]Ludwig-Maximilians-Universität, Munich, Germany

Abstract: Multiple system atrophy (MSA) is an adult-onset neurodegenerative disorder, clinically characterized by a highly variable combination of Parkinsonism, cerebellar ataxia and autonomic failure. The presence of aggregated α-Synuclein (α-Syn) within oligodendrocytes forming glial cytoplasmic inclusions (GCIs) is considered the main pathological hallmark, thus leading to glial and neuronal dysfunction and neurodegeneration. At present, there is no effective disease-modifying therapy. Previous studies reported that the active immunization with short immunogenic peptides (AFFITOPEs), targeting toxic forms of α-Syn, improved motor impairment and reduced α-Syn oligomer levels and microglial activation in a mouse model of MSA. Also, previous experiments showed that the aggregation inhibitor, Anle138b, reduced neurodegeneration and behavioural deficits in mouse models of α-Synucleinopathy and other proteinopathies.
Transgenic mice overexpressing α-Syn in oligodendrocytes under the proteolipid protein promoter (PLP-α-Syn mice), received either AFFITOPEs or Anle138b. Both approaches were also tested in a combined therapy to evaluate if a synergistic effect is able to potentiate the effects of the single therapy. Motor behavior was assessed. Brains and plasma samples were collected for neuropathological and immunological analysis.
We confirmed the efficacy of the single therapy with AFFITOPEs or Anle138b, observing motor improvement, a significant reduction in α-Syn oligomers and GCI density, and preservation of dopaminergic neurons. The combination of Anle138b+AFFITOPEs was also beneficial showing reduced motor deficits, preservation of dopaminergic neurons, decrease of GCI density and microglia activation in the substantia nigra of treated PLP-a-Syn mice, without further cumulative effect.

We conclude that both approaches show beneficial effects ameliorating the α-Syn pathology in MSA transgenic mice. Simultaneous application of Anle138b and AFFITOPEs in PLP-α-Syn mice do not potentiate the effects of single drug therapy.

Disclosures: **M. Lemos:** A. Employment/Salary (full or part-time):; Medical University of Innsbruck. **V. Refolo:** A. Employment/Salary (full or part-time):; Medical University of Innsbruck. **D. Weckbecker:** A. Employment/Salary (full or part-time):; MODAG GmbH. **A. Heras-Garvin:** A. Employment/Salary (full or part-time):; Medical University of Innsbruck. **P. Gruber:** A. Employment/Salary (full or part-time):; AFFiRiS AG. **G. Staffler:** A. Employment/Salary (full or part-time):; AFFiRiS AG. **C. Griesinger:** A. Employment/Salary (full or part-time):; Max Planck Institute for Biophysical Chemistry. **A. Giese:** A. Employment/Salary (full or part-time):; Ludwig-Maximilians-Universität. **N. Stefanova:** A. Employment/Salary (full or part-time):; Medical University of Innsbruck. **G.K. Wenning:** A. Employment/Salary (full or part-time):; Medical University of Innsbruck.

Poster

653. Genetic Models of Parkinson's Disease

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 653.05/D39

Topic: C.03. Parkinson’s Disease

Support: NIH Grant NS 047198

Title: Targeting alpha synuclein and amyloid beta proteins by a multifunctional brain penetrant dopamine agonist D520: Potential therapeutic application in Parkinson's disease with dementia

Authors: *A. K. DUTTA[1], D. YEDLAPUDI[1], D. LUO[1], G. JOSHI[2], L. XU[1], G. MARSH[2], S. V. TODI[2];
[1]Pharmaceut. Sci., [2]Pharmacology/Neurology, Wayne State Univ., Detroit, MI

Abstract: A significant number of people with Parkinson’s disease (PD) develop dementia in addition to cognitive dysfunction and is diagnosed as PD with dementia (PDD). This is characterized by cortical and limbic alpha synuclein (α-syn) accumulation; and high levels of diffuse amyloid beta (Aβ) plaques in the striatum and neocortical areas. In this regard, we have evaluated the effect of a brain penetrant novel multifunctional potent dopamine D2/D3 agonist, D-520 on the inhibition of Aβ and α-syn aggregation as well as on disintegration of α -syn and Aβ aggregates in vitro using purified proteins. In a cell culture model with human neuroblastoma MC65 cell lines which produce intracelluar Aβ induced toxicity, D-520 was evaluated to observe its effect on Aβ aggregation and Aβ induced toxicity. We further evaluated the effect of D-520 in *in vivo Drosophila* models of synucleinopathies and $A\beta_{1-42}$ dependent toxicity. We report that D-520 inhibits the formation of α-syn and Aβ aggregates *in vitro* and promotes disaggregation of

both α -syn and Aβ aggregates. In the cell culture model with MC65 cells, D-520 was shown to reduce both Aβ aggregates and Aβ induced toxicity to rescue the cells. Finally, in *in vivo Dorosophila* models, D-520 exhibited efficacy by rescuing fly eyes from retinal degeneration caused either by α-syn or Aβ toxicity. Our current experimental data indicates the potential therapeutic applicability of D-520 in addressing motor dysfunction and neuroprotection in PD and PDD, as well as attenuating dementia in people with PDD. Supported by NINDS (NS 047198, AKD)

Disclosures: **A.K. Dutta:** None. **D. Yedlapudi:** None. **D. Luo:** None. **G. Joshi:** None. **L. Xu:** None. **G. Marsh:** None. **S.V. Todi:** None.

Poster

653. Genetic Models of Parkinson's Disease

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 653.06/D40

Topic: C.03. Parkinson’s Disease

Support: CIHR

Title: Investigation of neuroinflammation in the brain of Parkinsonian monkeys with and without L-DOPA treatment and dyskinesias

Authors: M. MORISSETTE[1], L. GRÉGOIRE[1], N. MORIN[1], ***T. DIPAOLO**[1,2]; [1]Neurosciences, Ctr. de Recherche du CHU de Québec (CHUL), Quebec, QC, Canada; [2]Faculté de Pharmacie, Univ. Laval, Québec, QC, Canada

Abstract: Inflammation is documented to play a major role in the degeneration of dopamine neurons in Parkinson’s disease (PD). Proinflammatory markers, such as activated microglia, were found in the brains of PD patients and their presence correlates with damage to dopamine neurons in the nigrostriatal pathway. While neuroinflammatory responses seem to be associated with L-Dopa treatment, it is still unclear whether they are dependent from the dyskinetic outcome of the L-Dopa treatment and are causally linked to L-Dopa-induced dyskinesias (LID). We thus investigated the striatal inflammatory response and development of LID in MPTP-lesioned monkeys. Monkeys received MPTP and after stabilization of their motor behavior (6.6 months) they received for one-month daily L-DOPA inducing dyskinesias as compared to MPTP monkeys that received L-Dopa and MPEP (a metabotropic glutamate receptor negative allosteric modulator) that developed less dyskinesias as well as compared to intact controls and vehicle treated MPTP monkeys. Monkeys were euthanized 24h after their last L-Dopa treatment to study the brain long-term changes associated with L-Dopa and dyskinesias. We analyzed striatal changes by Western blot of the pan-macrophage/microglia marker Iba-1 and the astroglial protein GFAP as markers of neuroinflammatory response. Iba1 contents decreased in the caudate

nucleus of vehicle-treated MPTP monkeys. The L-Dopa treated dyskinetic MPTP monkeys had caudate nucleus Iba1 content not different from controls or MPTP-vehicle treated monkeys whereas MPTP monkeys that received L-Dopa + MPEP has decreased Iba1 content similar to untreated MPTP monkeys. In the putamen, Iba1 content was unchanged in vehicle-treated MPTP monkeys as well as MPTP monkeys treated with L-Dopa + MPEP whereas MPTP+ L-Dopa treated monkeys has elevated Iba1 contents. GFAP contents in the caudate nucleus were unchanged by the MPTP lesion and were elevated in MPTP + L-Dopa treated monkeys with or without MPEP treatment. In the putamen, GFAP content was elevated in all MPTP monkeys and this increase was larger in MPTP + L-Dopa treated monkeys. The present results showed a different effect of the MPTP lesion on GFAP and Iba1 in the caudate nucleus compared to the putamen; the latter region is associated with motor control. Moreover, we measured a greater increase of GFAP and Iba1 levels in the putamen of the MPTP + L-Dopa dyskinetic monkeys compared to the MPTP monkeys treated with L-Dopa + MPEP with less dyskinesias. In conclusion, these results showed an increase of inflammatory markers in the putamen associated with LID and that MPEP inhibition of glutamate activity reduced LID and levels of inflammatory markers.

Disclosures: **M. Morissette:** None. **L. Grégoire:** None. **N. Morin:** None. **T. DiPaolo:** None.

Poster

653. Genetic Models of Parkinson's Disease

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 653.07/D41

Topic: C.03. Parkinson’s Disease

Title: DT095435: A novel “pan” group III metabotropic glutamate receptor positive allosteric modulator for Parkinson’s disease

Authors: ***M. FRAULI**[1], A. BARRE[1], S. MAYER[1], A. COURTIN[1], L. DESHONS[1], M. HEYER[1], C. FRANCHET[1], M. BOURQUE[2], T. DI PAOLO[2], S. SCHANN[1];
[1]Domain Therapeut., Strasbourg, France; [2]Axe Neurosciences, Ctr. de Recherche du CHU de Québec-Université Laval and Faculté de Pharmacie, Univ. Laval, Laval, QC, Canada

Abstract: Most common medication for Parkinson's disease is L-DOPA. Effective early on, this treatment requires increasing doses that induce, in long term, abnormal and involuntary movements called dyskinesias. Amantadine (ionotropic glutamatergic receptor antagonist) is the only drug approved to treat dyskinesias; however, it has significant side effects and loses effectiveness after one year. Research is now turning to metabotropic glutamatergic receptors (mGluRs), which offer an alternative target for normalizing glutamatergic activity in Parkinson's disease.
High concentrations of neurotransmitters in some strategic basal ganglia synapses are involved in

the development of L-DOPA-induced dyskinesias (LID). The mGlu4 receptors are located pre-synaptically at these synapses, and their activation reduces neurotransmitter release. This explains the recently described anti-dyskinetic activity of Foliglurax, a selective mGluR4 Positive Allosteric Modulator (PAM), in a non-human primate model. Foliglurax is currently evaluated in Phase II clinical trials for its potential to reduce motor complications of L-DOPA therapy in Parkinson's patients.

During the optimization that led to the identification of Foliglurax, a new quinazolinone (QZ) series of PAMs was discovered. QZ compounds are “pan” group III mGluR PAMs, meaning that they do not only present single digit nanomolar PAM activity on mGluR4, but also comparable activities on other group III mGluRs (6, 7 and 8). Interestingly, the mGlu7 and mGlu8 receptors are also expressed at basal ganglia strategic synapses, suggesting that synergistic activation of mGluR4, 7 and 8 may provide better control of dyskinesias.

We present here PK data of our mGluR4/7/8 PAM candidate DT095435 in mouse, rat and monkey after oral administration at 10 mg/kg. Free brain concentrations ranged between 30 and 55 ng/mL in the different species: when compared to corresponding in vitro potency in calcium functional assay, this insured EC_{50} coverage of 0.5 to 0.9, thereby suggesting strong target engagement.

We also present *in vivo* evaluation of DT095435 in package of gold-standard PD models in mouse, rat and monkey. As expected from its PK profile, our candidate exhibited robust pro-motor activity after oral administration and remained active at dose as low as 0.1 mg/kg in mouse haldol-induced catalepsy model. Using two more advanced PD models, i.e. unilateral 6-OHDA lesioned rats & monkeys lesioned with MPTP toxin (both rendered dyskinetic by prolonged L-DOPA treatment), we have also compared efficacy of our non-selective mGluR4/7/8 PAM QZ candidate with that of selective mGluR4 PAM Foliglurax and/or amantadine in reducing LID.

Disclosures: **M. Frauli:** A. Employment/Salary (full or part-time):; DOMAIN THERAPEUTICS. **A. Barre:** A. Employment/Salary (full or part-time):; DOMAIN THERAPEUTICS. **S. Mayer:** A. Employment/Salary (full or part-time):; DOMAIN THERAPEUTICS. **A. Courtin:** A. Employment/Salary (full or part-time):; DOMAIN THERAPEUTICS. **L. Deshons:** A. Employment/Salary (full or part-time):; DOMAIN THERAPEUTICS. **M. Heyer:** A. Employment/Salary (full or part-time):; DOMAIN THERAPEUTICS. **C. Franchet:** A. Employment/Salary (full or part-time):; DOMAIN THERAPEUTICS. **M. Bourque:** None. **T. Di PAOLO:** None. **S. Schann:** A. Employment/Salary (full or part-time):; DOMAIN THERAPEUTICS.

Poster

653. Genetic Models of Parkinson's Disease

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 653.08/D42

Topic: C.03. Parkinson's Disease

Support: IT202417
DGAPA Apoyo beca estancia post-doctoral

Title: Unilateral implantation of SIO2/DA loaded hydrogel attenuate motor abnormalities in model of hemiparkinsonism

Authors: *E. A. RODRIGUEZ PEREZ[1], A. ESPADAS ALVAREZ[2], D. MEDINA BUENO[4], P. VERGARA ARAGON[3], A. ZAPATA ARENAS[3], E. GARCIA RAMIREZ[3], B. HERNANDEZ TELLEZ[3], G. REYNOSO GALVEZ, MS[3], R. BUSTAMANTE GARCIA[3], A. GOMEZ MARTINEZ[3];
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Abstract: Objective The purpose of the present study was to evaluate the toxicity of SiO2/DA loaded hydrogel, before been implanted in the brain (caudate) of rat in an induced hemiparkinsonism model. It is work mentioning that SiO2 with dopamine (SiO2/DA) hydrogel has achieved to reduce the dopamine oxidation and it allows its release in tissue through the nanopores that has. Results Significant dopamine depletion in the caudate ipsilateral to the side of infused with 6-hydroxydopamine (6-OHDA) in the substatia nigra. These animals displayed apomorphine-induced contralateral rotational behavior, when examined on the 21th day and attenuate motor abnormalities in 6-OH/DA model of hemiparkinsonism was observed after 7th days SiO2/DA implantation. Histological examination showed a hydrogel encapsulated without evidence of the inflammatory response of surrounding tissues caused by the foreign body and surrounding tissue remained well vascularized after implant. Conclusions The results of this acute analysis suggest that attenuate motor abnormalities in 6-OH/DA model of hemiparkinsonism, there is no contamination across the organs due to the implants. So, It has justified more investigations about it's the potential use of hydrogel as biomaterial for storing and releasing drugs.

Disclosures: E.A. Rodriguez Perez: None. **A. Espadas Alvarez:** None. **D. Medina Bueno:** None. **P. Vergara Aragon:** None. **A. Zapata Arenas:** None. **E. Garcia Ramirez:** None. **B. Hernandez Tellez:** None. **G. Reynoso Galvez:** None. **R. Bustamante Garcia:** None. **A. Gomez Martinez:** None.

Poster

653. Genetic Models of Parkinson's Disease

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 653.09/D43

Topic: C.03. Parkinson's Disease

Support: Intramural research program of the University of Cagliari

Title: Thalidomide and analogues attenuate L-DOPA-induced dyskinesia in a rat model of Parkinson's disease

Authors: *L. BOI[1], A. PISANU[2], N. H. GREIG[3], M. SCERBA[4], D. TWEEDIE[4], G. MULAS[1], S. FENU[1], E. CARBONI[1], S. SPIGA[1], A. CARTA[1];
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Abstract: L-DOPA therapy represents the gold-standard for Parkinson's Disease (PD). However, long-term administration results in treatment-related motor complications named L-DOPA-induced dyskinesia (LID). The pathophysiology of LID involves both classical neuronal mechanisms, as altered glutamatergic transmission and synaptic plasticity in the basal ganglia, and unconventional non-neuronal mechanisms. Indeed, preclinical studies have suggested a role of microglia-mediated neuroinflammatory responses and aberrant angiogenic processes in the development of dyskinetic movements. Among inflammatory mediators, TNF-α is a pro-inflammatory cytokine which affects recognized components of dyskinesia pathophysiology, such as angiogenesis and synaptic plasticity. Thalidomide and related analogues have immunomodulatory and antiangiogenic properties by inhibiting TNF-α; they are used clinically for inflammatory diseases and cancer and they are under investigation for neurological disorders. To test the efficacy of thalidomide and the more potent derivative 3,6'-dithiothalidomide on attenuating dyskinesia, rats were stereotaxically infused in the medial forebrain bundle with 6-OHDA and after 3 weeks they received 10 days treatment with L-DOPA plus benserazide (6 mg/kg each) and thalidomide (70 mg/kg) or 3,6'-dithiothalidomide (56 mg/kg). Dyskinesia as well as contralateral turning were recorded daily. Rats were euthanized 1 hr after the last L-DOPA injection, and levels of TNF-α, IL-10, OX-42 and vimentin immunoreactivity were measured in their striatum and substantia nigra reticulata (SNr) to evaluate neuroinflammation and angiogenesis. Striatal levels of GLUR1 were measured as a TNF-α-mediated postsynaptic dysfunction. Thalidomide and 3,6-dithiothalidomide significantly reduced the severity of LID while not affecting contralateral turning. Furthermore, both compounds inhibited the L-DOPA induced microgliosis and excessive TNF-α, while restoring physiological levels of the anti-inflammatory cytokine IL-10 in the striatum and SNr. L-DOPA-induced angiogenesis was inhibited in both basal ganglia nuclei, and L-DOPA-induced GLUR1 overexpression in the dorsolateral striatum was restored to normal levels. Our findings suggest that decreasing TNF-α levels may be a valuable strategy to reduce dyskinesia severity, and thalidomide and more potent derivatives might provide an effective therapeutic approach to dyskinesia.

Disclosures: L. Boi: None. **A. Pisanu:** None. **N.H. Greig:** None. **M. Scerba:** None. **D. Tweedie:** None. **G. Mulas:** None. **S. Fenu:** None. **E. Carboni:** None. **S. Spiga:** None. **A. Carta:** None.

Poster

653. Genetic Models of Parkinson's Disease

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 653.10/D44

Topic: C.03. Parkinson’s Disease

Title: RGS4 inhibition potentiates the antidyskinetic effect of NOP receptor agonist AT-403

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Abstract: L-dopa-induced dyskinesia (LID) is the most disabling side effect of dopamine replacement therapy for Parkinson’s disease. We previously reported that the nociceptin/orphanin FQ opioid peptide (NOP) receptor agonist AT-403 reduced LID expression without causing sedation in a narrow dose-range(1) We therefore investigated whether pharmacological inhibition of Regulators of G protein Signaling (RGS) type 4 (RGS4), an accessory protein that accelerates the extinction of signal mediated by GPCRs coupled to Gαi or Gαq, widens the therapeutic window of AT-403. Western blot analysis revealed a dramatic reduction of RGS4 protein levels in rats after 6-OHDA lesion and a normalization after chronic administration of L-dopa, both in the lesioned and unlesioned striatum (OFF L-dopa). Conversely, an increase of RGS4 was found in the lesioned compared to the unlesioned striatum ON L-dopa. To confirm an involvement of RGS4 in LID, the RGS4 inhibitor, CCG203920, alone and in combination with AT-403, was administered to L-dopa-primed 6-OHDA hemilesioned rats. AT-403 delayed the onset of axial, limb and orolingual abnormal involuntary movements (AIMs) (the rodent correlate of dyskinesia) without affecting maximal dyskinesia severity. CCG203920, ineffective alone, extended the anti-dyskinetic effect of AT-403, further delaying AIMs appearance by 20 min. To confirm that RGS4 blockade had an impact over biochemical pathways underlying LID, Western blot analysis revealed that the AT-403/CCG203920 combination normalized the striatal levels of phosphorylated ERK (pERK), a biochemical correlate of LID, whereas AT-403 and CCG203920 alone were ineffective. To confirm that RGS4 inhibition amplifies the negative modulation of D1 receptor signaling induced by NOP receptor stimulation, AT-403 attenuated the elevation of pERK-positive cell number induced by the D1 agonist SKF38393 in striatal slices of naïve mice, and CCG203920, ineffective alone, potentiated this effect. This study represents the first evidence of an interaction between RGS4 and the NOP receptor, and provides preliminary evidence of the potential of

RGS4 inhibitors to amplify the antidyskinetic effect of NOP receptor agonists. 1. Arcuri et al., Br J Pharmacol 175, 782-796 (2018)

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Poster

653. Genetic Models of Parkinson's Disease

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 653.11/D45

Topic: C.03. Parkinson’s Disease

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NIH Grant P30 ES006096
Kerman Family Fund
Gardner Family Center for Parkinson’s Disease and Movement Disorders
Selma Schottenstein Harris Lab for Research in Parkinson’s

Title: Evaluation of carnosine intervention in the Thy1-aSyn mouse model of Parkinson's disease

Authors: M.-L. BERMÚDEZ[1], ***K. B. SEROOGY**[2], M. B. GENTER[1];
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Abstract: Parkinson’s disease (PD) is a leading neurodegenerative disease, with multifaceted interacting mechanisms. Although the etiology of PD remains unknown, two well-known hallmarks of PD are the presence of Lewy bodies containing protein aggregates composed primarily of alpha-synuclein (aSyn) in multiple brain regions, and loss of dopaminergic neurons in the substantia nigra, resulting in motor dysfunction. Because no treatments to date slow or halt the degeneration of nigral dopaminergic neurons and progression of the disease, new therapeutic approaches for PD are urgently needed. Thy1-aSyn mice exhibit many features of PD patients, including sensorimotor dysfunction and aSyn protein aggregation. We tested the hypothesis that the dipeptide carnosine (beta-alanyl-L-histidine), which has anti-aggregating and metal-chelating properties, would provide beneficial effects on the motor and olfactory deficits observed in Thy1-aSyn mice. Two-month-old Thy1-aSyn mice and wild-type BDF1 mice were assessed for baseline motor [challenging beam traversal (CBT) test and spontaneous activity] and olfactory (buried pellet test) function. After baseline behavioral testing, mice were randomly assigned to treatment groups and administered carnosine either intranasally (2 mg/d) or in drinking water (10 mM). After 2 months of daily treatment, mice were re-assessed in the behavioral tests, and the olfactory epithelium was evaluated immunohistochemically for aSyn and expression of the

carnosine transporter PEPT2. Olfactory function was unaffected by carnosine treatment via either administration route. Thy1-aSyn vehicle-treated mice and those receiving drinking water carnosine showed progressive motor deficits in the CBT test over the 2-month treatment period. In contrast, the number of errors per step in the CBT test did not increase in Thy1-aSyn mice receiving intranasal carnosine. Moreover, carnosine-treated Thy1-aSyn mice exhibited decreased aSyn immunostaining in the olfactory epithelium compared to vehicle-treated Thy1-aSyn mice. Furthermore, the carnosine transporter PEPT2 was immunolocalized to the apical surface of the olfactory epithelium. These findings demonstrate that intranasal carnosine shows promise in slowing the progression of motor deficits and aSyn deposition in PD.

Disclosures: M. Bermúdez: None. **K.B. Seroogy:** None. **M.B. Genter:** None.

Poster

653. Genetic Models of Parkinson's Disease

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 653.12/D46

Topic: C.03. Parkinson's Disease

Support: NS100930

Title: Exploiting functional selectivity of dopamine D_1 receptors as therapeutics for Parkinson's disease in mice

Authors: V. M. POGORELOV[1], C. RAY[2], M. L. MARTINI[3], R. CHANDRASEKHAR[2], N. M. URS[4], J. JIN[3], M. G. CARON[2], ***W. C. WETSEL**[1];
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Abstract: L-DOPA is used as a common therapy for Parkinson's disease (PD); however, prolonged treatment is often accompanied by L-DOPA-induced dyskinesias (LIDs). L-DOPA is metabolized to dopamine (DA) which binds to the D_1 (D_1R) and D_2 receptors (D_2R) to activate signaling through G protein and β-arrestin (βARR) mediated mechanisms. Emerging evidence suggests that LIDs may be due to G protein-mediated signaling. We hypothesize that developing compounds that are functionally selective for DA receptors may be beneficial to prevent dyskinesias. DA transporter knockout mice were treated chronically with α-methyl-*p*-tyrosine to deplete tissue DA stores (DDD model), were administered L-DOPA plus benserazide (Benz) over 17 consecutive days, and were tested in the open field or a circular arena (20 cm in diameter). Locomotion decreased over time in both tests, while rearing and climbing increased only in the open field. Grooming stereotypies were enhanced more in the circular arena than open field ($P<0.001$), while oral stereotypy increased in both arenas. As a comparison, 6-

hydroxy DA (6-OHDA) lesioned mice were treated chronically with L-DOPA plus Benz and tested in the circular arena. Rotations and LIDs (oral and grooming stereotypies and postural dyskinesia) gradually increased across days. MLM 55-38 was tested with the full agonist SKF81297 as a control. Compared to DA, a Gs-mediated cAMP accumulation assay and a bioluminescence resonance energy transfer βARR assay revealed MLM 55-38 to be a balanced D_1R super-agonist for both G protein and βARR-mediated signaling. In the absence of L-DOPA there were no LIDs in DDD mice given MLM 55-38, whereas SKF 81297 increased face-washing. Compared to vehicle, L-DOPA plus Benz with MLM 55-38 increased rearing, climbing, and face-washing (P-values≤0.033); SKF 81297 augmented oral stereotypies ($P<0.022$). In 6-OHDA lesioned wild-type (WT) and βARR2 knockout mice in the absence of L-DOPA, MLM 55-38 and SKF 81297 facilitated rotations, stereotypies, and postural dyskinesias to a greater extent in mutants than WT controls (P-values≤0.013). However, when MLM 55-38 and SKF 81297 were given with L-DOPA plus Benz postural dyskinesia was more robust in the βARR2 KOs than WT mice ($P<0.001$). Together, these findings suggest that the circular maze may be more conducive to studying LIDs than the open field, the 6-OHDA model may be superior to the DDD model for screening these D_1R-biased compounds, and that D_1R βARR-biased compounds may reduce the incidences of LIDs while still promoting forward motor activity.

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Poster

653. Genetic Models of Parkinson's Disease

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 653.13/E1

Topic: C.03. Parkinson’s Disease

Title: A potent, highly selective and brain penetrant orphan receptor GPR6 inverse agonist as symptomatic treatment for Parkinson's disease

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Abstract: Parkinson’s disease (PD) is a progressive neurodegenerative disorder caused by the gradual loss of dopaminergic neurons of the substantia nigra that regulate information flow from the striatum to regions of the brain that coordinate movement. The effects of nigrostriatal dopamine are mediated via the dopamine receptors D1 and D2, which are expressed on intermingled gabaergic medium spiny neurons (MSNs) and define two opposing brain circuits:

The D1-type MSN originate the direct (striatonigral) pathway which initiates motor activity. The D2-type MSN originate the indirect (striatopallidal) pathway that suppresses motor activity. Pathological hyperactivity of the indirect pathway has been observed in PD patients and dopamine-depleted animals, and contributes to rigidity and hypokinesia. Normalization of the indirect pathway activity and improvement of motoric function in PD can be achieved by deep brain stimulation of the subthalamic nucleus with bilateral surgically implanted electrodes. Therefore, novel non-dopaminergic therapies for treating the motor symptoms of PD targeting the indirect pathway might have therapeutic potential. We identified the orphan GPR6 as a gene highly expressed in striatal D2-type MSNs of the indirect pathway in rodents, NHP and brain specimens from patients with PD. GPR6 is an excitatory, Gαs-coupled receptor with high apparent constitutive activity in heterologous expression systems. High-through-put screens and *in vitro* SAR strategies identified a potent GPR6 inverse agonist (Compound 1), which showed high selectivity against GPR3, GPR12 and other off targets. Compound 1 reduced striatal DARPP-32 phosphorylation of Thr-34 in brain slices and demonstrated oral bioavailability and GPR6 receptor occupancy *in vivo*. Compound 1 stimulated open-field-activity in wild type rodents, reversed haloperidol-induced catalepsy and completely restored mobility in the bilateral 6-OHDA lesioned rat model of PD. In addition, compound 1 administered once daily for 22 days did not induce abnormal involuntary movements (AIMs), a rodent correlate of dyskinesia, in unilateral 6-OHDA-lesioned rat model of PD. Lipidomic profiling revealed that compound 1 increases sphingomyelin species in the striatum of wildtype mice, but not in GPR6 knock out mice. PD is frequently accompanied by depression. Compound 1 also demonstrated robust efficacy in reversing anhedonia in the unpredictable chronic mild stress (uCMS) model. The nonclinical data obtained from our *in vitro* and *in vivo* studies support the development of compound 1 for the symptomatic treatment of Parkinson's disease.

Disclosures: **N. Kaushal:** None. **J. Russo:** None. **Y. Chen:** None. **N. English:** None. **H. Sun:** None. **S. Kikuchi:** None. **H. Reichard:** None. **J. Brown:** None. **M. Hopkins:** None. **J. Ray:** None. **S. Hitchcock:** None. **H.H. Schiffer:** None.

Poster

653. Genetic Models of Parkinson's Disease

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 653.14/E2

Topic: C.03. Parkinson's Disease

Support: Fogarty International NCOD-5D43TW008333
Texas Tech University Health Sciences Center El Paso, Graduate School of Biomedical Sciences
Multiple System Atrophy Coalition
Lizanell and Colbert Coldwell Foundation

El Paso Community Foundation
Hoy Family Research
Perez Family Research

Title: Nonimmunosuppressive mitochondria-localizing FTY720-mitoxy reverses behavioral impairment and enhances GDNF expression while reducing synucleinopathy and neuroinflammation in multiple system atrophy mice

Authors: G. VIDAL-MARTINEZ[1], I. SEGURA-ULATE[1], B. YANG[1], V. DIAZ-PACHECO[1], J. VARGAS-MEDRANO[1], ***R. G. PEREZ**[2];
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Abstract: Multiple system atrophy (MSA) is a rapidly progressing neurodegenerative disorder of aging with no effective treatments. MSA pathology is characterized by a toxic accumulation of α-synuclein (aSyn) protein inside oligodendroglia cells (OLGs), the myelinating cells of brain. Protection in MSA models is associated with glial-cell line-derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor (BDNF), which are abnormally expressed in brains of MSA patients and in MSA mice. We previously tested FTY720 in parkinsonian mice and MSA cell models, and found increased BDNF expression. Here we preclinically tested our mitochondria-localizing FTY720-analogue FTY720-Mitoxy, in mice that express aSyn in OLGs under control of the 2,' 3'-cyclic nucleotide 3'-phosphodiesterase (CNP) promoter. Nonimmunosuppressive FTY720-Mitoxy reversed motor impairment, increased soleus muscle size, and improved sweat function in MSA mice. Co-treating 9 mo old MSA mice with FTY720-Mitoxy, protected their motor function and succinate dehydrogenase activity against 3-nitropropionic acid (3NP) in mitochondria isolated from cerebellum, a brain area that regulates movement. FTY720-Mitoxy also reduced levels of stress associated HSP60 and mitochondrial fission factor (MFF) in soleus muscle against 3NP toxicity. Furthermore, FTY720-Mitoxy increased GDNF mRNA and protein levels in frontal hemicortex, an increase that paralleled the downregulation of mir-96-5p, a microRNA that reduces GDNF expression. Moreover, FTY720-Mitoxy reduced pathological aSyn aggregation in spinal cord and cerebellar white matter microglial activation as measured by Ionized-calcium-Binding-Adaptor-molecule1 (Iba1) immunoblot. Thus, FTY720-Mitoxy is a promising nonimmunosuppressive potential therapeutic with the capacity to slow or reverse both pathology and functional impairments of MSA.

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Poster

653. Genetic Models of Parkinson's Disease

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 653.15/E3

Topic: C.03. Parkinson’s Disease

Support: All work was supported by BlackThorn Therapeutics

Title: Effects of nociceptin/orphanin FQ (NOP) receptor antagonism with BTRX-246040 in animal models of Parkinson's disease

Authors: *T. L. WALLACE[1], E. BEZARD[2,3], E. PIOLI[3], W. J. MARTIN[1];
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Abstract: Pharmacological treatments for Parkinson’s disease (PD) aim to replace dopamine (DA) or to directly activate DA receptors to improve motor symptoms of the disease, but most have dose-limiting side effects that develop after chronic treatment, and do not improve the non-motor symptoms of PD. The nociceptin/orphanin FQ (NOP) system, which is involved in mood, stress, movement and other functions has revealed a link with PD in both preclinical and clinical studies. To further characterize the involvement of the NOP system in preclinical models of PD, we tested BTRX-246040, a selective NOP receptor antagonist, in a series of studies to evaluate its anti-PD and disease modifying effects. In the first studies, we used the MPTP-treated macaque model of PD. Following acute administration, BTRX-246040 (0.1, 0.3, 1.0 mg/kg, i.m.) elicited a robust anti-PD effect on motor symptoms, comparable to L-DOPA, but unlike L-DOPA, BTRX-246040 significantly reduced the level of dyskinesias in primed NHPs. Subsequently, we conducted two additional studies in the MPTP NHP model of PD to evaluate: 1) the L-DOPA sparing effects of BTRX-246040; and, 2) the impact of chronic administration of BTRX-246040. In both studies, the main findings indicate the compound was well-tolerated, but the anti-PD effects were non-significant despite expected pharmacokinetic properties of the compound. In a separate study designed to investigate the potential neuroprotective and disease modifying effects of BTRX-246040 and SB-61211 (comparator NOP receptor antagonist), we used the alpha-synuclein (α-syn) overexpression rat model, which caused a 23% depletion of the striatal DA level and degeneration of 48% of DAergic neurons in the substantia nigra (SN). BTRX-246040, SB-612111 and vehicle were administered subcutaneously twice daily for 7 weeks and started on day 7 after α-syn overexpression. The results of this study showed SB-612111, but not BTRX-246040, increased the number of TH-positive neurons in the SN. Both drugs had a positive effect on locomotor activity and interfered with synuclein levels suggesting disease-modifying activity. SB-612111 demonstrated neuroprotective properties while BTRX-246040 did not match this effect but displayed an intermediate profile between the vehicle and

the SB-612111 group. Collectively, these data suggest NOP receptor antagonism exhibits beneficial effects on motor symptoms and disease modifying properties in preclinical PD models, but further exploration is warranted to gain confidence around the therapeutic potential of this approach for the treatment of PD.

Disclosures: **T.L. Wallace:** A. Employment/Salary (full or part-time):; BlackThorn Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BlackThorn Therapeutics. **E. Bezard:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Motac Neuroscience. F. Consulting Fees (e.g., advisory boards); Motac Neuroscience. **E. Pioli:** A. Employment/Salary (full or part-time):; Motac Neuroscience. **W.J. Martin:** A. Employment/Salary (full or part-time):; BlackThorn Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BlackThorn Therapeutics.

Poster

653. Genetic Models of Parkinson's Disease

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 653.16/E4

Topic: C.03. Parkinson’s Disease

Support: NIH/NINDS 5 R21 NS099778-02

Title: A metabolically stable PACAP analog with PAC1/VPAC2 receptor selectivity crosses the blood-brain barrier and protects dopaminergic neurons in the substantia nigra of MPTP-treated mice

Authors: *I. J. MERCHENTHALER[1], M. LANE[1], B. DUDAS[2], W. BANKS[3];
[1]Epidemiology and Publ. Hlth., Univ. of Maryland Baltimore, Baltimore, MD;
[2]Neuroendocrinology, Lake Erie Osteo. Med., Erie, PA; [3]Intrnl. Med., Univ. of Washington, Seattle, WA

Abstract: PACAP is a promising molecule for the development of a therapeutic strategy to halt or slow the progression of Parkinson’s disease (PD) because it exhibits anti-apoptotic, anti-inflammatory, anti-oxidant, and cytoprotective activities. However, the short half-life of PACAP *in vivo* precludes its use as a pharmacological intervention in humans. PACAP is degraded by aminodipeptidases, especially dipeptidyl peptidase IV (DPP IV). Only peptides with a free amino group at the N-terminus are substrates for DPP IV, and acetylation of the N-terminus blocks also blocks degradation. The analog studied in these experiments, i.e., [Iaa[1],D-Ser[2]]PACAP38, is acetylated in the N-terminus and L-Ser in position 2 was replaced with D-Ser to further improve the peptide’s resistance to proteolysis. Although, PACAP has been shown to provide

neuroprotection in preclinical models of several neurodegenerative and autoimmune diseases and in humans, it has been administered intraperitoneally (ip) or intravenously (iv) and only occasionally subcutaneously (sc). However, chronic treatment of animals or humans ip or iv is not practical. In these experiments, we tested if a metabolically stable PACAP analog with PAC1/VPAC2 receptor activities, similarly to the native peptide, crosses the blood-brain barrier (BBB) and will protect substantia nigra pars compacta (SNpc) dopaminergic (DA) neurons in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated mice. The analog was administered by daily sc or ip injections or via sc-implanted Alzet pumps delivering 5 ug/mouse analog daily for 9 days. The effect of neuroprotection on the SNpc DA-ergic neuronal system and DA-ergic nerve terminals in the striatum was evaluated with immunoctochemistry. These studies were performed in male mice only as the frequency of PD is higher in men than women. For the BBB penetration studies, performed in the Banks lab, multiple-time regression analysis, the same methodology used to elucidate BBB/endogenous PACAP interactions was utilized. Brain/serum ratios in units of ul/g were determined with the equation: Brain/serum ratio (ul/g) = (cpm/whole brain)/[(wt in g of whole brain)(cpm/ul of arterial serum)]. The analog penetrated the BBB via a saturable transport mechanism. The unidirectional influx rate was 2.5 microliters/g-min and the r value was 0.954 ($p<0.00001$). The immunocytochemical analysis, performed in the Merchenthaler lab, using antibodies against tyrosine hydroxylase showed that the PACAP analog provided protection in the DA-ergic system (SNpc and striatum) independent of the route of administration.

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Poster

653. Genetic Models of Parkinson's Disease

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 653.17/E5

Topic: C.03. Parkinson’s Disease

Support: MJFF 15026

Title: A LRRK2 kinase inhibitor, PFE360, reduces behavioural and striatal dopaminergic deficits in a rat model of Parkinson’s disease alpha-synucleinopathy

Authors: *J. B. KOPRICH[1], S. JAFRI[1], V. OMANA[1], T. H. JOHNSTON[1], M. P. HILL[1], T. PARKKARI[2], N. MOORE[3], M. A. BAPTISTA[4], J. M. BROTCHIE[1];
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Abstract: Mutations in the Leucine-rich repeat kinase 2 (LRRK2) gene, are one of the most common genetic contributors to Parkinson’s disease (PD). The clinical and pathological features

of carriers of LRRK2 mutations overlap with those with sporadic PD and links to alpha-synuclein and LRRK2 biology continue to emerge. Given these considerable convergences, LRRK2 inhibitors are actively being pursued in drug development programs targeting PD widely. As PD is an alpha-synucleinopathy, it is important to evaluate LRRK2 kinase inhibition in animal models of PD based on deficits and pathology driven by alpha-synuclein (aSyn) expression. To this end, we have evaluated the prototypical LRRK2 kinase inhibitor, PFE360, in an AAV1/2-human A53T-aSyn (AAV1/2-hA53T-aSyn) rat model of PD. Three groups of 10 female rats were prepared: AAV1/2-empty vector (EV)/ vehicle, AAV1/2-hA53T-aSyn/ vehicle and AAV1/2-hA53T-aSyn/ PFE360. Rats received once daily administration of PFE360 (15 mg/kg, p.o.) or vehicle commencing one day after AAV1/2 delivery to the right substantia nigra [SN], i.e. on day 1 (D1) through to D43 (day of necropsy). Behaviour was assessed, off treatment, using the cylinder test on D21 and D42. Post-mortem, striatal dopamine, dopamine transporter (DAT) and SN dopamine neuron number, defined as tyrosine hydroxylase-positive (TH+ve) cells, were assessed.AAV1/2-hA53T-aSyn/ vehicle-treated animals showed significant forelimb asymmetry on D21 and D42, 35% and 36% increase from control respectively (both $P<0.05$). PFE360-treatment reduced forelimb asymmetry to a 17% and 1% increase from control on D21 and D42 respectively (both $P>0.05$). AAV1/2-hA53T-aSyn produced 44% and 47% reduction in striatal dopamine and DAT levels respectively, compared to control (both $P<0.05$). In contrast, in PFE360 treated rats, no significant deficits were observed in dopamine and DAT (both $P>0.05$). However, there was no effect of treatment with PFE360 on the number of TH+ve remaining in the SN ($P>0.05$). These results suggest an ability of LRRK2 inhibition to protect against at least some of the dopaminergic deficits induced by synucleinopathy and support the continued development of LRRK2 kinase inhibitors for the treatment of PD. Ongoing studies are focussed on determining levels of target engagement required for efficacy.

Disclosures: **J.B. Koprich:** A. Employment/Salary (full or part-time):; Atuka Inc.. 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.; Michael J. Fox Foundation. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Atuka Inc. **S. Jafri:** A. Employment/Salary (full or part-time):; Atuka Inc. **V. Omana:** A. Employment/Salary (full or part-time):; Atuka Inc. **T.H. Johnston:** A. Employment/Salary (full or part-time):; Atuka Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Atuka Inc. **M.P. Hill:** A. Employment/Salary (full or part-time):; Atuka Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Atuka Inc. **T. Parkkari:** A. Employment/Salary (full or part-time):; Charles River. **N. Moore:** A. Employment/Salary (full or part-time):; Charles River. **M.A. Baptista:** None. **J.M. Brotchie:** A. Employment/Salary (full or part-time):; Atuka Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Atuka Inc..

Poster

653. Genetic Models of Parkinson's Disease

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 653.18/E6

Topic: C.03. Parkinson's Disease

Title: Preclinical pharmacology of IRL752, a novel compound to treat postural instability and cognitive deficits in Parkinson's disease

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Abstract: In Parkinson's disease (PD) impaired cortical monoamine transmission is a core feature associated with progressive cognitive decline, and certain motor traits. In particular axial motor symptoms, relating to postural instability (balance) and falls, are strongly related to cognitive deficits in PD. This symptom cluster responds poorly to current anti-Parkinson treatment. Novel treatments addressing cognition and postural instability is thus a high priority area in PD.
IRL752 was discovered using phenotypic screening, based on broad data arrays generated *in vivo* (gene expression, monoamine biomarkers, behavioural studies in rats). Effects on extracellular levels of monoamine transmitters were assessed by *in vivo* brain microdialysis. The *in vivo* profile was compared to a comprehensive in-house database of CNS active compounds. Upon oral or parenteral dosing, at 3-100 micromoles/kg IRL752 displays a novel profile, with regio-selective enhancement of cortical DA and NE, along with increased cortical ACh. IRL752 induces IEGs related to neuronal activity, including *Arc, NPTX, NPAS4,* and *c-fos* in the frontal cortex, limbic and striatal areas. The effect on cortical *IEGs* is interpreted as enhanced synaptic activity. The increase of subcortical *IEGs* is presumably related to activation of cortico-striatal pathways. The *IEG* expression profile induced by IRL752 shares features with that induced by cognitive enhancers such as memantine.
IRL752 does not affect motor activity patterns in normal rats or in rats under the influence of psychostimulants, but partly attenuates Mk-801 induced hyperactivity. Thus, behavioural studies may suggest potential efficacy in psychiatric domains. IRL752 reverses tetrabenazine induced hypomotility, indicating efficacy in conditions with impaired catecholamine transmission, and hence, potential to improve motor function in PD. IRL752 also reverses deficits in novel object recognition (NOR) suggesting potential to enhance short-term memory. Main receptor targets and synergies involved in the effects of IRL752 are 5-HT7, alpha-2C and Sigma-1.
In conclusion, the preclinical profile supports a potential use for treatment of cognitive and axial

motor deficits in PD. IRL752 has been explored in Phase I and IIa clinical trials. Data indicates that it is safe and well tolerated in healthy volunteers as well as in patients with PD, with indications of efficacy with respect to improved balance, reduced falls and signs of improved cognition, which will be further explored in Phase IIb trials.

Disclosures: **S. Waters:** A. Employment/Salary (full or part-time):; Integrative Research Laboratories AB, Gothenburg. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Integrative Research Laboratories AB, Gothenburg. **C. Sonesson:** A. Employment/Salary (full or part-time):; Integrative Research Laboratories AB, Gothenburg. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Integrative Research Laboratories AB, Gothenburg. **N. Waters:** A. Employment/Salary (full or part-time):; Integrative Research Laboratories AB, Gothenburg. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Integrative Research Laboratories AB, Gothenburg. **J. Tedroff:** A. Employment/Salary (full or part-time):; Integrative Research Laboratories AB, Gothenburg. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Integrative Research Laboratories AB, Gothenburg. **P. Svensson:** A. Employment/Salary (full or part-time):; Integrative Research Laboratories AB, Gothenburg. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Integrative Research Laboratories AB, Gothenburg. **S. Hjorth:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); IRL AB. F. Consulting Fees (e.g., advisory boards); IRL AB.

Poster

653. Genetic Models of Parkinson's Disease

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 653.19/E7

Topic: C.03. Parkinson’s Disease

Support: NIH R01 NS101967
National Parkinson Foundation
Par fore Parkinson's
The Michael J. Fox Foundation

Title: Screening of non-electrophilic Bach1 inhibitors in *in vitro* and *in vivo* models of neuroprotection

Authors: ***M. AHUJA**[1], N. AMMAL KAIDERY[1], I. GAISINA[6], K. IGARASHI[7], I. PINA GOMEZ[2], M. HAMANN[2], O. ATTUCKS[8], S. SHARMA[3], B. THOMAS[1,4,5];

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Abstract: Bach1 [BTB (broad-complex, tramtrack and bric-a-brac) and CNC (cap'n'collar protein) homology 1] is transcription repressor that competes with Nrf2 in regulating antioxidant and cytoprotective cellular phenotypes. Mounting evidence accounts for Nrf2 to be a promising target for neuroprotective interventions in various neurodegenerative disease. However, canonical Nrf2 based drugs result in side-effects in part due to their electrophilic chemical properties that leads to irreversible alkylation of cysteine residues of cellular proteins. Genetic Bach1 ablation in experimental models has shown promising effects in neuroprotection studies. Nonetheless, the clinical application of Bach1 inhibition for neuroprotection is nonexistent due to lack of good pharmacological Bach1 inhibitors. Thus, we aimed to develop non-electrophilic Bach1 inhibitors and a screening method that can assist in discovering non-electrophilic Bach1 inhibitors. Using hemin, a physiological Bach1 inhibitor, as a prototype molecule few candidates were synthesized and selected. We validated the Bach1 inhibition in ARE-luciferase cell line in presence of mutated Bach1, followed by Chromatin immunoprecipitation (CHIP) and *in vitro* detection of ROS and glutathione (GSH) depletion. Bach1 inhibitor demonstrated significant MARE-luciferase activity in the presence of WT but not mutant Bach1, and CHIP binding characteristic to Bach1 inhibition, distinctive from canonical Nrf2 activators, with no cellular ROS generation and GSH depletion. We employed Mass spectrometry-based detection of Keap1 cysteine modification that revealed Bach1 inhibitor failed to modify Keap1 cysteine compared to a canonical Nrf2 activator. Parallelly, in a CRISPR/Cas9 mutated cell line carrying Keap1 cysteine 151 mutation, we established non-electrophilic properties of Bach1 inhibitor. In addition, we developed a screening assay employing Mass-spectrometric based Bach1 binding to discover novel molecules exhibiting select Bach1 binding/inhibition. Bach1 inhibitors showed neuroprotective effects in cellular and animal models of Parkinson’s disease. Taken together, our results unearth a successful pharmacological approach for Bach1 inhibition that is non-electrophilic and neuroprotective. Furthermore, we developed an efficient screening method that can be used to screen for novel Bach1 inhibitors.

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Poster

653. Genetic Models of Parkinson's Disease

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 653.20/E8

Topic: C.03. Parkinson's Disease

Support: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES)
Fundação Amazônia de Amparo a Estudos e Pesquisas do Pará (FAPESPA)

Title: Neuroprotective effects of beta-caryophyllene in the striatal 6-OHDA mouse model of Parkinson's disease

Authors: *A. VALENTE-AMARAL, R. D. M. GOMES, V. S. L. CARDOSO, L. L. AMADO, E. T. COSTA, E. S. YAMADA;
Federal Univ. of Pará, Belém, Brazil

Abstract: Parkinson's disease (PD) is traditionally classified as a motor disorder characterized by resting tremor, muscular rigidity, postural instability and bradykinesia. These symptoms are caused by progressive loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and consequently depletion of dopamine on striatum. The search for new therapeutical approaches that may delay or interrupt the neurodegeneration in PD is essential to promote a better quality of life for patients. Thus, beta-caryophyllene (BCP) is a promising dietary phytocannabinoid, because it is a selective and non-psychoactive agonist of type II cannabinoid receptors, with anti-inflammatory and antioxidant properties. Thereby, we investigated whether BCP has neuroprotective effects in a murine model of PD induced by 6-hydroxydopamine (6-OHDA). Forty male Swiss mice were divided in 4 groups: Vehicle/Vehicle (N = 7), Vehicle/BCP (N = 8), 6-OHDA/Vehicle (N = 12) and 6-OHDA/BCP (N = 13). Stereotaxic surgeries were performed in all animals to inject vehicle or 6-OHDA (10 µg) solution into the striatum, and BCP (50 mg/kg) was administrated for 7 days after stereotaxic surgeries. We performed behavioral tests such as apomorphine-induced rotation (2-4 weeks) and exploration in the open field (4 weeks). Immunostaining for tyrosine-hydroxylase (TH) and microglia/macrophages (IBA-1) were performed. In addition, we investigated quantitatively the degree of neurodegeneration and neuroinflammation through stereological estimations from neurons and microglial cells in the SNpc, respectively. For biochemical analyzes, we quantified the total antioxidant capacity against peroxyl radicals from striatum and midbrain. The apomorphine-induced rotation test showed that 6-OHDA/BCP group presented significant decrease of rotations compared to 6-OHDA/Vehicle group at 2 and 4 weeks. In the open field test, 6-OHDA/Vehicle group showed impairment in motor behavior with reduced distance travelled, low velocity and spent more time in the border of the apparatus, suggesting a thigmotaxis behavior. On the other hand, 6-OHDA/BCP did not present impairment in locomotion and remained less time in the peripheral zone. Stereological estimations showed that the BCP treatment was associated with reduced degeneration of TH+ neurons and reduced expression of microglial cells in the SNpc. But, BCP treatment was not able to increase the antioxidant capacity. Hence, BCP treatment has a potential neuroprotective effect in this mouse model of PD, which deserves to be better characterized for translational application.

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Poster

653. Genetic Models of Parkinson's Disease

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 653.21/E9

Topic: C.03. Parkinson’s Disease

Support: CONACYT 279310

Title: Feasibility of using deep brain stimulation electrodes coated with polypyrrole/iodine in a model of MPP+ hemi-parkinsonian rat model

Authors: *F. D. RUIZ DÍAZ[1], J. MORALES CORONOA[1], J. MANJARREZ MARMOLEJO[2], L. C. RIOS CASTAÑEDA[2], R. OLAYO GONZÁLEZ[1], A. DIAZ-RUIZ[2];
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Abstract: Parkinson's disease (PD) is the second neurodegenerative disease with the highest incidence worldwide. There are different therapeutic strategies to treat this condition in chronic stages, one of them is the use of deep brain stimulation (DBS), however since it is an invasive method and the electrodes remain chronically, various complications can occur such as: nervous tissue damage as a consequence of an inflammatory process that can lead to neuronal death. In addition the formation of gliosis around the implant, results in alterations of the stimulation efficacy. In this work we tested a new polymer in order to improve the physical and chemical characteristics of the interface. Recently, our group has shown that the polypyrrole / iodine (PPy / I) synthesized by plasma is a semiconductive biomaterial with neuroprotective effect and promoter of both motor and sensory functional recovery in models of spinal cord injury. This effect is due to its anti-inflammatory and anti-apoptotic capacity, so these characteristics could make PPy / I a useful material for coating DBS electrodes. We elaborated electrodes which were tested in a PD model induced by the striatal administration of 1-methyl-4-phenylpyridinium (MPP +) in male Wistar rats weighing 270 to 300 grams. The model was validated by subcutaneous administration of apomorphine and the electrodes were implanted in the right subthalamic nucleus (STh). The results showed that the electrodes with PPy / I have a uniform surface which is not altered when is subjected to various mechanical tests, as well the records of the electrical activity in the area of the implant are clearly displayed over eight weeks without increase the amplification of the signal for reading. With the findings of this work we propose that the PPY / I could be a good option to cover deep stimulation electrodes and improve the interphase in the brain of the rat.

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Poster

653. Genetic Models of Parkinson's Disease

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 653.22/E10

Topic: C.03. Parkinson's Disease

Support: R25 award NS079188

Title: Analysis of hippocampal synapses in the PINK1-deficient rats

Authors: *A. A. MEMON[1], R. B. CREED[2], A. W. AMARA[3], M. S. GOLDBERG[3], M. BAMMAN[4], L. L. MCMAHON[5];
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Abstract: Parkinson's disease (PD) is the second most common neurodegenerative disorder of aging. Although the diagnosis is based on motor features, PD is also associated with wide-ranging non-motor symptoms (NMS), including cognitive dysfunction. NMS often precede motor deficits, severely affecting the quality of life in PD. PTEN induced kinase 1 (PINK1) degrades dysfunctional mitochondria and mutations in PINK1 causes autosomal recessive PD. While the pathological hallmark of PD is loss of dopaminergic neurons in the substantia nigra and abnormal accumulation of alpha-synuclein aggregates, studies in PINK1 knockout (KO) mice report deficits in monoaminergic neurotransmitters within the limbic system including the hippocampus, which is implicated in memory functions. Indeed, approximately 14% of patients with PINK1-type PD show cognitive decline. It is unclear why or how alpha-synuclein aggregates and monoaminergic deficits occur in PINK1 KO rats, causing widespread motor and NMS. Synuclein is one of the most abundant synaptic proteins and is essential for synaptic vesicle movement and synaptic transmission, which leads us to hypothesize that defects in excitatory transmission occur in PINK1 KO rats. Also, PINK1 KO rats, in contrast to PINK1 KO mice, develop alpha-synuclein immunoreactive protein aggregates that appear similar to the alpha-synuclein protein aggregates observed in postmortem PD brains, including PINK1-linked PD. To test our hypothesis, we used electrophysiological methods to record extracellular dendritic field excitatory postsynaptic potentials in acute coronal slices (400 μm) of dorsal hippocampus from PINK1 KO and wild-type littermate controls at four months of age. We measure input-output curves, paired-pulse ratio, and long-term potentiation to assess the efficacy of hippocampal synaptic transmission. This novel work in progress allows investigation of possible deficits in the hippocampus that could contribute to learning and memory problems. It also advances the characterization of PINK1 KO rats as a model of PD and can provide valuable

insight into the mechanisms by which PD-linked loss-of-function mutations in PINK1 cause NMS and neurodegeneration.

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Poster

653. Genetic Models of Parkinson's Disease

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 653.23/E11

Topic: C.03. Parkinson’s Disease

Title: Relevance of choice of brain region and time point of analysis after MPTP lesioning in wildtype mice

Authors: *J. KEHR[1], V. SCHIFFER[2], S. YOSHITAKE[1], T. LOEFFLER[2], V. NIEDERKOFLER[2], S. FLUNKERT[2], E. AUER[2], T. YOSHITAKE[3], B. HUTTER-PAIER[2]; [1]Pronexus Analytical AB, Stockholm, Sweden; [2]QPS Austria GmbH, Grambach, Austria; [3]Dept. of Physiol. and Pharmacol., Karolinska Institutet, Stockholm, Sweden

Abstract: Introduction: Parkinson's disease (PD) is a common neurodegenerative disorder which cardinal clinical features include tremor, slowness of movement, stiffness, and postural instability. These symptoms are primarily attributable to the degeneration of dopaminergic neurons in the substantia nigra pars compacta and the consequent loss of their projecting nerve fibers in the striatum. Mice treated with MPTP selectively loose significant numbers of nigrostriatal dopaminergic neurons. MPTP-induced dopaminergic cell loss in the substantia nigra mimics clinical conditions of PD and is therefore a useful preclinical model to test anti-parkinsonian drugs. To use this model for compound tests against PD, it is important to understand the progressive development of MPTP lesioning to choose the correct timing for analysis after the MPTP lesion. Method: C57Bl/6 mice were treated with a MPTP regime and analyzed for Dopamine (DA), DOPAC and HVA in the substantia nigra at various time points after the MPTP injection. Furthermore, animals were MPTP lesioned and the striatum was analyzed for the same biomarkers 4 days after the treatment. In the latter group of animals, 7-nitroindazole was used as a positive control. Results: Analyses of DA levels shortly after the MPTP lesioning resulted in increased DA levels in the substantia nigra at very early and later time points but decreased levels after 12 hours. Similar effects could be observed for DOVAC while HVA levels stayed almost constant. Evaluations in the striatum 4 day after MPTP lesioning showed severely reduced DA, DOPAC and also HVA levels that could partially be rescued by 7-nitroindazole treatment. Conclusion/ Summary: Our results show that it is of high importance to select the correct brain region and time point after MPTP lesioning for evaluation of different readouts.

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Poster

653. Genetic Models of Parkinson's Disease

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 653.24/E12

Topic: C.03. Parkinson's Disease

Support: NIH Grant R01NS082565
NIH Grant F99NS108458

Title: Increased glutamatergic transmission at the corticostriatal synapse of PINK1 KO rats

Authors: *R. B. CREED[1], C. B. FARMER[2], R. C. ROBERTS[2], L. L. MCMAHON[3], M. S. GOLDBERG[1];
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Abstract: Mutations in the PTEN induced kinase 1 (PINK1) gene cause autosomal recessive Parkinson's disease (PD). The main pathological hallmarks of PD are loss of dopamine neurons in the substantia nigra pars compacta and the formation of α-synuclein rich aggregates termed Lewy body inclusions. We and others have demonstrated that PINK1 knockout (KO) rats have mitochondrial dysfunction, locomotor deficits, and α-synuclein aggregates in different brain regions including the substantia nigra, striatum, and cortex. PINK1 is a mitochondrial targeted kinase involved in the clearance of damaged mitochondria. In neurons, mitochondria are prominently located in the pre-synaptic terminal, where they provide energy needed for vesicle movement and synaptic transmission. Additionally, α-synuclein is also important in synaptic vesicle movement and synaptic transmission. Given the importance of mitochondria to synaptic transmission, and the effect of PINK1 deficiency on mitochondrial health and α-synuclein aggregation, we sought to determine whether PINK1 KO rats have altered synaptic transmission. We hypothesize that PINK1 KO rats have changes in cortical excitatory neurotransmitter release onto spiny projection neurons (SPNs) of the dorsal striatum. Using whole cell patch clamp electrophysiology recordings from SPNs in acute striatal slices of WT and PINK1 KO rats at ages 2, 4, and 6 months, we observed an age-dependent increase in frequency spontaneous glutamatergic EPSCs onto SPNs. In addition, glutamatergic synapses on SPNs in PINK1 KO rats took longer to recover following depletion of the readily-releasable pool of synaptic vesicles with a 50 Hz train. These studies reveal that PINK1 is required for normal corticostriatal synaptic transmission. Ongoing studies will measure the extent to which the altered presynaptic release could be due to impairments in dopaminergic neurotransmission or due to impairments in

presynaptic mitochondrial buffering capacity. Furthermore, we will measure whether the impairments in synaptic recovery following depletion may be due to perturbations in synaptic vesicle distribution or alpha synuclein homeostasis.

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Poster

654. Animal Models of Ataxia

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 654.01/E13

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: NINDS Grant R01NS086778

Title: Ataxin-3 isoforms confer differential toxicity in *Drosophila melanogaster*

Authors: *J. R. BLOUNT, S. L. JOHNSON, K. LIBOHOVA, B. RANXHI, W.-L. TSOU, S. V. TODI;
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Abstract: The most commonly inherited dominant ataxia, Spinocerebellar Ataxia Type 3 (SCA3), is caused by a CAG repeat expansion that encodes an abnormally long polyglutamine (polyQ) repeat in the disease protein ataxin-3, a deubiquitinase. Two major, full-length isoforms of ataxin-3 exist, both of which contain the same N-terminal portion and polyQ repeat but differ in their C-termini; one (denoted here as isoform 1) contains a motif that binds ataxin-3's substrate, ubiquitin, whereas the other (denoted here as isoform 2) has a hydrophobic tail. Most SCA3 studies have focused on isoform 1, the predominant version in the brain, yet both forms are expressed and a better understanding of their relative pathogenicity is needed. We took advantage of the fruit fly *Drosophila melanogaster* to model SCA3 and examine the toxicity of each ataxin-3 isoform. Our *Drosophila*-based assays reveal isoform 1 to be markedly more toxic than isoform 2 in all fly tissues. Reduced toxicity from isoform 2 coincides with much lower protein levels as a result of expedited degradation. When isoform 2 protein levels are engineered to be comparable to isoform 1, isoform 2 is no less toxic. Additional studies indicate that isoform 1 is more aggregation-prone than isoform 2 and that the C-terminus of isoform 2 is critical for its enhanced proteasomal degradation. According to our results, although both full-length ataxin-3 isoforms are neurotoxic, isoform 1 is likely the primary contributor to SCA3 disease pathogenesis due to its expression at higher levels. Ongoing work focuses on the possibility that the hydrophobic tail of isoform 2 functions as a proteasome degradation signal, or degron, that may be applicable in the clearance of other proteins outside the context of SCA3. Overall, our

findings provide new insight into the biology of this ataxia and the cellular processing of the underlying disease protein.

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Poster

654. Animal Models of Ataxia

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 654.02/E14

Topic: C.04. Movement Disorders other than Parkinson's Disease

Title: Repeat associated non aug initiated translation as a disease factor in spinocerebellar ataxia type 3

Authors: *S. JOHNSON, K. LIBOHOVA, W.-L. TSOU, S. TODI;
Wayne State Univ., Detroit, MI

Abstract: Spinocerebellar Ataxia Type 3 (SCA3) is an age-related neurodegenerative disease and the most frequent dominant ataxia in the world. It is caused by anomalous expansion in the polyglutamine (polyQ) repeat domain of the deubiquitinase, ataxin-3. The full scope of SCA3's toxicity remains unclear and there are currently no effective treatments in the clinic. Our exploration into the pathogenesis of SCA3 takes a step back from the causative protein in SCA3, ataxin-3, and looks into the potential involvement of the mRNA produced from the *ATXN3* gene. mRNA may play a toxic role in polyQ-induced degeneration beyond encoding for the polyQ protein. One primary notion for mRNA-induced toxicity in polyQ and other repeat expansion disorders is the possibility of repeat-associated non-AUG (RAN)-initiated translation. RAN translation allows for translational initiation and elongation through a nucleotide repeat strand, in the absence of an AUG initiation codon and in multiple reading frames, resulting in the production of multiple homo-polymeric repeat-containing proteins. This type of translation not only opens the door to the possibility of translation of CAG repeats into toxic polyQ fragments, but also the translation of polyalanine and polyserine fragments in alternate reading frames. Here, we present new evidence from mammalian cell- and *Drosophila*-based models of SCA3 that utilize novel *ATXN3* transgenes to examine the role of mRNA toxicity and RAN translation in SCA3. We observe RAN translation from *ATXN3* constructs in mammalian cells, as well as increased toxicity from transgenes that allow for RAN translation in flies compared to counterparts that prevent RAN translation. Our ongoing work is delving into tissue specific and molecular mechanisms that underlie the possibility of RAN translation and mRNA toxicity in SCA3.

Disclosures: S. Johnson: None. **K. Libohova:** None. **W. Tsou:** None. **S. Todi:** None.

Poster

654. Animal Models of Ataxia

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 654.03/E15

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: VA Merit Award 5 I01 BX001000-06
Center for Genetics of Transport and Epithelial Biology
NIH grant CA100603
NIH grant CA-204345
Maryland Cigarette Restitution Fund

Title: Disruption of polyamine catabolism causes purkinje cell damage and severe ataxia

Authors: K. ZAHEDI[1,3], M. BROOKS[1], S. BARONE[1,3], N. RAHMATI[4], T. MURRAY-STEWART[5], C. DESTEFANO-SHIELDS[5], M. DUNWORTH[5], N. DASGUPTA[6], S. DAVIDSON[9], D. M. LINDQUIST[7], C. E. FULLER[8], R. D. SMITH[2], J. L. CLEVELAND[10,11], R. A. CASERO, Jr.[5], *M. SOLEIMANI[3,1];
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Abstract: Polyamines, spermidine and spermine, are important in cell function and proliferation. However, the biological significance of polyamine catabolism under normal physiological conditions remains unknown. Studies described here demonstrate that mice with global deletion of the two main polyamine catabolic enzymes, spermine-oxidase (SMOX) and spermidine/spermine-N^1-acetytransferase (SAT1), are normal at birth, but develop age-dependent progressive ataxia; whereas wild type, *Sat1*-KO or *Smox*-KO mice show no apparent neurological phenotypic abnormalities. The *Smox/Sat1*-double KO (dKO) mice only exhibit cerebellar pathology, with no abnormalities in any other tissues. Microscopic and magnetic resonance imaging studies reveal severe cerebellar atrophy, myelin damage, neurodegeneration and late-onset leukocytic infiltration. Comparison of polyamines in the cerebellum and cerebral cortex of Wt, *Smox*-KO, *Sat1*-KO, pre-ataxic and ataxic-dKO animals revealed that polyamine levels of pre-ataxic- and ataxic-dKO mice were significantly different from those of aged matched Wt and *Sat1*-KO mice. Analysis of cerebellar transcriptomes shows increased expression of transcripts for transglutaminases and proteins associated with microglia and

astrocyte activation and neurodegenerative response polarization. Significant reduction in the expression levels of transcripts coding for Purkinje cell proteins, including those associated with movement disorders were detected. The expression of the aforementioned transcripts was not affected in the cerebrum of dKO mice. Examination of the cerebellum of dKO mice revealed the onset of Purkinje cell loss and gliosis prior to the development of severe white matter demyelination, ataxia and leukocyte infiltration. The α-synuclein expression, aggregation and polyamination levels were also significantly increased, while the expression of myelin basic protein decreased in the cerebellum of dKO mice. Pharmacological inhibition of transglutaminases significantly reduced the severity of ataxia and cerebellar injury, highlighting their critical role in tissue injury in dKO mice. These results indicate that the disruption of polyamine catabolism causes Purkinje cell damage and gliosis. The latter changes will ultimately lead to white matter demyelination, ataxia and severe neuroinflammation. These studies further highlight the importance of the concerted role of transglutaminases and polyamines in the mediation of neuronal injury. We propose that the *Smox*/*Sat1* double KO mice will be a useful model to study the molecular and mechanistic basis of neurodegenerative, demyelinating diseases.

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Poster

654. Animal Models of Ataxia

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 654.04/E16

Topic: C.04. Movement Disorders other than Parkinson's Disease

Title: Activation of eIF2B for the treatment of vanishing white matter disease

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Abstract: Activation of an essential translation initiation factor, eIF2B, releases the global translational brake induced by the integrated stress response (ISR) and attenuates induction of transcriptional ISR targets. Partial loss-of-function mutations in eIF2B cause the rare neurodegenerative disorder Vanishing White Matter (VWM) Disease, which is characterized by

progressive deterioration of white matter in the central nervous system and consequent neurological deterioration, impaired motor function, and ultimately death. No treatments exist for this fatal leukodystrophy. In addition to VWM, a chronically activated ISR has been linked to neurodegeneration, oncology, and fibrosis. Thus, molecules that activate eIF2B have potential to treat pathologies characterized by prolonged and excessive induction of the ISR.
We have assessed pharmacology in a mouse model of VWM having a mutation in the eIF2B5 gene (e.g., R195H human/ R191H mouse) that causes the severe "Cree leukoencephalopathy." These R191H homozygous (HO) mutant mice provide a model that recapitulates many aspects of VWM disease, such as spontaneous myelin loss, progressive ataxia and motor skill deficits. Administration of the potent eIF2B activator, 2BAct, demonstrated robust efficacy in this VWM mutant mouse model (Wong et al. eLife 2019;8:e42940. DOI: https://doi.org/10.7554/eLife.42940). Here we present work of a 2BAct analog.
The eIF2B activator was given in diet to R191H HO mice starting around 21-24 weeks of age and continued until tissue collection. Behavior and neural imaging data was assessed longitudinally. Brains and spinal cord were collected around 34-37 weeks of age and were assessed for changes in motor behavior, ISR gene induction, histological markers, and MR imaging. Treatment with 30 mg/kg, but not 0.3 or 3 mg/kg of the eIF2B activator in R191H mice was associated with a reversal of motor impairments in inverted grid and balance beam assays. In the cerebellum and spinal cord, induction of ISR-associated gene expression (e.g. TRIB3, ATF3, eif4ebp1) and increased protein levels of ISR markers were dose-dependently attenuated in HO mice that received the eiF2B activator. In the corpus callosum, elevated MRI T2w ratio (a measure of inflammation) and protein levels of GFAP in HO mice were also significantly reduced in a dose-dependent manner. Findings from this study are consistent with earlier findings that eIF2B activators can reverse or attenuate various aspects of the disease pathology and motor impairments when given after appearance of behavioral symptoms *in vivo*.

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Poster

654. Animal Models of Ataxia

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 654.05/E17

Topic: C.04. Movement Disorders other than Parkinson's Disease

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Title: Cerebellar neurodegeneration and neuronal circuit remodeling in Golgi pH regulator-deficient mice

Authors: Y.-S. SOU[1], S. KAKUTA[2,3], Y. KAMIKUBO[4], K. NIISATO[4], T. SAKURAI[4], L. K. PARAJULI[1], I. TANIDA[1], H. SAITO[5], N. SUZUKI[5], K. SAKIMURA[6], Y. MAEDA[7], T. KINOSHITA[7], Y. UCHIYAMA[3], ***M. KOIKE**[1];
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Abstract: The Golgi apparatus plays an indispensable role in posttranslational modification and transport of proteins to their target destinations. Although it is well established that the Golgi apparatus requires an acidic luminal pH for optimal activity, morphological and functional abnormalities at the neuronal circuit level because of perturbations in Golgi pH are not fully understood. In addition, morphological alteration of the Golgi apparatus is associated with several neurodegenerative diseases, including Parkinson's disease, Alzheimer's disease and amyotrophic lateral sclerosis. Here, we used anatomical and electrophysiological approaches to characterize morphological and functional abnormalities of neuronal circuits in Golgi pH regulator conditional knockout mice. Purkinje cells (PCs) from the mutant mice exhibited vesiculation and fragmentation of the Golgi apparatus, followed by axonal degeneration and progressive cell loss. Morphological analysis provided evidence for the disruption of basket cell (BC) terminals around PC soma, and electrophysiological recordings showed selective loss of large amplitude responses, suggesting BC terminal disassembly. In addition, the innervation of mutant PCs was altered such that climbing fiber terminals abnormally synapsed on the somatic spines of mutant PCs in the mature cerebellum. The combined results describe an essential role for luminal acidification of the Golgi apparatus in maintaining proper neuronal morphology and neuronal circuitry.

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Poster

654. Animal Models of Ataxia

Location: Hall A

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Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: KAKENHI 19K07987
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Title: Knockdown of Rubicon, a negative regulator of autophagy, suppresses polyglutamine-induced toxicity in *Drosophila*

Authors: *M. OBA[1,2], Y. NAGAI[3], K. FUKUI[2], K. SANGO[1], M. SUZUKI[1];
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Abstract: Accumulation of pathogenic misfolding proteins is thought to be a common mechanism of neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease and polyglutamine (polyQ) diseases. The autophagy-lysosome degradation system may have therapeutic potential against these diseases, because it can degrade even large protein aggregates. In this study, we focused on Rubicon, a negative regulator of autophagy, and examined whether suppression of Rubicon shows beneficial effects on polyQ disease model. We employed *Drosophila* as a model animal, which is suitable for genetic analysis. RNAi-mediated knockdown of a *Drosophila* homolog of Rubicon (dRubicon) was induced either in a whole body or specifically in neurons. Autophagic activity was analyzed by using GFP-mCherry-Atg8a and it was confirmed that steady-state autophagosome and autolysosome pools are significantly increased in the brain of dRubicon knockdown flies. Then, we examined the effects of dRubicon knockdown on locomotor dysfunction and shortened lifespan of the flies expressing polyQ in neurons. Knockdown of dRubicon in neurons dramatically suppressed locomotor dysfunction and shortened lifespan of polyQ-expressing flies. Furthermore, dRubicon knockdown markedly reduced polyQ inclusion bodies in the brain, which is accompanied with no change in the polyQ mRNA level, suggesting that increased autophagic activity by dRubicon knockdown may lead misfolding polyQ proteins to be degraded. To further confirm the effect of dRubicon, we established transgenic fly lines either expressing wild-type (WT) dRubicon or dRubicon deleted for the RUN domain (delta RUN), which is known to be required for suppression of the class III phosphatidylinositol 3-kinase in mammalian cells. Overexpression of WT dRubicon in neurons exacerbated locomotor dysfunction and shortened lifespan of polyQ-expressing flies. However, on the contrary to our expectation, delta RUN dRubicon also exacerbated the phenotypes of the polyQ flies as well as the WT, suggesting that the RUN domain of dRubicon is indispensable for the suppression of autophagy in *Drosophila* neurons. Taken together, we demonstrate that the expression level of dRubicon is critical for the polyQ-induced toxicity in the fly model. Our study will provide basic insights into the possibility of Rubicon as a molecular target for treatment of misfolding protein-associated neurodegenerative diseases.

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Poster

654. Animal Models of Ataxia

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 654.07/E19

Topic: C.04. Movement Disorders other than Parkinson's Disease

Title: Neuromagnetic resting state functional connectivity in Friedreich ataxia

Authors: G. NAEIJE[1], V. WENS[1], M. SJOGARD[1], M. VAN DER GHINST[1], S. GOLDMAN[2], M. PANDOLFO[1], *X. DE TIÈGE[2];
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Abstract: Background: Friedreich ataxia (FRDA) is the commonest spinocerebellar ataxia in Caucasian. Over 95% of patients are homozygous for expanded GAA triplet repeats in the first intron of the frataxin (*FXN*) gene. Most residual FXN expression is from the chromosome with the shorter repeat (GAA1). GAA1 explains 30-50 % of the variability in age of symptoms onset but fails to predict clinical evolution or disability. Pathologically, cerebellar dentate nuclei are progressively atrophied in FRDA. Clinically, cerebellar dysfunction leads to ataxia symptoms and, through the cerebellar connections with multiple cortical areas, to reduced cognitive processing speed, lower performance in complex visuospatial tasksand altered executive functions. Here, we used magnetoencephalography (MEG) to assessif impaired functional resting state connectivity (rsFC) in FRDA reflected disease pathology and seek if rsFC could serve as neurophysiological marker for disease pathophysiology and evolution.Methods: Neuromagnetic signals were recorded at rest during 5 min in 18 right-handed FRDA patients (mean age 27 yrs, 9 females; mean SARA score: 21.4) and matched healthy individuals. The MEG connectome was estimated as rsFC matrices involving thirty-seven nodes from the six major resting-state networks and the cerebellum. Source-level rsFC maps were computed in a broad-band (3-40 Hz) frequency bands using leakage-corrected envelope correlations. Post-hoc median-split was used to contrast source-level rsFC maps based on clinical characteristics of FRDA patients. Non-parametric permutations and Pearson rank correlation test were used for statistics.Results: Increased functional connectivity was found in FRDA with later age of onset compared to healthy subjects. High correlation rank indexes were found between rsFC and age of symptoms onset in FRDAmainly across ventral attention network, default mode network and cerebellar network nodes, patients with higher rsFC developing symptoms at older age.No correlation was found between rsFC and other clinical parameters. Conclusion: Higher rsFC in FRDA, that correlates with age of symptoms onset, suggests compensatory mechanisms for widespread neuronal network dysfunction and position rsFC as potential marker of disease evolution in FRDA.

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Poster

654. Animal Models of Ataxia

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 654.08/E20

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: R21NS087343
Center of Excellence Grant to D.R.L.

Title: Identification of biphasic effects of frataxin deficiency on TID1 protein levels in Friedreich ataxia cellular models

Authors: Y. DONG, N. A. WARREN, E. MERCADO AYON, *D. R. LYNCH;
Univ. of Pennsylvania Perelman Sch. of Med., Philadelphia, PA

Abstract: Friedreich ataxia (FRDA) is the most common recessive inherited ataxia resulting from homozygous GAA repeat expansion in intron 1 of the *FXN* gene, which leads to the deficiency of frataxin. Frataxin is a mitochondrial protein crucial for iron-sulphur cluster biogenesis, but its precise cellular function is controversial. Using Co-Immunoprecipitation (Co-IP) combined with mass spectrometry, we identified tumorous imaginal disc 1 (TID1), a mitochondrial J-protein cochaperone critical for apoptotic signal transduction, as an interacting protein of frataxin both *in vivo* in mouse cortex and *in vitro* in mouse cortical neurons and human embryonic kidney (HEK) 293 cells. The interaction between frataxin and TID1 was confirmed by both Co-IP and GST pulldown assays. Acute depletion of frataxin using RNA interference markedly increases TID1 protein levels in human skin fibroblasts. Similar results were also observed in cerebellar homogenates from doxycycline-inducible frataxin knockdown mice. In contrast, chronic frataxin deficiency decreases TID1 protein levels in multiple cell types from FRDA patients including skin fibroblasts, buccal cells, platelets and peripheral blood mononuclear cells. Our results show biphasic effects of frataxin deficiency on TID1 protein levels and suggest that TID1 might function as a downstream signaling molecule for frataxin and contribute to the pathogenesis of FRDA. The precise role of TID1 in FRDA remains to be examined.

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Poster

654. Animal Models of Ataxia

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 654.09/E21

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: MSU-Mankato, Department of Biological Sciences

Title: The novel protein FAM171B is recruited into intracellular polyQ aggregates

Authors: J. KIRLIN, *G. M. GOELLNER;
Minnesota State Univ., Mankato, MN

Abstract: Expansion mutation within polyglutamine (polyQ) tract proteins is known to underlie a number of severe neurodegenerative disorders such as Huntington's Disease and Spinocerebellar Ataxia. One of the pathologic hallmarks of polyQ expansion disease is the aggregation of mutant proteins into intracellular inclusion bodies. Our lab is actively investigating FAM171B- a relatively uncharacterized protein that also contains a stretch of consecutive glutamines within its primary amino acid sequence and is likely expressed in the nervous system. Since it too contains a short polyQ stretch, we surmised that FAM171B may also be recruited into polyQ aggregates formed by known pathologic proteins. To test this hypothesis, we transfected cells with an expanded version of SCA7-GFP to form intracellular aggregates, and utilized FAM171B specific antibodies, immunofluorescence, and confocal microscopy to assay FAM171B's intracellular location in relation to the SCA7 inclusion bodies. Our findings indicate that a portion of FAM171B does indeed alter its normally dispersed cytoplasmic subcellular distribution into SCA7 aggregates that locate near the peri-nuclear region of human glioblastoma tissue culture cells. Thus, the novel protein FAM171B may play a role in the molecular mechanisms underlying polyQ disease pathology.

Disclosures: J. Kirlin: None. **G.M. Goellner:** None.

Poster

654. Animal Models of Ataxia

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 654.10/E22

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: NIH Grant K01HD088762
2015 NFXF Summer Fellowship Award

Title: Inertial sensor-based tremor and bradykinesia quantification and potential for early disease identification in fragile X-associated tremor/ataxia syndrome (FXTAS)

Authors: *D. BANG[1], J. M. JOYCE[1], B. OUYANG[1], Y. LIU[1], E. ROBERTSON[1], D. A. HALL[2], J. A. O'KEEFE[1];
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Abstract: FXTAS is a neurodegenerative disorder characterized by tremor and cerebellar gait ataxia. It occurs in some carriers of a 55-200 CGG repeat size premutation in the *fragile X mental retardation 1* gene. However, early predictors of FXTAS onset are needed and quantitative measurements of tremor, bradykinesia and coordination may be useful in natural history studies, response to medications and as outcome measures in future clinical trials. The objective of our work was to quantify the severity of upper extremity (UE) tremor subtypes, bradykinesia and incoordination in FXTAS and potentially identify preclinical symptoms in premutation carriers (PMC) without a diagnosis of FXTAS using an inertial sensor system. 39 PMC with FXTAS (Mean age = 67.8$\pm$ 8.5), 20 PMC without FXTAS (Mean age = 53.5 $\pm$ 10.6), and 27 healthy controls (Mean age = 65.4 $\pm$ 9.1) performed a series of UE motor tasks while wearing an *ETsense*™ sensor with the *Kinesia One* system which quantifies several types of tremor, bradykinesia and rapid alternating movements. Regression analyses controlling for age, sex and CGG repeat size with FXTAS diagnosis group as the main predictor was performed to detect potential group differences. The FXTAS Rating scale (FXTAS-RS) was administered to determine whether these clinician-rated scores correlate with severity scores from the *Kinesia* system.We found that PMC with FXTAS had significantly worse postural and kinetic tremor compared to PMC without FXTAS (p=0.04; 0.03) and controls (p=0.001; 0.0001), respectively, and worse finger tap (p=0.0009), hand movement (p=0.0001) and rapid alternating movement speed (p=0.003) and amplitude (p=0.04) than controls. PMC without FXTAS had significantly worse finger tap (p=0.004), hand movement (p=0.01) and rapid alternating movement speed (p=0.003) and amplitude (p=0.02) than controls. All quantitative scores were significantly correlated with the FXTAS-RS scores (p=0.02 to < 0.0001) except for finger tap speed and amplitude. The *ETSense*™ system is a feasible, portable and low-cost method for quantifying UE tremor, bradykinesia and dysdiadokinesia in FXTAS and may have potential in detecting preclinical symptoms of UE speed and coordination deficits in PMC without FXTAS. Further validation of these measures and confirmation of preclinical disease identification in longitudinal studies with higher subject numbers is needed.
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Poster

654. Animal Models of Ataxia

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 654.11/E23

Topic: C.04. Movement Disorders other than Parkinson's Disease

Title: Blocking ran translation enhances FMRP and reduces toxicity in unmethylated full mutation fragile X stem cells

Authors: *S. E. WRIGHT[1], C. RODRIGUEZ[1], J. HAENFLER[1], F. RIGO[4], M. A. SUTTON[2], S. BARMADA[5], J. M. PARENT[1], P. K. TODD[3];
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Abstract: Expansion of a CGG repeat in the 5' UTR of the FMR1 gene underlies a heterogeneous set of human clinical disorders, including Fragile X Syndrome and Fragile X-Associated Tremor/Ataxia Syndrome. While full mutations (>200 repeat expansions) result in FXS typically lead to methylation and silencing of FMR1 expression, patients often display mosaicism of FMR1 methylation and CGG repeat length in individual cells. Large transcribed CGG repeats are potentially toxic as RNA or by triggering Repeat associated non-AUG initiated translation (CGG RAN). Moreover, large repeats can impede translation of FMRP even when transcription is sufficient. Therefore, effective therapies targeting large transcribed repeats will simultaneously block CGG RAN and enhance production of FMRP. To this end, our group developed a series of antisense oligonucleotides that selectively target RAN initiation sites (RAN ASOs) on the FMR1 transcript. Using patient-derived induced pluripotent stem cells (iPSCs) from an unmethylated full mutation (UFM) carrier, we generated human neurons that exhibit normal FMR1 mRNA transcription but very low FMRP expression. Application of RAN ASOs on these neurons effectively reduced accumulation of CGG RAN products and enhanced neuronal FMRP expression, suggesting that CGG RAN acts normally to inhibit FMRP synthesis. These biochemical corrections were associated with enhanced UFM neuronal survival. Blocking endogenous CGG RAN also altered activity dependent FMRP synthesis in response to mGluR5 stimulation, a critical regulatory component of long-term depression. Together, these data suggest a native function for CGG RAN in regulating FMRP synthesis and demonstrate that targeting CGG RAN has the potential to correct multiple disease relevant features in Fragile X-associated disorders.

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Poster

654. Animal Models of Ataxia

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 654.12/E24

Topic: C.04. Movement Disorders other than Parkinson's Disease

Title: Assessing benefits of antisense oligonucleotide therapy in a pre-symptomatic mouse model of spinocerebellar ataxia type 3

Authors: *A. J. ZALON[1], K. C. O'DONNELL[1], H. L. PAULSON[3], H. S. MCLOUGHLIN[2]; [2]Neurol., [1]Univ. of Michigan, Ann Arbor, MI; [3]Prof, Neurol, Univ. of Michigan Dept. of Neurol., Ann Arbor, MI

Abstract: Of the dominantly inherited ataxias, spinocerebellar ataxia type 3 (SCA3) is the most common. This polyglutamine repeat expansion disorder is characterized by progressive cerebellar ataxia and to date has no cure. Knockout of the disease-causing ATXN3 gene produces no overt phenotype in mice suggesting that SCA3 is a promising target for gene suppression therapies. Utilizing a well characterized SCA3 mouse model that expresses the full-length mutant ATXN3 (Q84) gene, we recently assessed proof-of-concept studies via CNS delivery of antisense oligonucleotides (ASOs) targeting mutant ATXN3 into an adult post-symptomatic mouse. In our recent reports, we determined anti-ATXN3 ASOs are therapeutically efficacious at reducing SCA3 disease protein levels and neuropathology. Additionally, a longitudinal ASO treatment beginning at 8 weeks of age in SCA3 Q84 mice was sufficient to rescue motor impairments, a result reported for the first time in this mouse model. One important aspect of the longitudinal ASO trial is that SCA3 mice did not show a recovery in weight overtime. Differences in weight between SCA3 and wild-type mice are not well understood. We asked the question, if peripheral SCA3 phenotypes, such as weight loss, are secondary to neuronal dysfunction in the CNS. We surmised that pre-symptomatic sustained delivery of anti-ATXN3 ASOs to the CNS may protect against secondary peripheral effects. Successful weight restoration of SCA3 mice treated pre-symptomatically will show that weight loss typical of SCA3 mice may be linked to primary CNS dysfunction.

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Poster

654. Animal Models of Ataxia

Location: Hall A

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Program #/Poster #: 654.13/E25

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: NS 094946
T32HD043730

Title: Movement initiation and motor output error in SCA6

Authors: *S. DELMAS[1], A. CASAMENTO-MORAN[1], B. YACOBI[1], S. SUBRAMONY[2], D. E. VAILLANCOURT[1,2], E. A. CHRISTOU[1];
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Abstract: Spinocerebellar Ataxia Type 6 (SCA6) is an autosomal-dominant neurodegenerative disease resulting in almost pure cerebellar degeneration. A major role of the cerebellum is the integration of sensory consequences of movement (efference copy) with sensory feedback to adjust the motor command and improve motor performance. The current hypothesis is that, due to the degeneration of the cerebellum, SCA patients rely on feedback mechanisms such as visual feedback and react to visual stimuli rather than relying on the sensory prediction for movement control. The purpose of this study was to determine whether SCA6 use a different strategy to initiate a movement relative to healthy controls. Fourteen healthy controls and seventeen individuals diagnosed with SCA6 performed 15 trials of an isometric ankle dorsiflexion constant task and traced a target with their force outcome. The target consisted of 4s of rest, followed by increasing force and matching a 1.5s ramp at a rate of 10%MVC/s, and maintaining force for 20 s at 15% MVC. We quantified the initiation of force, as the first time point where the force trace was greater than 0.075% MVC. Force initiation was significantly different for healthy controls and SCA6 ($p = 0.01$). Specifically, healthy controls initiated their force ~100 ms before the targeted ramp, whereas SCA6 initiated their force ~100 ms after the targeted ramp. The adaptation across the fifteen trials, quantified as the change from the first to the last 3 trials, was similar for the two groups. SCA6 also exhibited greater error than healthy controls in matching the first 150 ms of the ramp ($p<0.05$; 27.5±6.5 vs. 13.6±2.5). Finally, the time of force initiation correlated with the ramp rate error during the first 150 ms ($R^2=0.25$; $p<0.01$) indicating that ramp error was greater with delayed force initiation. These findings suggest that SCA6 use a different strategy to match the ramp force than healthy adults. Specifically, SCA6 appear to use a reactive feedback strategy, whereas healthy controls use a predictive strategy for performing the movement. The reactive feedback strategy used by SCA6 relates to movement errors during the feedforward part of the contraction, further suggesting an impaired motor command.

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Poster

654. Animal Models of Ataxia

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 654.14/E26

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: Vivian F. Giangiardi has scholarship granted by CAPES (Coordination for the Improvement of Higher Education Personnel).

Title: Factors associated with functional mobility and falls of individuals with hereditary degenerative cerebellar diseases

Authors: *V. F. GIANGIARDI, M. PERRACINI, M. SILVA, G. B. R. SETTI, M. VEGAS, S. ALOUCHE;
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Abstract: Introduction: The dysfunctions related to hereditary degenerative cerebellar diseases (HDCD) cause substantial limitation to functional mobility and negative impact on individual independence. However, the increased impairment and limitations that follow the progression of HDCD are not well characterized. Furthermore, which signs can predict the loss of mobility and the risk of falls in these individuals are not known. The understanding of these outcomes may facilitate the comprehension of functional prognosis and may help to guide rehabilitation interventions, promoting the independence of individuals with HDCD. **Objectives:** The present study aimed to characterize the factors associated with functional mobility and falls in individuals with HDCD. **Methods:** Individuals with spinocerebellar ataxia diagnosis were categorized into different ranges of impairments of using the Scale for the Assessment and Rating of Ataxia (SARA). Aspects of the body function, activity, and participation were also assessed. Linear regressions models were conducted to investigate the main predictors of functional mobility and falls in individuals with HDCD. For functional mobility, individuals were assigned into three groups according to their mobility status: independent, walking with assistant devices and restricted to wheelchair. Regarding falls, individuals were divided into two groups characterized by the number of falls in the last year: fallers and non-fallers. Groups comparisons were conducted using One-way ANOVA. **Results:** The BEST-test is the main outcome measure that explains the loss of mobility in individuals with HDCD ($\beta_0 = 3{,}34$, $\beta_1 = -.030$; CI 95% - .035, - .024). Of all BEST-test items, only the limit of stability was not different among the independent group and the walking with assistant devices group ($p = 0{,}184$), and among the wheelchair group and the walking with assistant devices group ($p = 0{,}161$). Regarding falls, SARA is the outcome measure most associated with the history of falling. **Conclusion:**

Balance and the severity of ataxia are respectively associated to functional mobility and falls in individual with HDCD and should be carefully assessed. Future longitudinal studies may be conducted to identify what are the main predictors that compromise these outcomes over the progression of the disease.

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Poster

654. Animal Models of Ataxia

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 654.15/E27

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: JSPS Grant 18K07503

Title: Ataxic phenotype with altered Cav3.1 channel property in a mouse model for spinocerebellar ataxia 42

Authors: *H. DOI[1], S. HASHIGUCHI[1], M. KUNII[1], Y. NAKAMURA[2], M. SHIMUTA[2], E. SUZUKI[2], M. OKUBO[1], T. SASAOKA[3], H. TAKEUCHI[1], T. ISHIKAWA[2], F. TANAKA[1]; [1]Dept. of Neurol. and Stroke Med., Yokohama City Univ. Sch. of Med., Yokohama-shi, Japan; [2]Dept. of Pharmacol., The Jikei Univ. Sch. of Med., Tokyo, Japan; [3]Brain Res. Institute, Niigata Univ., Niigata,, Japan

Abstract: Spinocerebellar ataxia 42 (SCA42) is a neurodegenerative disorder recently shown to be caused by c.5144G>A (p.Arg1715His) mutation in *CACNA1G*, which encodes the T-type voltage-gated calcium channel Cav3.1. To determine whether this mutation causes ataxic symptoms and neurodegeneration, we generated knock-in mice harboring c.5168G>A (p.Arg1723His) mutation in *Cacna1g*, corresponding to the mutation identified in the SCA42 family. Both heterozygous and homozygous mutants developed an ataxic phenotype from the age of 11 weeks and showed loss of Purkinje cells at 50 weeks old. Degenerative change of residual Purkinje cells and atrophic thinning of the molecular layer were conspicuous in homozygous knock-in mice. Electrophysiological analysis of Purkinje cells using acute cerebellar slices from young mice showed that the point mutation altered the voltage dependence of Cav3.1 channel activation and reduced the rebound action potentials after hyperpolarization, although it did not significantly affect the basic properties of synaptic transmission onto Purkinje cells. Finally, we revealed that the resonance of membrane potential of neurons in the inferior olivary nucleus was decreased in knock-in mice, which indicates that p.Arg1723His Cav3.1 mutation affects climbing fiber signaling to Purkinje cells. Altogether, our study not only shows that a point mutation in *CACNA1G* causes an ataxic phenotype and Purkinje cell degeneration in

a mouse model, but also reveals that the electrophysiological abnormalities at an early stage of SCA42 precede the loss of Purkinje cells.

Disclosures: S. Hashiguchi: None. **H. Doi:** None. **M. Kunii:** None. **Y. Nakamura:** None. **M. Shimuta:** None. **E. Suzuki:** None. **M. Okubo:** None. **T. Sasaoka:** None. **H. Takeuchi:** None. **T. Ishikawa:** None. **F. Tanaka:** None.

Poster

654. Animal Models of Ataxia

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 654.16/E28

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: European Community's Seventh Framework Programme (FP7/2007-2013) 2012-305121
DLR 01ED1507 NeuroGem

Title: New knock in mouse models with hyper-expansion of the murine polyQ tract show massive progressive aggregate formation and moderate motor phenotype

Authors: E. HAAS, R. INCEBACAK, Y. MARINGER, N. CASADEI, T. HENTRICH, J. SCHULZE-HENTRICH, T. SCHMIDT, *O. RIESS, J. HUEBENER-SCHMID;
Inst. for Med. Genet. and Applied Genomics, Univ. of Tuebingen, Tuebingen, Germany

Abstract: Spinocerebellar ataxia type 3 (SCA3) is the most common dominantly inherited ataxia worldwide. Though the disease causing mutation in the ATAXIN-3 gene is long known, there is no cure available and symptoms can only be treated with limited success. Mouse models available for the disease do not represent the situation in a satisfactory way as most of them are transgenic and therefore simulate the disease under quite artificial conditions. In the few existing knock in (KI) models the polyglutamine (polyQ) tract is expanded within a similar length as in human patients. This seems not to be efficient to trigger a disease-relevant phenotype in mice. To overcome this obstacle, we generated three new KI mouse lines by zinc-finger-technology, one with a polyQ tract of 97Q, comparable to the length found in human patients, and two lines with a hyper-expansion of the polyQ tract containing 305 or 326 glutamines in the murine ataxin-3 protein. These mice were either heterozygous (WT/97, WT/326Q, WT/305Q) or homozygous (305Q/305Q) for the expanded murine ataxin-3 protein and were characterized over 18 months using molecular biological, histological, behavioral and RNA sequencing methods. In all lines we could show the expression of the expanded ataxin-3 in brain and peripheral organ tissue and in the lines with hyper-expansion observed massive aggregate formation starting with 3 month of age and rapidly progressing over time. Brain regions especially affected in these two models are the deep cerebellar nuclei, the pons (both associated with SCA3 pathology) and the

hippocampus. Further, we observed reduction in body weight and size accompanied by massive hunchback formation in the hyper-expanded lines but not so for the line expressing 97Q in the ataxin-3 protein. These changes led to gait and posturing abnormalities comparable to those seen in SCA3 patients and abnormal anxiety behavior in these mice. Moreover, RNA sequencing of cerebellar tissue of symptomatic and pre-symptomatic 305Q/305Q mice revealed 400 differentially expressed genes affected in symptomatic animals. Interestingly, eight of these genes were already affected in the pre-symptomatic stage, indicating mis-regulation of gene expression before aggregate manifestation. Taken all our data together we state that 97Q in the ataxin-3 protein is not enough to trigger a phenotype in mice and that our hyper-expanded KI lines are great models for SCA3 as it allows following the progression of the disease over time. This makes them ideal for testing treatment options like drug delivery or external stimuli (e.g. enriched environment, stress, etc.) and their effect on aggregate formation and motor phenotype development.

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Poster

654. Animal Models of Ataxia

Location: Hall A

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Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: National Ataxia Foundation (Young Investigator Award)
Faculty of Medicine Tuebingen (Forschungsorientierte Gleichstellungsförderung)

Title: Analyzing the ubiquitin-proteasome system in SCA3 *in vivo*

Authors: J. SCHMIDT[1,2,3], A. GRUN[1,2,3], M. PRADELA[1,2,3], O. RIESS[1,2,3], ***T. SCHMIDT**[1,2,3]; [1]Med. Genetics, Univ. of Tuebingen, Tuebingen, Germany; [2]Ctr. for Rare Dis. ("ZSE"), Univ. Hosp. Tuebingen, Tuebingen, Germany; [3]NGS Competence Ctr. Tuebingen (NCCT), Tuebingen, Germany

Abstract: Spinocerebellar ataxia type 3 (SCA3) or Machado-Joseph disease (MJD) is an inherited neurodegenerative disorder caused by the expansion of a CAG repeat within the *ATXN3* gene resulting in an expanded polyglutamine repeat in the encoded protein ataxin-3. SCA3/MJD therefore belongs to the group of polyglutamine diseases. Up to now, no treatment is available for this disease. One hallmark of this and other neurodegenerative diseases is the formation of inclusion bodies (protein aggregates) in the brain. Ataxin-3 is a deubiquitinating enzyme and involved in the degradation of proteins via the ubiquitin-proteasome system by

editing ubiquitin chains. Ubiquitin chains can be assembled by the attachment of ubiquitins to different lysine residues. Ubiquitins linked via lysin 48 (K48) represent the main signal for proteasomal degradation. In order to further study the role of ubiquitination in SCA3, we crossed one of our previously generated mouse models for SCA3 with mice transgenic for mutated ubiquitin (K48R mice). The mutation in K48R mice (Lysine at position 48 is replaced by Arginine) leads to premature termination of K48 poly-ubiquitin chain assembly, hence to the formation of higher amounts of short K48-linked ubiquitin chains. We used RotaRod and CatWalk tests to measure the motor-coordinative abilities and observed that transgenic SCA3 mice which simultaneously express the mutant ubiquitin transgene (MJD/K48R) showed an alleviated motor phenotype compared to single transgenic SCA3 mice. To investigate the cause of these improved motor abilities in detail we performed immunoprecipitation and Western blot analyses. Aggregate load was checked via filter trap and immunohistochemistry. We further characterized the proteasomal activity and distribution of proteasomal subunits using immunohistochemistry. We hypothesize that the presence of higher amounts of short K48-linked ubiquitin chains leads to a higher proteasomal turnover of the expanded transgenic ataxin-3 protein resulting in the alleviated phenotype in MJD/K48R mice. We aim to further explore the feasibility to translate this approach into a therapeutic strategy.

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Poster

654. Animal Models of Ataxia

Location: Hall A

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Topic: C.04. Movement Disorders other than Parkinson's Disease

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Richard Chin and Lily Lock Machado-Joseph Disease Research Fund

Title: Blood-brain barrier dysfunction in spinocerebellar ataxia type 3 (Machado-Joseph disease): Results from mouse and human brain tissues

Authors: *R. J. NOBRE[1,2,3,4], D. LOBO[1,4,2], C. O. MIRANDA[1,2,4], D. PEREIRA[1,2,4], J. CASTELHANO[5], J. SERENO[5], M. CASTELO-BRANCO[5,6], L. PEREIRA DE ALMEIDA[1,3,4,7]; [1]Ctr. For Neurosci. and Cell Biol. (CNC), Coimbra, Portugal; [2]Inst. for Interdisciplinary Res. (III), Coimbra, Portugal; [3]Viravector - Viral Vector for Gene Transfer Core facility, Coimbra, Portugal; [4]Ctr. for Innovative Biomedicine and Biotech. (CIBB), Coimbra, Portugal; [5]Inst. of Nuclear Sci. Applied to Hlth. (ICNAS), Coimbra, Portugal; [6]Coimbra Inst. for Clin. and Biomed. Res. (iCBR), Coimbra, Portugal; [7]Fac. of Pharm. (University of Coimbra), Coimbra, Portugal

Abstract: Blood-brain barrier (BBB) disruption is a shared feature for several neurodegenerative diseases, such as Alzheimer's and Huntington's. Impairments in the assembly of tight junctions (TJ) between adjacent brain endothelial cells along with neuroinflammation have been reported to contribute to BBB dysfunction. However, in spinocerebellar ataxias such as Machado-Joseph Disease (MJD), BBB integrity has not been assessed. In this disorder, an expansion of CAG repeats in the *MJD1* gene that codifies for mutant ataxin-3 results in neurodegeneration and further progressive cerebellar ataxia. Accordingly, the aim of this work was to evaluate the BBB integrity in MJD, by analyzing a transgenic mouse model and human *post-mortem* brain tissues. In order to assess BBB permeability in MJD transgenic mice, Evans blue (EB) was intravenously injected and quantified in the brain by spectrophotometry. Additionally, immunofluorescence against fibrinogen and quantification of its extravasation across BBB was performed. Mechanisms involved in BBB disruption were explored by analyzing: i) the presence of mutant ataxin-3 aggregates in brain blood vessels and ii) the levels of TJ proteins in mice cerebella by Western blot. Brain vascular permeability was also evaluated in live animals by Dynamic Contrast Enhanced-Magnetic Resonance Imaging (DCE-MRI).
Regarding EB concentration in the cerebella of MJD mice, we observed a 5-fold increase in comparison to wild-type mice. Likewise, fibrin extravasation and DCE-MRI corroborated a higher vascular permeability in the cerebella of transgenic mice. Interestingly, mutant ataxin-3 aggregates, the hallmark of MJD, were found in brain blood vessels, which also indicated occludin fragmentation and redistribution of Claudin-5. Concerning human brain tissues, immunofluorescence images suggest a higher fibrinogen extravasation across BBB in MJD tissues when compared to the control group, as well as the presence of ataxin-3 aggregates in brain blood vessels, supporting the evidences found in the transgenic mouse model.
In conclusion, the present work reports for the first time BBB alterations in a transgenic mouse model of MJD and in *post-mortem* brain tissues of MJD patients.

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Poster

654. Animal Models of Ataxia

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 654.19/E31

Topic: C.04. Movement Disorders other than Parkinson's Disease

Title: Characterization of molecular and clinical phenotypes in a rat model for Griscelli syndrome type 1

Authors: *D. R. MICHAUD[1], P. P. NGHIEM[1], G. STOICA[2], R. SRINIVASAN[3], S. MATA LOPEZ[1], C. BALOG-ALVAREZ[1];
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Abstract: Background. Griscelli Syndrome (GS) type 1 is an ultra-rare, autosomal recessive disease caused by a mutation in the *Myosin-Va* gene, leading to a loss of respective protein expression and altered vesicle and membrane trafficking (Çağdaş et al., 2012). Myosin-Va (MYOVA) is an unconventional motor protein that is essential for transporting mRNA (McCaffrey & Lindsay, 2012; Salerno et al., 2008) and mRNPs (Yoshimura et al., 2006), smooth endoplasmic reticulum (Wagner, Brenowitz, & Hammer Iii, 2010), secretory granules (Eichler, Kögel, Bukoreshtliev, & Gerdes, 2006), and other proteins in the neuron to dendritic spines. Due to the loss of intracellular neuronal transportation, patients with type 1 GS exhibit severe neurological deficits such as developmental delays, intellectual disabilities, seizures, and motor impairment, as well as hypopigmentation of the hair and skin. We have a line of rats that spontaneously exhibited a point mutation in a donor splice site early in the *MyoVa* gene, which leads to a premature stop codon and the subsequent loss of MYOVA protein expression and function (Landrock et al., 2018). These affected rats are an ideal model for GS type 1 that show the characteristic dilute hair color, loss of dopaminergic neurons, muscle weakness, seizures, and a shortened life-span that is observed in Griscelli patients (Landrock et al., 2018; Stoica et al., 2012). Hypothesis. We hypothesize that the affected rats exhibit abnormal molecular mechanisms related to decreased resistance to neuronal oxidative stress compared to wildtype littermates, as well as impaired motor function. Methods. Naïve wildtype, heterozygous or homozygous (mutant) rats will be measured for weight and grip strength for up to 30 days of age. Brain and muscle tissue will be harvested and analyzed for RNA, protein, and morphological differences using qPCR, western blots, and immunofluorescent microscopy. Results. We have found significant evidence that the affected and heterozygous rats exhibit higher levels of susceptibility to oxidative stress compared to their wildtype littermates by measuring sensors of oxidative stress such as Park7. Furthermore, we have shown significant clinical loss of muscle function in the affected rats compared to wildtype, and have evidence of histological abnormalities in muscle tissue in the affected rats. Future work. We will continue to assess the role of oxidative stress in this model rat model of Griscelli syndrome type 1, and will explore the changes in mitochondrial function in the affected and carrier rats.

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Poster

654. Animal Models of Ataxia

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 654.20/E32

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: F31NS105406
R01NS050808

Title: Cerebellar dysfunction in spinocerebellar ataxia type 3

Authors: *K. PALARZ[1], A. CARVALHO[2], P. E. MACIEL[2], K. KHODAKHAH[3];
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Abstract: Ataxia (uncoordinated movement) is a debilitating disorder that interferes with a patients' ability to perform activities of daily living. Ataxia is often caused by dysfunction of the cerebellum, a brain area involved in motor coordination and maintenance of balance. Spinocerebellar ataxia type 3 (SCA3) is the most common dominantly inherited ataxia, caused by a trinucleotide CAG repeat expansion of the ATXN3 gene. A mouse model of SCA3, CMVMJD135, recapitulates the progressive, adult onset phenotype seen in humans. However, it is still not clear if and how cerebellar dysfunction is contributing to disease in this SCA3 mouse model. This project seeks to elucidate potential cerebellar abnormalities in SCA3 through behavioral, electrophysiological, and proteomic analysis of the cerebellum in the CMVMJD135 SCA3 mouse model.
As assessed by the parallel rod floor test and using the disability scale, SCA3 mice have a progressive ataxic motor phenotype from 12-60 weeks of age. It has previously been shown that regularity of the cerebellar output nuclei can predict disability in several mouse models of ataxia. With *in vivo* single unit recordings, we demonstrate that the firing of cerebellar nuclei neurons and the Purkinje cells (the principle neuron of the cerebellar cortex) is irregular at 12, 34, and 60 weeks of age in the SCA3 mice. To determine if abnormal intrinsic pacemaking of Purkinje cells contribute to the irregular firing seen *in vivo*, as noted in a number of mouse models of ataxia, we performed extracellular recordings from Purkinje cells in acutely prepared cerebellar slice from 34 week old mice. Consistent with a contribution of abnormal pacemaking to the irregular firing of Purkinje cells *in vivo*, we found that with fast synaptic transmission blocked the activity of mutant Purkinje cells was irregular. Our data suggests that defects both in intrinsic pacemaking and in synaptic transmission may contribute to cerebellar dysfunction in SCA3. To help identify the potential molecular and signal transduction pathways that might be defective in the cerebellum of SCA3 mice, we performed a quantitative proteomic analysis on cerebellar lysates from mutant mice and littermates. This approach has identified a number of signaling pathways

that warrant further scrutiny. Taken together, these data implicate the cerebellum in the pathogenesis of SCA3, and provide a path for future work aimed at identifying the potential mechanisms that contribute to cerebellar dysfunction.

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Poster

654. Animal Models of Ataxia

Location: Hall A

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Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: NIH Grant R01NS050808
NINDS 5F31 NS090725-04

Title: Elucidating the mechanism underlying stress and caffeine induced attacks in episodic ataxia type 2

Authors: *H. D. SNELL[1], A. VITENZON[2], E. TARA[1], K. KHODAKHAH[3];
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Abstract: Episodic ataxia type 2 (EA2) is a disorder that arises from loss of function mutations in the *CACNA1A* gene which encodes for the P/Q-type voltage-gated calcium channels. These mutations cause a decrease in the calcium current density through the P/Q type calcium channels. In this disorder, a mild baseline ataxia is interrupted by attacks of severe motor dysfunction that are triggered by physical or emotional stress, or consumption of caffeine or alcohol. Previous work using the *tottering* mouse, a model of EA2, showed that Purkinje cell (PC) firing in these mice becomes markedly more erratic during attacks triggered by the stressors. Stress, and caffeine induce attacks by increasing PC irregularity via activation of the α1 adrenergic, and inhibition of the adenosine 1 (A1) receptors, respectively. Both receptors have been shown to modulate the activity of mGluR1-mediated signaling: α1 adrenergic activation, and A1 receptor inhibition, increase mGluR1 activity. **We hypothesized that stress and caffeine might induce attacks in the *tottering* mice by increasing mGluR1 activity.** *In vivo*, caffeine- and stress-induced attacks were blocked by systemic, or intra-cerebellar infusion of an mGluR1 antagonist. Additionally, we found that systemic injection of a positive allosteric modulator (PAM) of mGluR1 receptors was sufficient to induce attacks in the *tottering* mouse. To better understand the mechanism by which these stressors induce attacks, we recorded the activity of PCs in acutely prepared cerebellar slices from *tottering* and wild type (WT) mice. Caffeine and norepinephrine (NE) increased the irregularity of PC activity in cerebellar slices. Similar to the *in vivo* studies, caffeine and NE-induced irregularity was blocked by pre-application of an

mGluR1 receptor antagonist, suggesting involvement of mGluR1 mediated signaling. Acute application of a α1 adrenergic receptor agonist did not induce irregularity of firing of PC in WT or *tottering* mice slices. To test basal mGluR1 activity, we acutely applied an mGluR1 PAM. This caused a significant increase in PC irregularity in WT, but not in *tottering* slices. Co-application of both α1 adrenergic agonist and mGluR1 PAM induced PC irregularity in *tottering* mice, but not WT mice slices. Taken together these data suggest stress-induced increases of NE in the cerebellum affect PC activity through activation of α1 adrenergic receptors, and indirect activation of mGluR1s. Caffeine, through the block of A1 receptors, indirectly activates mGluR1s on PCs. This data highlights the usefulness of α1 adrenergic receptor blockers, A1 adenosine receptor agonists, and mGluR1 blockers as potential therapeutic agents for EA2.

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Poster

654. Animal Models of Ataxia

Location: Hall A

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Program #/Poster #: 654.22/E34

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: NIH/NINDS Grant 2R37NS027699
HHMI Support

Title: Exploring drivers of regional vulnerability in spinocerebellar ataxia type 1 reveals diverse functions of ataxin-1 and the mechanisms underlying neurodegeneration

Authors: *C. J. ADAMSKI[1], V. GENNARINO[2], E. CRAIGEN[2], A. DE MAIO[2], H. YALAMANCHILI[2], A. JAIN[3], S. YUN JUNG[3], H. T. ORR[4], H. Y. ZOGHBI[5];
[1]Baylor Col. of Medicine/Howard Hughes Med. Inst., [2]Baylor Col. of Med., Jan and Dan Duncan Neurolog. Inst., Houston, TX; [3]Baylor Col. of Med., Houston, TX; [4]Univ. of Minnesota, Minneapolis, MN; [5]Baylor Col. of Medicine/Howard Hughes Med. Inst., Jan and Dan Duncan Neurolog. Res. Inst., Houston, TX

Abstract: Spinocerebellar ataxia type 1 (SCA1) is a neurodegenerative disease caused by expansion of a CAG repeat encoding a polyglutamine (polyQ) tract in Ataxin-1 (Atxn1). SCA1 is characterized by loss of balance, and breathing and swallowing difficulties leading to premature death. Both the cerebellum and brainstem are vulnerable in SCA1, however, whether such vulnerabilities are mediated by the same pathogenic mechanism is unclear. We have shown in *SCA1*$^{154Q/2Q}$ mice that recapitulate SCA1 features, that halving the levels of the Atxn1 native partner, Capicua, rescues motor deficits but not survival. We also showed that abolishing the interaction between Atxn1 and Capicua prevents Purkinje cell degeneration and ataxia, suggesting that Capicua is the main driver of Purkinje cell but not the brainstem degeneration. To

gain insight into the driver(s) of brainstem pathogenesis we searched for *in vivo* binding partners of Atxn1 in the cerebellum and brainstem and identified regional and polyQ specific interactors. Interestingly, apart from Capicua, there is very little overlap in Atxn1 binding partners between these two brain regions. In wild-type mice, the brainstem interactors were enriched for RNA binding proteins (RNAbps) but no such enrichment was detected in the cerebellum. This suggested that Atxn1 might have different functional consequences to mediate degeneration in these two different brain regions. To explore this possibility, we performed RNA-seq on SCA1 mice to investigate the transcriptional and splicing changes mediated by polyQ Atxn1 in the two regions. Overall, there was very little overlap in gene expression changes and splicing alterations between the cerebellum and brainstem and distinct biological pathways were enriched in each region. The majority of changes seen in the cerebellum are transcriptional while those in the brainstem mostly involved splicing alterations. Using RNAbp motif enrichment analysis and proteomics we identified RNAbps that interacted with Atxn1 in the brainstem and whose binding motif was enriched in the transcripts showing altered splicing. We are currently validating these interactions and splicing changes in both brain regions to pinpoint the molecular changes driving regional vulnerability. Our studies, thus far, suggest that SCA1 pathogenesis may be mediated by distinct by polyQ expanded Atxn1 driven mechanisms in different regions.

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Poster

654. Animal Models of Ataxia

Location: Hall A

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Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: NS044916
NS069688
NS100300

Title: AnkyrinR is required for cerebellar Purkinje cell survival

Authors: S. R. HA, ***M. N. RASBAND**;
Neurosci., Baylor Col. of Med., Houston, TX

Abstract: Ankyrin (AnkR, AnkB, AnkG) proteins are the primary link between the submembranous spectrin-based cytoskeleton and the cytoplasmic domain of multiple transmembrane proteins in the nervous system and other tissues. Although AnkG and AnkB are well recognized as important domain organizers within the nervous system, few studies have

investigated AnkR's role. Our lab recently showed a pre-existing pool of AnkR protein can compensate for a loss of AnkG and cluster Na^+ channels at nodes of Ranvier. Additionally, disruptions in AnkR have been indicated in multiple studies of various neurological disturbances, including cerebellar dysfunction. However, the role of AnkR in the nervous system remains poorly understood. Our expression analyses show, unlike the other ankyrin proteins found widely throughout the brain, AnkR is highly expressed in just a subset of neurons, including cerebellar granule and Purkinje cells (PCs). To elucidate the role of AnkR in the nervous system,we created AnkR conditional knockout mice (AnkR cKOs) by flanking exons26 and27 of*Ank1* with*loxP* sites, upstream of the spectrin binding domain. We used Nestin-Cre, Viaat-Cre, and Pcp2-Cre to mediated removal of these exons, causing a frame-shift mutation resulting in a premature stop codon, selectively removing AnkR from neural stem cells, GABAergic neurons, and PCs, respectively. We found that all AnkR cKO mice have progressive PC degeneration marked by increasing amounts of abnormal protein accumulation and dystrophic axons, resulting in PC loss by 6-months of age. Interestingly, most of the degeneration seen in cKO mice occurs in the anterior cerebellum, lobules I-V. Coronal images reveal PCs in cKO animals degenerate in a striped pattern, suggesting specific populations of PCs may be more susceptible to degeneration following loss of AnkR. Additionally, gait analyses show disrupted gait, action tremor, and ataxia in all cKO animals. Interestingly, mutations of beta-III spectrin underlie spinocerebellar ataxia type 5 (SCA5), characterized by disrupted gait and progressive PC degeneration, phenotypically similar to AnkR cKO mice. Indeed, our data confirms AnkR and beta-III spectrin co-localize in PCs and interact in the cerebellum. Taken together, these data suggest AnkR plays an important role in stabilizing the spectrin cytoskeleton in PCs; however, loss of AnkR may be more detrimental to certain PC populations. Future studies using our novel AnkR cKO will further explore the role of AnkR in PCs, including investigating candidate membrane proteins that AnkR could interact with in the cerebellum to determine precise molecular mechanisms underlying these changes.

Disclosures: S.R. Ha: None. **M.N. Rasband:** None.

Poster

654. Animal Models of Ataxia

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 654.24/E36

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: CIHR PJT-153150
McGill Biology excellence doctoral award (Anna Cook)
Healthy Brains for Healthy Lives PhD fellowship (Anna Cook)

Title: Exercise and 4-AP work as an effective combination therapy in a mouse model of spinocerebellar ataxia type 6

Authors: *A. A. COOK[1], S. JAYABAL[2], T. C. LEUNG[1], K. C. SHENG[1], A. J. WATT[1]; [1]Dept. of Biol., McGill Univ., Montreal, QC, Canada; [2]Dept. of Neurobio., Stanford Univ., Stanford, CA

Abstract: Spinocerebellar ataxia type 6 (SCA6) is a late-onset neurodegenerative disease characterised by a loss of motor coordination and eventual cerebellar degeneration. The disease is caused by a CAG expansion mutation in the *CACNA1A* gene. The underlying pathophysiology is poorly understood and treatment options are limited, but our lab has recently identified several promising therapeutic approaches. We have used a knock in mouse model harbouring a CAG expansion mutation in the *CACNA1A* gene (SCA6 84Q/84Q). At 7 months these mice display significant deficits in motor coordination as well as in the precision and frequency of Purkinje cell firing. We found that the FDA-approved drug 4-Aminopyrimidine (4-AP) was able to ameliorate motor coordination deficits. 4-AP rescued Purkinje cell firing precision but not Purkinje cell firing frequency (Jayabal et al., 2016). Since brain-derived neurotrophic factor (BDNF) levels are reduced in post-mortem brain tissue from SCA6 patients, and BDNF is upregulated with exercise, we wondered whether exercise might improve motor deficits in SCA6. Here we show that 1 month of voluntary exercise can act therapeutically to rescue motor coordination and Purkinje cell firing deficits in SCA6 84Q/84Q mouse. In contrast to 4-AP, exercise improved Purkinje cell firing frequency without affecting firing precision. We therefore hypothesised that a combination therapy approach would be able to rescue the deficits in both Purkinje cell firing and regularity, proving more effective than either exercise or 4-AP alone. Providing 4-AP and exercise to SCA6 84Q/84Q mice, we rescued both firing frequency and precision deficits from Purkinje cells. Performance on an accelerating rotarod protocol was also ameliorated, indicating a rescue of motor coordination. Our results suggest that both the firing frequency and precision deficits in Purkinje cells contribute to motor coordination deficits in SCA6, and a combination therapy approach represents a promising strategy for the treatment of this disease.

Disclosures: A.A. Cook: None. **S. Jayabal:** None. **T.C. Leung:** None. **K.C. Sheng:** None. **A.J. Watt:** None.

Poster

654. Animal Models of Ataxia

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 654.25/E37

Topic: C.04. Movement Disorders other than Parkinson's Disease

Title: Assessment of locomotion, learning, and memory post-seizure recovery in *Drosophila melanogaster*

Authors: *S. CHEN, D. LENT;
California State University, Fresno, Fresno, CA

Abstract: People of all ages are affected by epilepsy, a neurological disorder characterized by seizures that often lead to other health concerns and current therapeutics are not universally effective. The focus of this study is to induce single and multiple seizures to observe its effects on locomotion, learning, and memory. *Drosophila melanogaster* serves as ideal model systems due to current genetic tools. Seizure sensitive flies were generated using the Gal4/UAS system to express temperature sensitivity and mechanosensitivity (bang) channels in the nervous system, which enabled the activation of seizures at any time. Pan-neuronal flies (458) was the Gal4 driver crossed with temperature sensitive flies (26701) and bang-sensitive flies (458) to express seizure sensitivity in all neurons. In the first experiment, male and female virgins were collected and a single seizure was induced at 1 day old by placing them in separate vials into a hot water bath at 39C for 10 seconds. Flies that received multiple seizures underwent the same treatment every hour for 24 hours. After a 24 hour recovery period, the flies were observed using a negative geotaxis assay to assess its climbing behavior for any deficits. Controls did not have activation of seizures and underwent the same assay. Results showed single seizure flies completed the task at similar times to the control. Flies with multiple seizures took longer to complete the assay. In the second experiment, seizures were induced to male and female virgin bang-sensitive flies at 1 day old using a vortex at maximum speed for 10 seconds. Again, flies that received multiple seizures had the same treatment each hour for 24 hours and the controls did not receive seizures. These flies were given 24 hours to recover before a visual place learning assay. The flies were examined to see if they can recall the location of the cool spot using visual cues in a heated arena. Results showed flies with single seizures were still able to associate visual cues with the cool spot. Flies that received multiple seizures exhibited greater decline in their cognitive abilities. These experiments showed that single seizures have no lasting effects on behavior, but flies that received multiple seizures over 24 hour periods had lasting deficits.

Disclosures: **S. Chen:** None. **D. Lent:** None.

Poster

654. Animal Models of Ataxia

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 654.26/E38

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: NINDS intramural research program
NEI intramural research program

Title: Structural magnetic resonance imaging measures of neurodegeneration in a spinocerebellar ataxia type 7 cohort

Authors: *J. PARKER[1], S. MERCHANT[3], S. ATTARIPOUR ISFAHANI[1], P. MCGURRIN[1], L. A. HURYN[2], M. HALLETT[1], S. G. HOROVITZ[1];
[1]NINDS, [2]NEI, NIH, Bethesda, MD; [3]Med. Univ. of South Carolina, Charleston, SC

Abstract: Spinocerebellar Ataxia type 7 (SCA7) is an autosomal dominant neurodegenerative disease characterized by progressive cerebellar ataxia and retinal degeneration. Postmortem neuropathology has revealed that while atrophy is primarily restricted to the cerebellum and brainstem, subtle microstructural abnormalities are found throughout the CNS. Despite the ability of neuropathology to reveal structural abnormalities, it cannot be used to track how this pathology evolves *in vivo*. Therefore, the spatiotemporal pattern of neurodegeneration and how it relates to disease progression remains unclear. Conventional imaging analyses such as voxel-based morphometry and diffusion tensor imaging (DTI) are unable to fully assess structural abnormalities *in vivo* as they are normally limited to specific tissue types. Additionally, an increase in CSF-like free water in and around the tissues, as can happen in neurodegeneration, can dramatically affect the measures derived from the classical DTI model. To address these challenges, we used two recently developed DTI methodologies. First, we registered subject DT images to a study-specific template using information from the full diffusion tensor, which means the alignment was accurate across all anatomical structures. This enabled us to assess microstructural abnormalities, as measured by diffusion metrics such as Trace and fractional anisotropy, across the whole brain. The transformations computed from this method also enabled us to quantify volume loss across the whole brain through diffusion tensor-based morphometry. Second, we fit a dual-compartment DTI model that can account for an increase in CSF-like free water in order to control for possible neurodegeneration-related biases. Using these methodologies, we find *in vivo* a pattern of neurodegeneration similar to the one revealed by neuropathology. Gross volumetric decreases were found to be constrained to specific areas including cerebellar gray matter and white matter (WM), cerebellar peduncles, brainstem, cerebral peduncles, optic tract, thalamus, and superior corona radiata. Microstructural abnormalities were found not only in these areas, but also throughout much of the brain including areas potentially involved in clinical manifestation such as the optic radiation, occipital lobe, the corticospinal tract, and the sensorimotor cortices. Additionally, we found a correlation between the average Trace of the WM in patients with a clinical scale of ataxia severity. These methodologies could be used in a longitudinal analysis to characterize the full spatiotemporal pattern of pathological changes taking place during SCA7 progression.

Disclosures: J. Parker: None. **S. Merchant:** None. **S. Attaripour Isfahani:** None. **P. McGurrin:** None. **L.A. Huryn:** None. **M. Hallett:** None. **S.G. Horovitz:** None.

Poster

654. Animal Models of Ataxia

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 654.27/E39

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: University of Iowa CCOM

Title: Developmental characterization of brain structure and motor function in SCA1$^{154Q/2Q}$ mice

Authors: *J. HESKJE[1], L. SPENCER NOAKES[3], S. NOPOULOS[1], A. JYOTIS[1], T. KOSCIK[1], D. THEDENS[2], E. AXELSON[1], L. DUVICK[4], H. T. ORR[4], P. C. NOPOULOS[1], K. L. PARKER[1];
[1]Psychiatry, [2]Univ. of Iowa, Iowa City, IA; [3]Mouse Imaging Ctr., The Hosp. for Sick Children, Toronto, ON, Canada; [4]Univ. of Minnesota, Minneapolis, MN

Abstract: Spinocerebellar ataxia type-1 (SCA1) is a dominantly-inherited, late-onset neurodegenerative disorder characterized by cognitive decline, motor dysfunction, and premature death. The genetic basis of SCA1 is a CAG trinucleotide repeat encoding for a polyglutamine expansion in the ataxin-1 protein. While transcriptional dysregulation and Purkinje cell pathology caused by mutant ataxin-1 are believed to be crucial for development of the SCA1 phenotype, little is known about regional changes in brain structure that accompany disease progression. In juvenile-onset Huntington's disease, another polyglutamine neurodegenerative disorder, decreases in striatal volume are accompanied by proportional enlargement of the cerebellum suggesting a compensatory role of the cerebellum for striatal loss. We hypothesized an inverse relationship for SCA1, whereby proportional decreases in cerebellar volume may be accompanied by proportional enlargement of the striatum. Using MRI, longitudinal changes in brain structure were assessed from SCA1$^{154Q/2Q}$ mice (N=40) in a sex and genotype balanced design from postnatal week 1 to 20, at which point the disease phenotype is manifest. Preliminary analyses include volumetric measures of the striatum and cerebellum in proportion to whole brain volume, as global atrophy is known to occur. Motor assays including rotarod, balance beam, open field, and gait analysis with DigiGait™ were performed on the same timeline as neuroimaging. Correlation between regional changes in brain structure, motor performance on the different tasks, and CAG repeat length were analyzed. Associative motor learning distinguishable from motor impairment was also assessed in a separate cohort of SCA1$^{154Q/2Q}$ mice using the Erasmus Ladder™. Preliminary results indicate that relative to whole brain volume, there are no significant differences in proportional cerebellar or striatal volume at any developmental timepoint up to week 20 between SCA1$^{154Q/2Q}$ mice and wildtype littermate controls. Future analyses will investigate the precise regional differences in the cerebellum by parcellating white and grey matter, lobules, and deep nuclei using advanced cerebellar masks.

Furthermore, ataxin-1 aggregates have been reported in the cerebellum only after 20 weeks but are prominent in cerebral cortex, hippocampus, and thalamic nuclei by postnatal week 6 so these regions represent additional candidates for analysis. Ultimately, the identification of a specific brain region(s) as a predictive index of disease progression could enable better tracking of SCA1 in both clinical treatment and for the evaluation of new therapies.

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Poster

654. Animal Models of Ataxia

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 654.28/E40

Topic: C.04. Movement Disorders other than Parkinson"s Disease

Support: INI accelerator grant
Nellie Ball
NIH K01 MH106824
NIH RO1 MH118240

Title: The contribution of the cerebello-thalamo-cortical circuit to interval timing performance in rats

Authors: *J. R. LEWIS, H. E. HALVERSON, B. J. DECORTE, K. L. PARKER;
Dept. of Psychiatry, Univ. of Iowa, Iowa City, IA

Abstract: Despite a body of work implicating the cerebellum in cognition, its precise role is unknown. One mechanism through which the cerebellum may mediate frontal cortex dependent executive functioning is through lateral cerebellar nucleus (LCN) relays via the ventrolateral thalamus. This is clinically significant as many psychological disorders (e.g., schizophrenia, depression, and autism spectrum disorder) are characterized by dysfunction of the frontal cortex. Our work and that of others has shown that cerebellar stimulation may modulate frontal cortex and may help to recover cognitive functioning in patients with schizophrenia which involves disrupted frontal cortex activity. Currently, it remains unknown which aspects of cognition are influenced by this cerebello-thalamo-cortical circuit. The current study aims to probe the role of this pathway through systematic pharmacological inactivations of the LCN, ventrolateral thalamus, and the medial frontal cortex (MFC) in rats. We have previously shown that the cerebellum is involved in a simple interval task that requires time estimation in the suprasecond range. Here we have improved on this task by using two-intervals (4-second and 12-second) that require the animal to respond at a specific location to demonstrate temporal discrimination

between two cues (a light and a tone) in the same session. Male Long Evans rats were trained on the task and implanted with drug infusion cannulae bilaterally in the medial prefrontal cortex, the ventrolateral thalamus, and the LCN. To investigate the contributions of each area in this proposed pathway to performance of this task, inactivations of each location were done both bilaterally and unilaterally using direct infusions of muscimol, a $GABA_A$ agonist. Additionally, we tested the effect of pharmacological stimulation of the LCN using GABAzine, a $GABA_A$ antagonist, during simultaneous disruption of MFC functioning with D1-receptor antagonist (SCH23390). In concurrence with previous reports, preliminary data suggest that inhibition of the MFC causes impaired accuracy of cue discrimination, while LCN inhibition resulted in a subtle shift toward earlier responding. Bilateral ventrolateral thalamic inhibition caused a complete abolition of task performance and results from unilateral infusions are ongoing. These results support the need for further work probing the role of the cerebello-thalamo-cortical circuit in frontal-dependent cognitive processes which may require more precise tract based techniques such as DREADDs or optogenetics.

Disclosures: **J.R. Lewis:** None. **H.E. Halverson:** None. **B.J. Decorte:** None. **K.L. Parker:** None.

Poster

655. Neurodegeneration and Neuromuscular Diseases

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 655.01/E41

Topic: C.06. Neuromuscular Diseases

Support: National Multiple Sclerosis Society Pilot Grant # PP 1708-29186

Title: Transcranial direct current stimulation (tDCS) in multiple sclerosis: Is one application of 2 ma before or during a 6 minute walk test sufficient to improve walking distance?

Authors: *C. D. WORKMAN[1], B. J. POSTON[2], E. JESTER[1], J. SMITH[1], V. SMITH[1], K. MCALLISTER[1], J. KAMHOLZ[1], T. RUDROFF[1];
[1]Univ. of Iowa, Iowa City, IA; [2]Univ. of Nevada Las Vegas, Las Vegas, NV

Abstract: Approximately 85% of people with Multiple Sclerosis (PwMS) in the U.S. report gait difficulty as a major disabling impairment. Transcranial direct current stimulation (tDCS) over the motor cortex (M1) has been used to improve motor and cognitive function in PwMS, but the optimal timing of tDCS (before or during) is still unclear. Recent evidence suggests that tDCS may be more effective during a task than before as it may enhance normal increases in cortical excitability and synaptic efficiency in task-activated cortical circuits. The efficacy of a single tDCS session on motor function in PwMS is also inconclusive. The purpose of this exploratory randomized, double-blind study was to determine the effect of a single dose of tDCS (2 mA),

applied before or during a 6 Minute Walk Test (6MWT) in seven moderately-disabled PwMS. Distance walked in the 6MWT was the primary outcome. Gait characteristics (velocity, cadence, stride length (SL), and lumbar and trunk angles) were secondary outcomes. It was hypothesized that tDCS applied during the 6MWT would result in a longer distance walked. PwMS were randomized into BEFORE (n = 3) and DURING (n=4) groups and attended three sessions. In the first, baseline 6MWT and maximum voluntary isokinetic extension/flexion contractions of the hip, knee, and ankle joints of both legs were performed. The more-affected leg was determined via right/left asymmetry ≥ 10%. tDCS or sham over M1 of the more-affected leg were randomly allocated to sessions two or three. The results indicated that the distance walked during the 6MWT was not different between groups or stimulation conditions ($p > 0.12$). However, a stimulation*group interaction ($p = 0.03$) indicated that BEFORE had smaller coronal trunk angles with tDCS (4.9° ± 2.1°) compared to sham (6.1° ± 2.7°; $p = 0.05$; Cohen's **d** = 0.5). A stimulation*group interaction trend ($p = 0.05$) indicated that DURING had smaller lumbar sagittal angles with tDCS (6.7° ± 1.0°) compared to sham (8.0° ± 0.8°; $p = 0.03$; Cohen's **d** = 1.36). There was a stimulation*group interaction trend for the SL of the more-affected leg ($p = 0.06$) and a stimulation trend for the SL of the less-affected leg ($p = 0.09$). These preliminary results indicate that a single application of tDCS at 2mA before or during a 6MWT is insufficient to improve the distance walked in PwMS. However, a significant interaction, along with statistical trends and large effect sizes, suggest that tDCS may alter walking characteristics in PwMS and may help improve other aspects of gait (e.g., SL and trunk/lumbar control). Future studies should include larger sample sizes, multiple tDCS sessions, higher tDCS intensities with longer durations, and measures of perceived effort.

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Poster

655. Neurodegeneration and Neuromuscular Diseases

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 655.02/E42

Topic: C.06. Neuromuscular Diseases

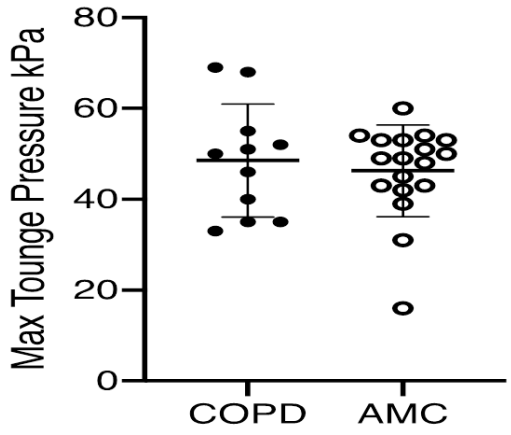
Support: NHMRC 1138920
UNSW Scientia Award

Title: Analysis of tongue strength and swallowing in COPD and healthy ageing

Authors: *I. EPIU[1], C. BOSWELL-RUYS[2], S. GANDEVIA[2], J. E. BUTLER[3], A. HUDSON[2]; [1]Neurosci. Res. Australia - UNSW, Sydney, Australia; [2]Neurosci. Res. Australia, Sydney, Australia; [3]Neurosci. Res. Australia, Randwick, NSW, Australia

Abstract: Swallowing disorders seen in ageing and other neurodegenerative disorders impact the quality of life of patients and caregivers. Muscle wasting in ageing and disease affects the coordination and muscle strength needed for swallowing. This dysphagia contributes to malnutrition and dehydration, and is a major predisposing condition for aspiration, leading to pneumonia, and in some cases, death. The aim of our study was to evaluate tongue strength in chronic obstructive pulmonary disease (COPD) which has not been done before.
Tongue strength measures of peak anterior pressure were obtained with the Iowa Oral Performance Instrument in 11 of 18 participants with COPD age 75±10.2 (mean±SD) and 18 age-matched controls (AMC) age 71±6.3. Using a two-sample t-test our results were compared to published weighted averages in subjects >60 years old who had a mean pressure of 57.4±13.0 kPa. Swallowing function was assessed using the eating assessment tool (E10), timed water swallow test (TWST) and test of mastication and swallowing of solids (TOMASS) and compared to published reference values.
Tongue strength was 48.55±12.44 kPa in the COPD group and 46.28±10.12 kPa in the AMC group, both significantly lower than published weighted averages (p=0.03; CI for the difference: 1.18-16.56
COPD, and p<0.001; CI for the difference: 6.00-16.28, AMC). For swallowing function, none of the AMC participants and 18% COPD had TWST scores, and 11% AMC and 36% COPD participants had TOMASS scores below the lower limit of normal (< 2SD from the mean). Our COPD group had a longer E10 when compared to AMC 3.3(4.9) and 0.9(1.6) respectively; p = 0.06 (CI for the difference, -0.73 to 5.53).
In conclusion, tongue strength in our Australian sample is 18% lower than published data and is associated with impaired swallowing function in some participants. These groups may benefit from exercises to increase tongue strength, improve swallowing and airway protection to reduce the risk of aspiration.

Figure showing maximum tongue pressure in COPD and Age Matched Controls



Disclosures: I. Epiu: None. **C. Boswell-Ruys:** None. **S. Gandevia:** None. **J.E. Butler:** None. **A. Hudson:** None.

Poster

655. Neurodegeneration and Neuromuscular Diseases

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 655.03/E43

Topic: C.06. Neuromuscular Diseases

Title: Neuro-cardio-autonomic modulations in children with Duchenne muscular dystrophy

Authors: *T. N. SATHYAPRABHA, A. MEGHANA, V. PREETHISH-KUMAR, A. JOHN, P. PRATHUYSHA, T. R. RAJU, A. NALINI;
NIMHANS, Bangalore, India

Abstract: Background: Duchenne muscular dystrophy (DMD) is an X-linked devastating progressive muscle disease. Death is usually secondary to cardiorespiratory complications. Preclinical /early detection of cardiac autonomic disturbances prior to routine identification by standard techniques of cardiac assessment, may help in timely initiation of cardio-protective therapy. **Methods:** A prospective study of 38 DMD boys and 37 age-matched healthy controls was conducted. Heart rate variability (HRV), blood pressure variability (BPV; DMD=34, control=10) and baroreceptor sensitivity (BRS; DMD=35, control=10) data was analysed and correlated with disease severity and genotype according to Multiplex Ligation-dependent Probe Amplification (MLPA). **Results:** In the DMD group**,** the median age at assessment was 8 years [Interquartile range 7-9 years], median age at onset of illness was 3 years [Range, 2-6 years] and mean duration of illness was 4 years [Range, 2.5-5] years. MLPA showed deletions in 34/38 (89.5 %) and duplications in 10.5 % patients. The mutation was distal in 29/38 and proximal in 9 cases. The median heart rate was significantly higher in DMD children compared to controls [101.19 (Range, 94.71-108.49)] /min vs [81 (Range, 76.2-92.76)] /min. All the assessed HRV and BPV parameters were significantly reduced in DMD cases except diastolic BP, mean BP and aortic impedance. BRS parameters were also significantly reduced in DMD cases except the alpha-LF. A positive correlation was found between alpha HF with age at onset and duration of illness. There were no significant changes in HRV/BPV/BRS parameters between the proximal and distal mutation groups. **Conclusion:** This study shows a definite early impairment of neuro-autonomic control in DMD. Simple non-invasive tests like HRV, BPV and BRS can thus be used to identify pre-clinical cardiac dysfunction in DMD patients making early institution of cardio-protective therapies possible.

Disclosures: T.N. Sathyaprabha: None. **A. Meghana:** None. **V. Preethish-Kumar:** None. **A. John:** None. **P. Prathuysha:** None. **T.R. Raju:** None. **A. Nalini:** None.

Poster

655. Neurodegeneration and Neuromuscular Diseases

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 655.04/E44

Topic: C.06. Neuromuscular Diseases

Support: Lundbeck Foundation

Title: Incretin hormones attenuate motor axon dysfunction in a mouse model of type 2 diabetes mellitus

Authors: *C. KRARUP[1], C. HOLSCHER[2], M. MOLDOVAN[3];
[1]Rigshospitalet, Copenhagen, Denmark; [2]Res. and Exptl. Ctr., Henan Univ. of Chinese Med., Zhengzhou, China; [3]Univ. of Copenhagen, Copenhagen, Denmark

Abstract: BackgroundAnalogues of incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) provide various degrees of neuroprotection in sensory-motor diabetic polyneuropathy (DPN) as well as in other neurodegenerative disorders. Muscle weakness occurs at late stages of DPN. We hypothesize that the slow progression of motor impairment allows a time-window to investigate the effects of incretin hormones on motor axon dysfunction preceding axonal degeneration in DPN.AimThe aim of this study was to assess the effect of treatment with a dual GLP-1/GIP receptor agonist (DA-CH5) on motor axon dysfunction in the most widely used mouse model of Type 2 diabetes mellitus, the genetically leptin receptor-deficient mouse (db/db).MethodsInvestigations were carried out in mature (5-month old) female db/db in a double-blind, sham-controlled trial. A daily dose of DA-CH5 (30 nmol/kg i.p.) or vehicle was administered for 3 weeks. Motor nerve function was investigated by in vivo neurophysiology using conduction studies and multiple measures of excitability by threshold-tracking, a clinically available method that can inform on membrane potential and axonal ion channel function. The tibial nerve was stimulated distally at ankle and the evoked compound muscle action potential (CMAP) was recorded from plantar muscles under anesthesia and temperature control. Age-matched wild-type (WT) mice were used for comparison.ResultsAs compared to WT, the db/db were severely overweight and hyperglycemic. Conduction studies in db/db showed a prolonged CMAP latency and a borderline reduction in amplitude. Their rheobase was reduced, indicating a hyperexcitable state of the distal axon. Consistently, the other excitability measures showed a reduced deviation during both depolarizing and hyperpolarizing threshold electrotonus and a marked increase in refractoriness at the expense of the superexcitable period of the recovery cycle. These abnormalities were attenuated in db/db treated with DA-CH5. Mathematical modeling predicted that effect of DA-CH5 could largely be explained by a hyperpolarizing shift in membrane potential.ConclusionOur data suggest that motor axons are depolarized in the DPN of db/db. Treatment with a dual GLP-

1/GIP receptor agonist attenuated this depolarization. It is possible that improved energy metabolism increased the resting Na^+/K^+ pumping with a net hyperpolarizing effect. Motor nerve excitability studies could thus provide translational biomarkers to assess the axonal effect of incretin neuroprotection.

Disclosures: **C. Krarup:** 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.; Collaborator drug study. D. Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus); Speakers' bureau. F. Consulting Fees (e.g., advisory boards); Advisory board. **C. Holscher:** Other; Inventor of GLP-1/GIP analogue. **M. Moldovan:** None.

Poster

655. Neurodegeneration and Neuromuscular Diseases

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 655.05/F1

Topic: C.06. Neuromuscular Diseases

Support: 1R01NS108114

Title: Vulnerability of fast- and slow-twitch motor units in a mouse model of spinal and bulbar muscular atrophy

Authors: *E. MOLOTSKY[1], A. PLUCIENNIK[2], D. E. MERRY[3];
[1]Biochem. and Mol. Biol., [3]Dept Biochem & Molec Biol, [2]Thomas Jefferson Univ., Philadelphia, PA

Abstract: Spinal and bulbar muscular atrophy (SBMA) is an X-linked neuromuscular disease caused by a polyglutamine repeat expansion in the androgen receptor (AR). The symptoms of muscle atrophy, weakness, and fasciculations occur due to the combined loss of lower motor neurons in the spinal cord and brainstem and atrophy of the associated innervated muscle fibers. While it is known that lower motor neuron degeneration contributes to the disease phenotype, it is unknown why certain motor neurons are more susceptible than others to the toxic properties of the mutant AR. In SBMA patients, fiber type grouping and decreased tongue pressure and grip power reveals fast motor unit-selective degeneration. Fast-fatigable motor units atrophy earliest in SOD1 mouse models, SMA patients, and during normal aging, as well as in a myogenic model of SBMA. Using a transgenic mouse model of SBMA that expresses the AR with a polyglutamine expansion of 112 repeats (AR112Q) primarily in neuronal tissue, we analyzed spinal cord motor neurons and the neuromuscular junctions (NMJs) of multiple hindlimb muscles in order to study the vulnerability differences of motor units. Mouse tibialis anterior (primarily fast-twitch) and soleus (primarily slow-twitch) muscles stained for synaptophysin

(presynaptic) and α-bungarotoxin (postsynaptic acetylcholine receptors (AChRs)) were analyzed for histological measurements of pre- and post-synaptic area, post-synaptic compactness, and synaptophysin/α-bungarotoxin colocalization. Preliminary data revealed an early decrease in compactness prior to significant loss in NMJ area (pre- and post-synaptic) in the tibialis anterior (TA). Histological analysis of the soleus showed early changes in colocalization and compactness, implicating a change in both the pre- and post-synaptic structures at the NMJ. Further evaluation of neurofilament heavy chain (NF-H) phosphorylation revealed decreases in unphosphorylated NF-H in the soma of anterior horn motor neurons as well as a decrease in phosphorylated NF-H at the axon terminal of the TA, concomitant with disease motor phenotype. These aspects of neuromuscular junction pathology may provide insights into the mechanisms underlying vulnerability of motor neurons and muscle in patients with SBMA.

Disclosures: E. Molotsky: None. **A. Pluciennik:** None. **D.E. Merry:** None.

Poster

655. Neurodegeneration and Neuromuscular Diseases

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 655.06/F2

Topic: C.06. Neuromuscular Diseases

Support: the Rehabilitation Research and Development Service of the Department of Veterans Affairs A1262-R

Title: Brain derived neurotrophic factor is an important factor for pudendal nerve motor branch functional recovery

Authors: *B. M. BALOG[1,2,3], T. L. ASKEW[4], D. LI[5], B. HANZLICEK[2], M. S. DAMASER[6]; [1]Biomed. Engin. Dept., Cleveland Clin. Lerner Res. Inst., Cleveland, OH; [2]Res., Louis Stokes VA Med. Ctr., Clevleand, OH; [3]Dept. of Biol., Univ. of Akron, Akron, OH; [4]Biomed. Engin., [5]Biomed. Engin. Dept., [6]Dept of Biomed. Engin., Cleveland Clin., Cleveland, OH

Abstract: Increased motor nerve latency in women with stress urinary incontinence (SUI) suggests that pudendal nerve (PN) function and recovery are important to the multifactorial continence mechanism. A PN crush (PNC) model of SUI in female rats demonstrates that brain derived neurotrophic factor (BDNF) is upregulated after PNC, suggesting that it is necessary for PN regeneration. We hypothesized that BDNF is essential to PN functional recovery following PNC. In this experiment, we reduced active BDNF by administering its receptor, TrkB, to block the action of BDNF and determine if this reduces recovery from PNC. Sprague-Dawley rats were divided into three groups; 1/3 of the rats received sham bilateral PNC with implanted osmotic pumps (Alzet model 2002) containing saline (SPNC + S). The other 2/3 rats received bilateral PNC with osmotic pumps, containing either saline (PNC + S) or Fc-TrkB chimera (PNC +

TrkB). Three weeks later the animals underwent functional testing consisting of leak point pressure (LPP) with simultaneous PN motor branch potential (PNMBP) recording and PN sensory branch potential recording during clitoral brushing (PNSBP). With PNC + S serving as the control, a One-way ANOVA on Ranks followed by a Dunn's test was used to indicate significant differences ($p<0.05$). After functional testing, plasma and the urethras were harvested and fresh frozen and cryosectioned. Plasma underwent ELISA analysis for BDNF concentration. Urethra sections were stained with Masson's trichrome for identification of muscle and extracellular matrix and immunofluorescence for identification of innervation of neuromuscular junctions. Slides were evaluated by two blinded observers. PNC + TrkB BDNF plasma concentrations were significant decreased compared to PNC + S, while SPNC + S BDNF concentration was not significantly different compared to PNC + S. PNC + TrkB PNMBP firing rate was significantly decreased compared to PNC + S, while PNC + S was not significantly different from SPNC + S. PNSBP firing rate & amplitude was not significantly different between any of the groups. LPP was not significantly different between the groups. PNC + Trkb neuromuscular junction staining showed neuromuscular junctions were not well reinnervated by axons, while PNC + S were well reinnervated. PNC + S neuromuscular junction morphology were similar to SPNC + S neuromuscular junctions. BDNF is essential to PN motor branch regeneration after PNC; however, BDNF may be necessary but not essential for PN sensory branch regeneration. Continence is maintained by multiple factors, explaining why a decrease in PN motor function did not lead to a decrease in LPP, a comprehensive measure of continence.

Disclosures: B.M. Balog: None. **T.L. Askew:** None. **D. Li:** None. **B. Hanzlicek:** None. **M.S. Damaser:** None.

Poster

655. Neurodegeneration and Neuromuscular Diseases

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 655.07/F3

Topic: C.06. Neuromuscular Diseases

Title: Glyceryl tribenzoate, a flavoring ingredient, inhibits glycine encephalopathy

Authors: *M. KUNDU[1], A. ROY[2], K. PAHAN[1];
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Abstract: Glycine encephalopathy (GE) or non-ketotic hyperglycinemia is a rare genetic disorder of glycine metabolism where high levels of glycine are accumulated in the body. Clinically, GE is characterized by lethargy, seizures, cognitive impairment, developmental delays, and myoclonic jerks, ultimately leading to apnea and even death in early childhood. Mutations in glycine decarboxylase (gldc) gene, an important member of the glycine cleavage system located in mitochondrial membrane, are frequently observed in patients with GE. In this

study, we have generated a preclinical model of GE by knocking down GLDC with lenti shRNA. After lenti-gldc-shRNA insult, the level of glycine increased in serum, urine and cortex of mice. Accordingly, after GLDC knockdown, mice also exhibited impairment in memory and learning. Glycerol tribenzoate (GTB) or tribenzoin belonging to the family of benzoic acid is a flavoring ingredient. Here, we delineate that oral GTB treatment was capable of lowering the level of glycine in serum, urine and cortex of lenti-gldc-shRNA-insulted mice. GTB-treated mice also showed improved motor function and advanced memory compared to untreated lenti-gldc-shRNA-insulted mice. Taken together, these data suggest that GTB may have therapeutic implication in GE.

Disclosures: M. Kundu: None.

Poster

655. Neurodegeneration and Neuromuscular Diseases

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 655.08/F4

Topic: C.06. Neuromuscular Diseases

Support: NIH Grant NS054154
NIH Grant NS1000328
NIH Grant NS098523

Title: Activation of the integrated stress response contributes to the disease mechanism of tRNA-sythetase related peripheral neuropathy

Authors: *R. W. BURGESS, E. L. SPAULDING, T. J. HINES;
Jackson Lab., Bar Harbor, ME

Abstract: Charcot-Marie-Tooth type 2D (CMT2D) is a dominant axonal neuropathy caused by mutations in glycyl tRNA-synthetase (*GARS*). The GARS enzyme charges glycine onto its cognate tRNAs for translation, but like many neurodegenerative diseases, this “housekeeping gene” causes a very specific disease phenotype when mutated. To better understand the disease mechanism underlying mutations in *GARS* and CMT2D, we profiled transcription and translation specifically in motor and sensory neurons in mouse models of CMT2D. Consistent with findings in Drosophila, *in vivo* non-canonical amino acid tagging showed reduced protein synthesis in motor neurons. To determine if this was directly due to the disease mechanism, due to cell stress, or a combination of these mechanisms, we also performed gene expression profiling, using ribosome tagging to specifically examine the motor neuron “translatome,” and also using whole spinal cord RNAseq. Both approaches revealed signatures consistent with activation of the integrated stress response (ISR). Confirmation of upregulated ATF4 target genes by *in situ* hybridization showed the ISR was selectively activated in alpha-, but not gamma-motor neurons,

and in medium and large sensory neurons that constitute a mix of mechanoreceptors and proprioceptors. We postulated that the ISR was activated through GCN2 kinase, one of four sensors of various cell stresses best known for responding to amino acid insufficiency. To test this, we combined the *Gars*/CMT2D mouse model with a knockout of *Gcn2*. We found that double mutant mice no longer had gene expression changes indicating activation of the ISR. In addition, the phenotype of the double mutant mice was much milder than *Gars* mutations alone, suggesting that chronic activation of the ISR contributes to the severity of the neuropathy. We are currently using a combination of *in vivo* and *in vitro* approaches to test hypotheses about how dominant mutations in *GARS* might lead to activation of GCN2 in such a cell type-specific manner, including by the presence of uncharged tRNAs or stalled ribosomes. Interestingly in humans, dominant mutations in at least five tRNA synthetase genes lead to peripheral neuropathy. Preliminary studies in a mouse model of dominant intermediate CMT type C (DI-CMTC), caused by mutations in tyrosyl tRNA-synthetase (*YARS*), indicate a very similar signature of gene expression changes, consistent with activation of the ISR and a similar mechanism in this related disease.

Disclosures: R.W. Burgess: None. **E.L. Spaulding:** None. **T.J. Hines:** None.

Poster

655. Neurodegeneration and Neuromuscular Diseases

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 655.09/F5

Topic: C.06. Neuromuscular Diseases

Support: H-ABC foundation grant

Title: A novel mouse Tubb4a$^{D249N/D249N}$ to model hypomyelination and atrophy of basal ganglia and cerebellum and development of potential therapeutic strategies

Authors: *S. SASE[1], A. ALMAD[2], A. BOECKER[4], P. GUEDES-DIAS[6], J. LI[4], A. TAKANOHASHI[2], T. MCCAFFREY[2], D. SIRDESHPANDE[2], Q. PADIATH[7], E. HOLZBAUR[5], S. SCHERER[8], A. VANDERVER[3];
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Abstract: Hypomyelination and Atrophy of Basal ganglia and Cerebellum (H-ABC) is a rare hypomyelinating leukodystrophy with causal variants in tubulin alpha 4 (*TUBB4A*) and p.Asp249Asn (D249N) is a recurring heterozygous variant occurring in the majority of affected individuals. H-ABC typically begins in infancy characterized by dystonia, ataxia, altered gait and progressive motor dysfunction. To date, there is no therapeutic approach available. To facilitate

development of therapeutic strategies, our group has developed a knock-in mouse model harboring heterozygous (*Tubb4a*^{D249N}) or homozygous (*Tubb4a*$^{D249N/D249N}$) *Tubb4a* mutations using a CRISPR-Cas9 approach. This H-ABC mouse model (*Tubb4a*$^{D249N/D249N}$) displays progressive motor dysfunction with tremor, abnormal gait, ataxia and decreased survival. Neuropathological and electron microscopy analysis of *Tubb4a*$^{D249N/D249N}$ mice shows initial delay of myelination followed by ultimate demyelination along with loss of oligodendrocytes (myelinating cells in CNS). Further, *Tubb4a*$^{D249N/D249N}$ shows severe cerebellar atrophy and significant striatal neuronal loss. Cell-autonomous effects were observed in neurons and oligodendrocytes in culture along with unstable microtubule dynamics in neurons of *Tubb4a*$^{D249N/D249N}$ mice. Thus, *Tubb4a*$^{D249N/D249N}$ mouse recapitulates H-ABC disease with decreased survival, making it a unique model to develop pre-clinical strategy for H-ABC disease. One approach to treat H-ABC is to reduce the TUBB4A expression as partial phenotypic data displays that *Tubb4a Knockout* (KO) mouse are developmentally normal, suggesting that TUBB4A is redundant in a cell. To reduce TUBB4A expression in the mouse, ongoing studies are focused on screening a panel of anti-sense oligonucleotide (ASO) *in vitro* to establish the most effective ASOs. Subsequently, the best candidate ASO will be administered in *Tubb4a*$^{D249N/D249N}$ mouse at different time points and different route of administration to test if ASO treatment can rescue the hypomyelination, cerebellar ataxia and tremors observed in the *Tubb4a*$^{D249N/D249N}$ mice. Additionally, dose escalation experiments will be performed to establish dose response curve in mice. This work will serve as pre-clinical proof of principal for testing if use of ASO is a viable approach in treatment of H-ABC.

Disclosures: **S. Sase:** None. **A. Almad:** None. **A. Boecker:** None. **P. Guedes-Dias:** None. **J. Li:** None. **A. Takanohashi:** None. **T. McCaffrey:** None. **D. Sirdeshpande:** None. **Q. Padiath:** None. **E. Holzbaur:** None. **S. Scherer:** None. **A. Vanderver:** None.

Poster

655. Neurodegeneration and Neuromuscular Diseases

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 655.10/F6

Topic: C.06. Neuromuscular Diseases

Support: University of Sydney Bridging Support Grants 2015-17

Title: Forced expression of MuSK in dystrophic (mdx) mouse muscles partially restores expression of utrophin and beta-dystroglycan to the sarcolemma

Authors: J. BAN, J. HUANG, ***W. D. PHILLIPS**;
Physiol., The Univ. of Sydney, Sydney, Australia

Abstract: *Mdx* mice lack dystrophin and are used to model the changes in muscle structure and function that occur in Duchenne muscular dystrophy (DMD). Muscle Specific Kinase (MuSK; a transmembrane tyrosine kinase) is vital for stabilizing the mammalian neuromuscular junction (NMJ) and *mdx* muscles have been found to express lower levels of MuSK compared to wild-type muscles. We have used Adeno-associated viral (AAV) expression vector (serotype 6) to supplement MuSK in the tibialis anterior muscle of 8-week old male *mdx* and wild-type (C57BL10) mice. We previously reported that, when studied one month later, *mdx* muscles injected with AAV-MuSK were less fragile. Fragility was assessed by the drop in maximum isometric contractile force that occurs after the dystrophic muscle is challenged with a series of four eccentric contractions. Here we describe changes in the sarcolemmal expression of dystrophin-associated proteins that might explain the protective effects of AAV-MuSK. Within fast twitch muscles, such as the tibialis anterior, endogenous MuSK is concentrated mainly at the motor endplate. The most obvious effect of injecting AAV-MuSK upon MuSK expression was the appearance of MuSK immunofluorescence throughout the extrasynaptic sarcolemma of muscle fibers, at densities comparable to endplate levels. This is distinctly different from wild-type muscles and *mdx* contralateral control muscles (injected with empty AAV vector), which showed only weak anti-MuSK labeling outside the endplate. Consistent with previous reports *mdx* (control) muscles showed relatively low intensity staining for β-dystroglycan in their extrasynaptic sarcolemma, when compared to wild-type muscles. Importantly, injection of AAV-MuSK-GFP significantly increased the sarcolemmal density of β-dystroglycan in *mdx* muscles. This was associated with a significant increase in total muscle β-dystroglycan protein, assessed by immunoblotting. Immunofluorescent labeling also revealed a marked increase in the density of utrophin in the sarcolemma of *mdx* muscles expressing MuSK-GFP, which may help explain the partial restoration of β-dystroglycan in AAV-MuSK muscles. These results suggest that expression of MuSK in the extrasynaptic sarcolemma can reduce the fragility of dystrophic *mdx* muscle fibers by restoring the sarcolemmal expression of utrophin and β-dystroglycan. This might help explain why the soleus muscle (which naturally expresses MuSK throughout it's sarcolemma) seems to be less fragile than the fast-twitch muscles of *mdx* mice.

Disclosures: **J. Ban:** None. **J. Huang:** None. **W.D. Phillips:** None.

Poster

655. Neurodegeneration and Neuromuscular Diseases

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 655.11/F7

Topic: C.06. Neuromuscular Diseases

Support: Charcot-Marie-Tooth Association
NIH/NCATS KL2 Career Development Award (CTSI-KL2-FY19-0X)

Title: Kinase inhibitors improve neurofilament distribution in Charcot-Marie-Tooth 2E human motor axons

Authors: *R. MACIEL, R. CORREA, J. BOSSO TANIGUCHI, I. P. ARAUJO, M. A. SAPORTA;
Neurol., Univ. of Miami, Miami, FL

Abstract: Length-dependent axonal degeneration is the pathologic hallmark of several neurodegenerative disorders, including inherited peripheral neuropathies (or Charcot-Marie-Tooth disease, CMT). CMT is currently an untreatable disorder. This is partially due to lack of translational models suitable for drug discovery. *In vitro* models of CMT have been hindered by the two-dimensional configuration of neuronal cultures, which limits visualization and orientation of axons. To overcome these limitations, we cultured iPSC-derived spinal motor neurons in agitation to form three-dimensional spheroids, which grow axons in a centrifugal fashion when plated. Using these iPSC-derived spinal spheroids, we demonstrate a consistent and reproducible phenotype, namely discrete deposits of neurofilament protein in the motor neuron axons of three independent patients with CMT type 2E, caused by mutations in neurofilament light chain (*NEFL*) gene, but none of four unaffected controls (p=0.001). NEFL is a component of the neuronal cytoskeleton, which provides structural support for the axon and regulate radial axonal growth, determining its final diameter. Other neurofilament subtypes, including NEFM, NEFH and phosphorylated NEFH, co-accumulated is these deposits. We also demonstrate that measuring neurofilament light chain protein in culture supernatant of motor neurons is a sensitive strategy to detect axonal degeneration in CMT2E, both at baseline conditions and in response to axon toxic drugs, such as the chemotherapy agent Vincristine, and may be a useful phenotype for use in high throughput screening. Despite advances in understanding its pathophysiology, there is no disease-modifying therapy for CMT2E. By targeting kinases involved in neurofilament phosphorylation, including PLK1 and CK2, in our tridimensional system, we identified two kinase inhibitors that promoted over 50% reduction in the normalized area of neurofilament deposits (p=0.001), in three patients with CMT2E. In summary, we developed a human tridimensional *in vitro* system that models axonopathies, recapitulates key pathophysiologic features of CMT2E, is particularly useful to study length-dependent processes and may facilitate the identification of new therapeutic compounds for neurodegenerative disorders where axon degeneration plays a key role in pathogenesis. We also identified candidate kinase inhibitors as potential therapies for CMT2E.

Disclosures: R. Maciel: None. **R. Correa:** None. **J. Bosso Taniguchi:** None. **I.P. Araujo:** None. **M.A. Saporta:** None.

Poster

655. Neurodegeneration and Neuromuscular Diseases

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 655.12/F8

Topic: C.06. Neuromuscular Diseases

Support: DFG BI 195/77-1
BMBF 16SV7701 CoMiCon
LUMINOUS -H2020-Fetopen-2014-2015-RIA (686764)
Wyss Center for Bio and Neuroengineering, Geneva

Title: Quality of life in individuals on verge to completely locked-in state

Authors: *A. RANA[1], A. TONIN[1], A. JARAMILLO GONZALEZ[1], M. KHALILI ARDALI[1], N. BIRBAUMER[2], U. CHAUDHARY[1];
[1]Eberhard Karls Univ. of Tuebingen, Tuebingen, Germany; [2]Wyss Ctr. for Bio and Neuroengineering, Geneve, Switzerland

Abstract: Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative motor neuron disorder which causes an individual to be in locked-in state (LIS) and later in a completely locked-in state (CLIS). When the individuals are still in LIS and can communicate with eye trackers different studies have shown that these patients report to have a good quality of life (QoL). Once these individuals lose the means of communication, i.e., they are either on verge to CLIS or in CLIS, it becomes difficult to ascertain their quality of life, therefore there is no QoL data available on such patients. Recently we developed an auditory electrooculogram (EOG) + electroencephalogram (EEG) based BCI which enabled individuals who cannot use the eye-trackers for communication because of their inability to fixate the gaze but can perform micro movement of the eyes, not discernible by naked eyes, to answer “yes” and “no”. Four individuals on the verge of CLIS answered QoL questionnaire. The QoL questionnaire was developed based on the QoL questionnaire for patients in LIS and for patients with the spinal cord injuries. The sample questions asked were, “Are you happy today?”, “Are you tired?”.
Questions with reference to time were also included to evaluate the change in emotional levels, e.g., “You feel relaxed today”. The results show that the QoL in individuals on verge to CLIS answered positively to questions pertaining to good quality of life. The study will be repeated several times. The results of this study might help ALS patients to make an informed decision about their life in the later stages of the disease and the healthcare programs could be tailored as per the requirement of these individuals.

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Poster

655. Neurodegeneration and Neuromuscular Diseases

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 655.13/F9

Topic: C.06. Neuromuscular Diseases

Support: Grant-in-Aid (AMED-PRIME, Precursory Research for Innovative Medical care, 15666161 in Advanced Research and Development Programs for Medical Innovation) from AMED (Japan Agency for Medical Research and Development)

Title: Label free imaging of abnormal lipid accumulation in muscle fibers from inclusion body myositis patients using Raman spectroscopy

Authors: *Y. NAGASHIMA[1], J. SHIMIZU[1,2], A. IWATA[1], K. YOSHIOKA[3], J. OMACHI[5], J. YUMOTO[4], M. KUWATA-GONOKAMI[4], T. TODA[1];
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Abstract: [Background] Inclusion body myositis (IBM) is the most common late-onset myopathy, characterized by progressive asymmetric weakness predominantly affecting the quadriceps and/or finger flexors. Muscle biopsy usually shows inflammatory cells surrounding and invading non-necrotic muscle fibers, rimmed vacuoles, congophilic inclusions, and protein aggregates. Disease pathogenesis remains to be elucidated and it is hypothesized to include inflammatory and degenerative aspects. [Aims] In this study, we aimed to measure molecular vibrational spectra of abnormal muscle fibers from IBM patients. Vibrational spectra obtained using Raman spectroscopy provides vibrational information characteristic of chemical groups or bonds in a molecule without any labeling procedures. Measuring vibrational spectra enables us to locate and quantitate accumulated molecular species within tissues in a molecular specific manner. [Methods] Vibrational spectra of frozen sections of muscles biopsied from IBM patients were obtained using spontaneous Raman microspectroscopy and compared with the spectra in the local database of major lipid species measured *in vitro*. [Results] We found that the Raman spectra measured in the internal edges, i.e., the “rim” of rimmed vacuoles showed prominent peaks such as 1305cm^{-1}, 1450cm^{-1} and 1650cm^{-1}, which is typical of phospholipid backbone structures. From detailed correlation analysis of its spectral pattern with the spectral database, phosphatidylcholine showed the highest correlation. [Discussion] Previous reports have shown that rimmed vacuoles found in IBM are colocalized with various protein aggregates, such as β-amyloid, α-synuclein and TDP-43, which is considered as an evidence of degenerative aspect of the disease. These protein aggregates are usually co-stained immunohistochemically with p62 and LC3B, which is the marker molecule of autophagosome. In our observation, Raman spectra

of rimmed vacuole demonstrated a pattern of phospholipid backbone structures, lacking any spectral signature indicative of protein, such as Raman shift of phenylalanine breathing mode around 1000cm^{-1}. Because peak intensity in Raman spectrum reflects stoichiometric amount of material, our result showed the primary component of rimmed vacuole is probably phospholipids. [Conclusions] Raman spectroscopic observation showed the primary molecular species constituting rimmed vacuoles in IBM patients are phospholipids. This result supported the idea that rimmed vacuoles are disrupted autophagosomes and IBM has a degenerative aspect in its disease pathogenesis.

Disclosures: **Y. Nagashima:** None. **J. Shimizu:** None. **A. Iwata:** None. **K. Yoshioka:** None. **J. Omachi:** None. **J. Yumoto:** None. **M. Kuwata-Gonokami:** None. **T. Toda:** None.

Poster

655. Neurodegeneration and Neuromuscular Diseases

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 655.14/F10

Topic: C.06. Neuromuscular Diseases

Support: MDA P0096346

Title: Dissecting the transcriptome of the myotonic dystrophy type 1 CNS

Authors: ***B. A. OTERO**[1], T. KIMURA[2], K. A. HAGERMAN[3], J. B. SAMPSON[3], J. W. DAY[4], C. A. THORNTON[5], E. T. WANG[1];
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Abstract: Myotonic Dystrophy type 1(DM1) is an autosomal dominant multisystemic disease caused by a CTG microsatellite expansion in the 3' UTR of the dystrophia myotonica protein kinase (DMPK) locus. Although patients report that CNS symptoms significantly diminish quality of life, little research has been done to understand underlying pathomechanisms in this tissue relative to muscle and heart. CNS symptoms are significant yet variable and include mental illness, hypersomnolence, and visuospatial/executive dysfunction. There is a variety of tissue pathology, including grey matter atrophy, white matter lesions, gliosis, and neurofibrillary tangles. A critical gap exists in our knowledge of molecular mechanisms causing CNS dysfunction in DM1, as well as why there is extreme variability across patients. To elucidate underlying causes of CNS dysfunction in patients, we have generated RNAseq transcriptomes from the frontal cortex of 26 DM1 patients and 8 age-matched unaffected individuals. We have identified numerous splicing and expression changes, many of which correlate with one another in a manner possibly reflecting disease severity. Analyses reveal mis-regulation of multiple

synapse-related transcripts such as neurotransmitter receptor subunits, ion channels and signaling molecules. Interestingly, within this group of synapse-related transcripts, several splicing changes produce isoforms that may enhance inhibitory versus excitatory balance. This project will be valuable to understand the pathogenesis of DM; the variability of CNS phenotypes experienced by patients, and broadly, how changes to RNA regulation can cause CNS disease symptoms.

Disclosures: B.A. Otero: None. **T. Kimura:** None. **K.A. Hagerman:** None. **J.B. Sampson:** None. **J.W. Day:** None. **C.A. Thornton:** None. **E.T. Wang:** None.

Poster

655. Neurodegeneration and Neuromuscular Diseases

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 655.15/F11

Topic: C.06. Neuromuscular Diseases

Support: NSCA Doctoral Research Grant
Ohio State Doctoral Fellowship

Title: Increased white matter volume may explain resting motor threshold maintenance in individuals with a history of traumatic musculoskeletal injury

Authors: *S. D. FLANAGAN[1], F. PROESSL[1], A. J. STERCZALA[1], A. Z. BEETHE[1], C. DUNN-LEWIS[1], B. C. NINDL[1], W. J. KRAEMER[2];
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Abstract: Introduction: Increasing evidence is pointing towards corticomotor involvement in loss of function subsequent to traumatic musculoskeletal injury, as exemplified by anterior cruciate ligament rupture (ACLR). Nevertheless, little is known about structural sensorimotor adaptations, and their functional implications in individuals with ACLR. **Purpose:** Compare structural morphology in individuals with previous ACLR and healthy controls (CON) and determine the association between brain volume and corticospinal excitability. **Methods:**Twenty age-, physical activity-, height- and weight matched females (10 CON; mean age: 20.9±2.9 years) completed 3-Tesla T1-weighted structural magnetic resonance scans to determine cortical thickness, grey- and white matter at a voxel-level, and in 95 regions of interest (ROI). Using transcranial magnetic stimulation, resting motor thresholds (RMT) in both legs were determined and the average was computed. Between-group differences in RMT and brain volume were analyzed *a priori*for sensorimotor regions (bilateral precentral [M1] and postcentral gyrus [S1], paracentral lobule) via independent t-tests (α=0.05). Pearson correlations were used to assess the relationship between ROI volume and rMT. **Results:** Individuals with ACLR completed rehabilitation on average 3.1±1.1 years prior to enrollment. Five injured the left leg. RMT was

similar between groups (CON: 76.56±3.10, ACLR: 79.69±2.41, p=0.50). Voxel-wise comparisons revealed cortical thinning in sensorimotor regions in ACLR relative to CON. ACLR further demonstrated increased white matter volume in the left M1 compared to CON (10.81±0.78 vs. 8.97±0.32 cm^3, p=0.04), and increased, yet non-significant in the left S1 (8.59±0.3 vs. 1.04±0.71 cm^3,p=0.07). No differences were found for the paracentral lobule. Left M1 white matter volume was strongly correlated with RMT in CON (r= -0.75, p=0.02) but not in ACLR (r= -0.46, p=0.21). **Discussion:** Individuals with ACLR demonstrated corticomotor differences from CON, as indicated by decreased cortical thickness and increased white matter volume in sensorimotor regions. The association of left M1 white matter with RMT in healthy, but not in individuals with ACLR suggests a potential structural compensation in order to maintain function, which warrants further investigation.

Disclosures: S.D. Flanagan: None. **F. Proessl:** None. **A.J. Sterczala:** None. **A.Z. Beethe:** None. **C. Dunn-Lewis:** None. **B.C. Nindl:** None. **W.J. Kraemer:** None.

Poster

655. Neurodegeneration and Neuromuscular Diseases

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 655.16/F12

Topic: C.06. Neuromuscular Diseases

Support: NIH R03AG050877

Title: Social isolation and loss of physical function: Defining a novel neuromuscular phenotype

Authors: *D. CHUGH, C. IYER, P. BOBBILI, M. L. HALLEY, W. ARNOLD;
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Abstract: Social connections are critically important for physical and psychological resiliency across the lifespan, from early stage development to senescence in older adults. Social isolation and loneliness may affect close to one half of older adults. A recent meta-analysis of studies examining the effect of social isolation and loneliness on mortality demonstrated a 29% increased risk of mortality from social isolation and 26% increase in mortality risk from loneliness. Social networks are more likely to diminish as people get older due to a variety of factors including age-associated loss of independence and immobility. Likewise, social isolation further worsens physical and mental health of older adults. Hence, social isolation, loneliness, and loss of physical function form a vicious cycle of decline and loss of resilience in older adults. In the present study, we asked whether social isolation exacerbates loss of physical function in aging mice. Baseline measures of compound muscle action potential (CMAP) and motor unit number estimate (MUNE) were performed in group-housed 27-month-old male and female C57BL/6J mice. Mice were then randomized into group- and single-housed cages. Longitudinal

in vivo assessments were performed blinded to the housing condition. Isolated female mice showed a significant decline in CMAP amplitude, as well as in motor coordination and muscle endurance as assessed by Rotarod behavioral test at week 4 after social isolation. We next wanted to determine if social isolation induced neuromuscular decline was age-dependent. In contrast to aged mice, young mice showed no differences in CMAP or MUNE but interestingly did show findings of neuromuscular junction transmission failure on single fiber electromyography. We are exploring the potential maladaptive mechanisms underlying our social isolation-related neuromuscular effects. Preliminary analyses revealed age- and gender-specific alterations in fecal corticosterone levels. We are also exploring spinal cord gene-expression changes using Nanostring Neuroscience Gene Expression panel to better understand the neuromuscular phenotype in socially isolated mice.
Social isolation related stress is a well-established stressor in social species with a range of adverse effects. Our results demonstrate that social isolation in young and aged mice impacts neuromuscular health and function. Understanding this phenomenon could have translational implications in older adults experiencing traumatic life events such as losing a spouse or a loved one, retirement, or hospitalization which may all be associated with dire mental and physical health implications.

Disclosures: D. Chugh: None. **C. Iyer:** None. **P. Bobbili:** None. **M.L. Halley:** None. **W. Arnold:** None.

Poster

656. Neurotoxicity, Inflammation, and Neuroprotective Mechanisms: Preclinical

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 656.01/F13

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: 1R01NS083054-01A1

Title: RANTES-induced increased trafficking of Th17 cells in substantia nigra potentiates dopaminergic cell loss in MPTP-induced mouse model of Parkinson's disease

Authors: *D. DUTTA[1], M. KUNDU[1], S. MONDAL[1], A. ROY[1], K. PAHAN[1,2];
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Abstract: Enhanced gliosis, inflammation and accumulation of peripheral T cells are unequivocally found in substantia nigra (SN) of Parkinson's disease (PD) brains. RANTES (regulated on activation, normal T cell expressed and secreted) is one of the major chemokines which was found to be up-regulated in SN and serum of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-intoxicated mice, monkeys and in postmortem PD patients.

RANTES supplementation was also found to help continuous trafficking of T cells in SN of MPTP-intoxicated mice and thereby it promotes progressive loss of nigral DAergic neurons. However, which particular T cell subsets are recruited in the brain by RANTES was not clear. In the present study, immunodeficient Rag1 (-/-) mice, which are known to resist MPTP toxicity, were adoptively transferred with Th1, Th17 and Treg cells isolated from Tomato red mice followed by acute MPTP insult. RANTES was supplemented in mice following MPTP treatment twice in a week, 3.5 days apart from each. The data revealed that infiltration of Th1 and Treg cells is not perturbed by exogenous Rantes administration. However, invasion of Th17 polarized cells in SN of MPTP-challenged mice was significantly increased following RANTES supplementation. Furthermore, RANTES could significantly increase the percentage of MPTP-induced TH cell loss in mice receiving Th17 polarized cells. The aggravated loss of nigral TH neurons also paralleled with significant DA loss in striatum and significant motor deficits in RANTES supplemented MPTP-intoxicated animals. The findings clearly suggest that RANTES specifically recruits peripheral Th17 cells in the brain and thereby promotes progressive DAergic neuronal loss and associated PD pathology.

Disclosures: **D. Dutta:** None. **M. Kundu:** None. **S. Mondal:** None. **A. Roy:** None. **K. Pahan:** None.

Poster

656. Neurotoxicity, Inflammation, and Neuroprotective Mechanisms: Preclinical

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 656.02/F14

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: NIH Grant NS075527
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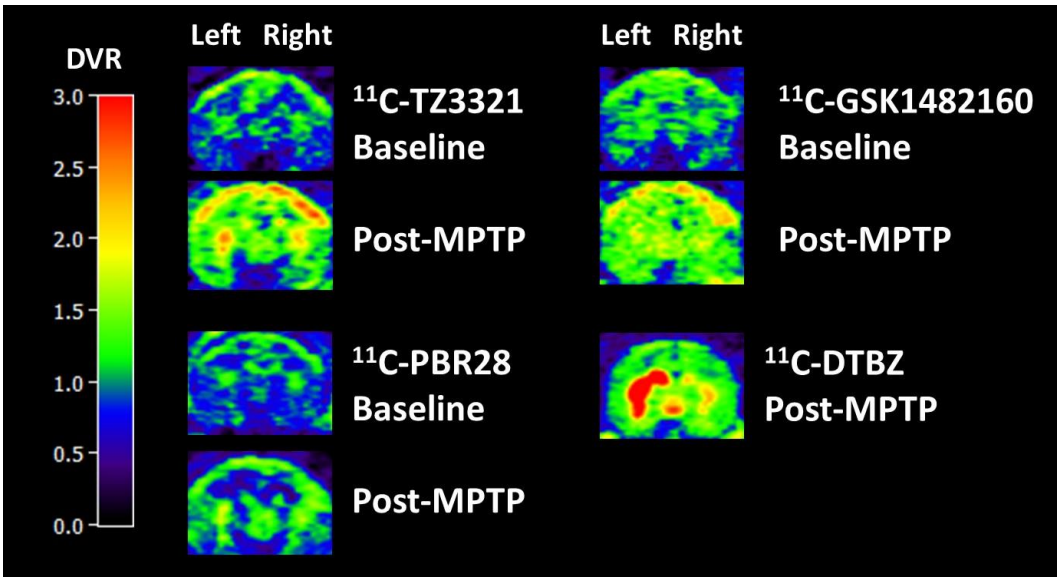
the American Parkinson disease association (APDA)
the greater St. Louis chapter of the APDA
the Fixel foundation

Title: PET imaging studies of neuroinflammation in a nonhuman primate model of Parkinson

Authors: H. LIU[1], Y. ZHOU[1], Z. LUO[1], J. GU[1], Y. YU[1], H. WHITE[1], S. A. NORRIS[1], H. FLORES[1], L. L. DUGAN[2], Z. TU[1], ***J. S. PERLMUTTER**[1];
[1]Washington Univ. Sch. of Med., St. Louis, MO; [2]Dept Medicine/Geriatrics & Vanderbilt Brain Inst., Vanderbilt Univ. Med. Ctr., Nashville, TN

Abstract: Objectives Neuroinflammation plays a key role in the pathogenesis and progression of Parkinson disease (PD). Herein we reported our initial evaluation of 2 new PET radioligands targeting neuroinflammation, along with ^{11}C-PBR28 for translocator protein (TSPO), in an MPTP-induced PD model in nonhuman primates (NHPs). ^{11}C-TZ3321 binds to sphingosine-1-phosphate receptor 1 (S1P1) that is highly expressed in inflammatory cells. ^{11}C-GSK1482160 targets P2X purinoceptor 7 (P2X7 receptor) which reflects glial activation. **Methods** Four male adult macaques underwent a series of 2-hour PET scans (36 scans in total) before and after unilateral internal carotid MPTP. Post-MPTP scans of the ^{11}C-DTBZ and 3 inflammation-targeting tracers were done at week 4 and week 7-8 respecitively. A simplified reference tissue model was used to analyze PET data. **Results** Test-retest variability analysis of baseline scans revealed good reproducibility for all tracers. Ipsilateral nigrostriatal injury was confirmed by an 80% reduction in ipsilateral striatal ^{11}C-DTBZ uptake. The tracer uptake of all 3 tracers remarkably increased throughout the whole brain post MPTP. The increase percentages were 89% for ^{11}C-TZ3321, 32% for ^{11}C-GSK1482160, and 12% for ^{11}C-PBR28. The tracer uptake in right frontal cortex (ipsilateral to MPTP) was significantly higher (1.19-1.37 fold) than the left side. Post-MPTP DVR values in all 11 brain regions of these 3 tracers had strong positive correlations with each other (r^2 = 0.7-0.8). **Conclusion** All 3 tracers for neuroinflammation showed small test-retest variability and were able to detect inflammatory responses in NHP brains post MPTP. ^{11}C-TZ3321 had the highest tracer uptake post MPTP relative to baseline with excellent reproducibility in this animal model. Immunohistological examination is in progress to explore the correlation of increased tracer uptake with glial activation. Further investigations are warranted to demonstrate the S1P1 ligand as a reliable biomarker for quantitative assessment of inflammatory responses and without genotype polymorphism in humans.



Disclosures: H. Liu: None. **Y. Zhou:** None. **Z. Luo:** None. **J. Gu:** None. **Y. Yu:** None. **H. White:** None. **S.A. Norris:** None. **H. Flores:** None. **L.L. Dugan:** None. **Z. Tu:** None. **J.S. Perlmutter:** None.

Poster

656. Neurotoxicity, Inflammation, and Neuroprotective Mechanisms: Preclinical

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 656.03/F15

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: Marie Skłodowska-Curie Grant 749506

Title: Imaging microglia and astrocytes activation using diffusion MRI

Authors: *S. DE SANTIS[1], R. GARCIA-HERNANDEZ[1], N. TOSCHI[2,3], C. MAINERO[2], S. CANALS[1];
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Abstract: Neuroinflammation is currently a hot topic in brain research, due to its involvement in the pathogenesis of several neurodegenerative and psychiatric disorders. However, non-invasive techniques capable to characterize brain inflammation *in vivo* are lacking. Here, we present a strategy to image microglia and astrocyte activation in grey matter using diffusion MRI in rats, and demonstrate its translational value in humans.We used a rat model of inflammation based on intracerebral lipopolysaccharide (LPS) administration, which activates microglia and astrocytes with different delays. We injected LPS (2 µl at 2.5 µg/µl,) in the dorsal hippocampus of 18 rats in one hemisphere, and saline in the contralateral side. After different post-injection delays, the rats were scanned in a Bruker 7T MRI scanner using a diffusion-weighted sequence and immediately perfused for immunohistological analysis of microglia (Iba-1+) and astrocytes (GFAP+). Imaging data were fitted to a multi-compartment microstructural model (MCM), developed ad hoc to model brain parenchyma, and which accounts for the different glia compartments. Histology showed a reduction in microglial cell process density at 8 h, that progressed at 24 h with an additional increase in the microglial cell body size. Astrocytes showed no alteration at 8 h but an increase in cell size at 24 h. Importantly, these differential time courses were mirrored by distinct imaging parameters. At 8 h, the MCM model predicted a decrease in cell process density, reflecting microglia activation and, at 24 h, an increase in the cell size compartment, coincident with the concomitant microglia and astrocytic activation. To disentangle the contribution of both cell types to the 24 h imaging signature, we treated 10 additional animals with PLX5622 to deplete the microglia. At 24 h after LPS injection and with a 99% microglial depletion, we observed only an increase in the cell size compartment, unveiling the fingerprint of the astrocytic reaction. Finally, as a proof of concept for the translational validity of these results, we adapted the MRI protocol to a human 3T scanner and acquired data from a healthy cohort (n=6, age/SD 30/11, 2 females). The MCM model applied to these data returned values for process density and cell sizes comparable to those measured in rats. We demonstrate, for the first

time, that diffusion MRI captures the imaging fingerprint associated to a microglial and/or astrocytic reaction. An instrument to characterize relevant aspects of tissue microstructure during inflammation *in vivo* and non-invasively, is expected to have a tremendous impact on our understanding of the pathophysiology of many brain diseases.

Disclosures: S. De Santis: None. **R. Garcia-Hernandez:** None. **N. Toschi:** None. **C. Mainero:** None. **S. Canals:** None.

Poster

656. Neurotoxicity, Inflammation, and Neuroprotective Mechanisms: Preclinical

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 656.04/F16

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: Smoking Research Foundation

Title: Peripheral inflammation induced cognitive impairment is attenuated by the regulation of activated glial cells and histone deacetylase

Authors: N. TAKADA, *Y. NAKAMURA, K. NAKASHIMA, N. MORIOKA;
Pharmacol., Hiroshima Univ., Hiroshima, Japan

Abstract: [BACKGROUND] Microglia are the major type of glial cells in the central nervous system and crucial in inflammatory responses such as the release of pro-inflammatory cytokines. Several studies showed that inflammation in central nerve systems induces the impairment of cognitive functions. Thus, microglia could be a candidate for therapeutic target for cognitive disorders including Alzheimer's disease. In addition, it has been demonstrated that peripheral inflammation also evoked cognitive disfunction in animal studies. In fact, suppression of peripheral inflammation by chronic treatment with NSAIDs could reduce the risk of Alzheimer's disease. However, the mechanisms underlying peripheral inflammation-evoked cognitive disfunction are unclear. The current study investigated the effect of minocycline, which inhibits microglial activation, and a histone deacetylase (HDAC) inhibitor on peripheral inflammation-evoked cognitive disfunction. [METHOD] Male ddY-mice (6 weeks) were intraperitonially injected with lipopolysaccharide (LPS). Either minocycline or a non-selective HDAC inhibitor suberoyl anilide hydroxamic acid (SAHA, Vorinostat) were injected 1 hour before LPS injection. Twenty-four hours after LPS injection, the cognitive function was determined by novelty objective recognition test. Morphological analysis of glial cells and inflammatory cytokine levels were evaluated by immunohistocal study and real-time PCR, respectively. [RESULTS] The treatment with LPS reduced the discrimination ability, indicating peripheral inflammation induced the cognitive impairment. Moreover, LPS treatment induced activation of microglia/astrocytes and the upregulation of interleukin-1β mRNA in the hippocampus.

Pretreatment with either minocycline (50 mg/kg) or SAHA (50 mg/kg) significantly suppressed the LPS-evoked cognitive impairment and the upregulation of IL-1β mRNA. [CONCLUSION] These data suggest that the glial activation in hippocampus and epigenetic modification such as acetylation of histone could be involved in peripheral inflammation-induced cognitive disfunction. Therefore, HDAC inhibitors and the regulation of activated glial cells might be potential therapeutic targets for cognitive disorders.

Disclosures: N. Takada: None. **Y. Nakamura:** None. **K. Nakashima:** None. **N. Morioka:** None.

Poster

656. Neurotoxicity, Inflammation, and Neuroprotective Mechanisms: Preclinical

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 656.05/F17

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: Peter Deane Trust

Title: Apobec1 knockout is a genetic risk factor that exacerbates effect of mild traumatic brain injury (mTBI)

Authors: *E. M. O'CINNEIDE[1], K. GAGNIDZE[3], J. MARROCCO[2], N. F. PAPAVASILIOU[4], K. BULLOCH[1];
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Abstract: Recent work has shown that post-transcriptional modifications, such as RNA- editing by *Apobec1* (Apolipoprotein B Editing Complex 1), is an important regulator of myeloid phagocytic cell function and diversity (Harjanto et al., 2016). Microglia (MG) are a heterogeneous population of phagocytic cells that reside within the central nervous system (CNS), maintain brain homeostasis and act as sentinels for the immune system. Within the CNS, microglia are the only cell type that expresses obligatory components for the RNA-editing function of *Apobec1*. Deletion of *Apobec1* in mice initiates age-related disruption of microglial homeostasis leading to neuroinflammation with increases in pro-inflammatory cytokines, abnormal myelin formation/maintenance and behavioral deficits (Cole et al., 2017). Although these abnormalities are not apparent in the younger *Apobec1* KO mice, we hypothesize that certain inflammatory challenges may provoke the early onset of such deficits in younger mice. mTBI is known to involve a microglia-mediated inflammatory reponse underlying behavioral deficits. Thus, in the current study we examined the effect of *Apobec1* deletion in young adult and middle-aged male mice following a single mTBI. Our results show that young adult *Apobec1*

KO mice display a severe acute neurological response, evident by longer loss of righting reflex following mTBI compared to young adult WT mice. Impairment in Rotarod motor performance following mTBI in young adult *Apobec1* KO, but not young adult WT mice was also observed. Interestingly, injured young adult *Apobec1* KO mice showed similar acute neurological response and motor learning impairment to KO and WT middle-aged mice. Taken together, these findings indicate that *Apobec1* deletion increases vulnerability to mTBI resulting in MG dysregulation and an accelerated aging phenotype following injury. This study identifies *Apobec1* polymorphisms as a novel genetic risk factor for poor outcome following mTBI.

Disclosures: E.M. O'Cinneide: None. **K. Gagnidze:** None. **J. Marrocco:** None. **N.F. Papavasiliou:** None. **K. Bulloch:** None.

Poster

656. Neurotoxicity, Inflammation, and Neuroprotective Mechanisms: Preclinical

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 656.06/F18

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: PAPIIT IN221819
CONACyT 239594

Title: Time-restricted feeding prevents neuronal cell death in the hippocampus by diminishing active gliosis in lithium-pilocarpine-induced seizure model

Authors: *V. ARRIAGA-AVILA[1], O. F. MERCADO-GOMEZ[2], J. SANTILLAN-CIGALES[3], R. GUEVARA-GUZMAN[4];
[1]Univ. Nacional Autonoma de Mexico, Mexico City, Mexico; [2]Natl. Autonomous Univ. of Mexico, Mexico City, Mexico; [3]Physiol., Univ. Nacional Autonoma De Mexico, FM, Ciudad De Mexico, Mexico; [4]Lab. Sensorial, Dept. de Fisiología, Facultad de Medicina, Univ. Nacional Autónoma De México (UNAM), Ciudad De Mexico, Mexico

Abstract: Introduction: Epilepsy is characterized by the development of recurrent and spontaneous seizures. Neuronal death and inflammatory processes mediated by reactive glia have been described as the pathophysiology that plays an important role in the mediation of the damage so that an inadequate regulation in the activation of this neuronal system might contribute to the progression of the pathology and its chronicity. **Objective**. The main aim of this study is to evaluate the effect of TRF on the activation of astrocytes, microglia, and neuronal cell death after 1 and 5 days post-*status epilepticus*. **Methodology.** Male Wistar rats weighing 200 g were divided into four groups (Control AL, *SE,* TRF and TRF plus *SE*). Control group had free access to water and food. TFR group had only access to food for two hours daylight during 21 days with free access to water. Lithium injection was made 18 h previous and scopolamine

injection was performed 30 min previous pilocarpine injection. Pilocarpine dose injection was 60 mg/kg s.c. and diazepam injection to attenuate seizures was 5 mg/kg after 90 min of SE. All animals were euthanatized at 1 and 5 days post SE and their brains were embedded in paraffin to obtain coronal sections. Reactive astrocytes and microglia were morphologically evaluated by immunofluorescence (GFAP and Iba1, respectively) and neuronal cell death was evaluated with FluoroJade C (FJC) staining. **Results**. Our preliminary results indicate that TRF reduces GFAP marker optical density in CA1 and CA3 fields in both time points and hilus and dentate gyrus (DG) only were reduced after 1 day post-SE. In addition, optical density of Iba1 marker was reduced only in CA1 field in both time points and hilus after 5 days following SE. Moreover, TRF significant reduces FJC-positive cells in DG after 24 post SE and CA1 and hilus region after 5 days following SE. **Conclusion:** TRF exerts a direct effect on the modulation of the quantity and distribution of the resident immune system (microglia) and diminishes the activation of astrocytes Moreover, TRF generates neuroprotection in some regions from hippocampus and this effect might contribute to diminish the early damage and seizures during the development of SE.

Disclosures: V. Arriaga-Avila: None. **O.F. Mercado-Gomez:** None. **J. Santillan-Cigales:** None. **R. Guevara-Guzman:** None.

Poster

656. Neurotoxicity, Inflammation, and Neuroprotective Mechanisms: Preclinical

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 656.07/F19

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: FONDECYT 1171645

Title: Relevance of scavenger receptor-A for the neurotoxic outcome of the inflammatory activation of glial cell

Authors: *R. VON BERNHARDI[1], F. MANZUR[1], L. F. VELASQUEZ[1], P. MUNOZ[1], E. PONCE[1,2], S. BELTRAN[1], J. J. TRIVINO[1], V. RODRIGUEZ[1,2], S. MARCA[1,2], C. ZUNIGA-TRASLAVINA[1], M. TRIOLO-MIESES[1], F. NOVILLO[1], J. EUGENIN[2];
[1]Neurol., Pontificia Univ. Catolica de Chile, Santiago, Chile; [2]Biol., USACH, Santiago, Chile

Abstract: The main risk factor for late onset Alzheimer's disease (LOAD) is aging. Neuroinflammation is a characteristic finding in aging and a conspicuous actor even at early stages of AD. Our "glia-dysregulation" hypothesis states that AD is caused by the impairment of glial cell regulation leading to a neurotoxic environment responsible for neuronal dysfunction and neurodegeneration. In aged mice, microglia show increased expression of cytokines and an exacerbated inflammatory activation of glia. Interestingly, expression and protein levels of

scavenger receptor-A (SR-A) are reduced in 12-month old WT mice, compared with 3-month old mice; whereas SR-A is already reduced at 3 months of age in APP/PS1 mice, compared with WT mice. We reported that SR-A is involved in β-amyloid (Aβ) uptake and the inflammatory activation of glia. Thus, we compared the activation of microglia (MG) obtained from WT, SR-$A^{-/-}$ and APP/PS1/SR-$A^{-/-}$ mice, to evaluate the role played by SR-A in determining the profile of microglia activation. Signal transduction pattern, inflammatory- and regulatory- cytokines production, and the neurotoxicity of microglia conditioned media (CMs), on hippocampal neurons, was assessed. Cytokine levels were measured by ELISA, and the activation of various signaling pathways by western blot. Neuronal apoptosis was evaluated by TUNEL. Glia from SR-$A^{-/-}$ and APP/PS1/SR-$A^{-/-}$ mice had basal levels that were up to 7-fold higher for pro-inflammatory cytokines (TNFα and IL1β), and several-fold lower for anti-inflammatory cytokines (IL10 and TGFβ), compared with WT cells. SR-$A^{-/-}$ cells showed complex changes in both the activation of signaling pathways and the release of cytokines in response to inflammatory stimulation. In terms of cytotoxicity, conditioned media (CMs) of non-stimulated microglia from SR-$A^{-/-}$ mice was more neurotoxic than that of WT mice. In contrast SR-$A^{-/-}$ microglia stimulated with LPS was less neurotoxic that WT cells, whereas Aβ and Aβ+LPS-stimulated microglia induction of hippocampal neurons apoptosis was similar for all the genotypes. Our results show that activation by LPS results in reduced cytotoxicity in SR-$A^{-/-}$ mice in contrast to the preserved activation by Aβ.Thus, SR-A appears to participate in a complex regulation of the inflammatory activation of microglia, which depends on the nature of the stimulus.

Disclosures: **R. von Bernhardi:** None. **F. Manzur:** None. **L.F. Velasquez:** None. **P. Munoz:** None. **E. Ponce:** None. **S. Beltran:** None. **J.J. Trivino:** None. **V. Rodriguez:** None. **S. Marca:** None. **C. Zuniga-Traslavina:** None. **M. Triolo-Mieses:** None. **F. Novillo:** None. **J. Eugenin:** None.

Poster

656. Neurotoxicity, Inflammation, and Neuroprotective Mechanisms: Preclinical

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 656.08/F20

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: Chinese National Natural Science Foundation of China(No. 81773711)
The Science and Technology Program of Guangzhou, China (No. 201704020103)
Introduction of the Innovative R&D Team Program of Guangdong Province (No. 2013Y104)
Chinese National Major Scientific and Technological Special Project for "Significant New Drugs Development"(No. 2016ZX09101026)

Title: Activating Nrf2/HO-1 pathway alleviates inflammatory activation of microglia in theoptic nerves and protects retinal ganglion cells from ischemia-reperfusion injury in acute intraocular hypertension model of glaucoma

Authors: L. SHENG[1], B. LU[1], C. CHEN[1], W. CAI[2], Y. YANG[3], Y. ZHOU[1], Y. DU[1], W. YIN[2], *S. LIN[3], G. YAN[1];
[1]Dept. of Pharmacology, Zhongshan Sch. of Medicine, Sun Yat-sen Univ., Guangzhou, China; [2]Dept. of Biochemistry, Zhongshan Sch. of Medicine, Sun Yat-sen Univ., Guangzhou, China; [3]Guangzhou Cellprotek Pharmaceut. Co. Ltd., Guangzhou, China

Abstract: Elevated intraocular pressure (IOP) is considered the most important risk factor for acute glaucoma, which is one of the leading causes of irreversible visual-field loss. The increasing clinic evidence demonstrated that the inflammatory response and oxidative stress induced by IOP play the key role in the axonal degeneration in optic nerves (ONs) and retinal ganglion cells (RGCs) loss. Moreover, it is reported the depletion of NF-E2-related factor 2 (Nrf2), a master regulator of the antioxidant response, account for the damages of the trabecular meshwork, optic nerve head astrocytes, retinal Müller glial cells, and RGCs as well. But whether the Nrf2 pathway involves in the regulation of microglia in optic nerves is largely unknown. We here use an acute intraocular hypertension (AIH) model of glaucoma and a previously demonstrated neuroprotective steroid of 5α-androst-3β, 5α, 6β-triol (TRIOL) which exhibit antioxidative activities with unclear mechanisms to explore the role of NRF2 in microglia. We find that 10 μM TRIOL significantly inhibits the inflammatory activation of BV2 microglia induced by 100 ng/mL LPS treatment for 12 hours, and notably activates the NRF2 pathway characterized by the nuclear accumulation and enhanced the protein level of NRF2 along with its downstream heme oxygenase-1 (HO-1) by negative regulation of Kelch-like ECH-associated Protein-1 (Keap1). Next, intravitreal injection of TIROL (80 μg /eye) significantly protects RGCs and its axons/dendrites from ischemia-reperfusion (I/R) injury in the rat and mice AIH models. Meanwhile, the effects of Triol on the activation of the NRF2 pathway and suppression of inflammatory activation observed in vitro are further confirmed in microglia of the optic nerves in vivo. Furthermore, the microglia in the optic nerves of the Nrf2 knockout mice are extensively activated after the AIH treatment, which accompanied by the significant RGCs lose and axons/dendrites damage, indicating Nrf2 deletion contribute to the activation of microglia and abrogate the neuroprotective benefits of Triol observed in wild type mice. In summary, our study sheds new light on the inflammation modulation for Nrf2 to the optic nerves microglia and provide a promising neuroprotectant candidate for the therapeutics of acute glaucoma.

Disclosures: L. Sheng: None. **B. Lu:** None. **C. Chen:** None. **W. Cai:** None. **Y. Yang:** None. **Y. Zhou:** None. **Y. Du:** None. **W. Yin:** None. **S. Lin:** None. **G. Yan:** None.

Poster

656. Neurotoxicity, Inflammation, and Neuroprotective Mechanisms: Preclinical

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 656.09/F21

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: Beca CONACYT No. 587113
Dirección General de Asuntos del Personal Académico, UNAM, Mexico (Grant IN202018)

Title: Optogenetic modulation of hippocampal microglia influences cortical and hippocampal network activity and intensify epileptiform activity in anesthetized mice

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Abstract: Epilepsy is accompanied by microglial-induced neuroinflammation in both epilepsy patients and animal models, mainly at seizure-associated brain regions such as the hippocampus. Although putative pharmacological microglial activation seems to promote seizures, there are reports contradicting this notion. To address this, we selectively modulated hippocampal microglia with optogenetics and tested its effects on cortical and hippocampal epileptiform activity induced with 4-aminopyridine (4AP) in anesthetized mice. We found that optogenetic modulation of hippocampal microglia alters cortical and hippocampal network activity and changes microglial morphology towards an amoeboid-like shape. Moreover, optogenetic microglial modulation aggravates cortical and hippocampal 4AP-induced epileptiform activity, in a stimulus duration-dependent manner. Our study revealed that microglial activation promotes seizures, providing new insights on epileptogenesis and revealing new targets against epilepsy.

Disclosures: B. Villasana-Salazar: None. **R. Hernández-Soto:** None. **B. Ordaz:** None. **F. Pena-Ortega:** None.

Poster

656. Neurotoxicity, Inflammation, and Neuroprotective Mechanisms: Preclinical

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 656.10/F22

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: Knut and Alice Wallenberg foundation

Title: Microglia mediated neuroinflammation and endogenous regeneration. Are they connected?

Authors: *P. NIKOLAKOPOULOU[1], D. VOULGARIS[2], I. MATTHIESEN[2], T. E. WINKLER[2], A. HERLAND[2,1];
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Abstract: Neurodegenerative diseases result in both neuronal injury and subsequent neuronal loss, as well as in an extensive and sustained neuroinflammation. Microglia are the resident immune cells of the brain. Originating from the yolk sac, they infiltrate the central nervous system just before the blood-brain-barrier is fully formed and they play a crucial role in neurogenesis. In adulthood and throughout life, activated microglia mediate and regulate the vast majority of inflammatory processes while resting microglia continuously survey their microenvironment to facilitate brain homeostasis maintenance. Adult brain regeneration can be achieved via endogenous neural stem cell (eNSC) activation. eNSCs share common characteristics with microglia; they are highly plastic cells, they self-renew, and they differentiate upon certain stimuli. Recent findings support the active interaction between microglia and neural stem cells, which may play a crucial role in adult neurogenesis and neuroprotection.
Multipotent cytokines such as microphage migration inhibitory factor (MIF) can be activated rapidly upon stimuli and show both mitogenic and proinflammatory functions. MIF regulates NSCs and improves their survival and proliferation *in vitro*. It also regulates cytokine production in immune cells, such as microglia for the brain tissue. Metformin, a very common treatment for diabetes, suppresses plasma MIF concentrations in obese patients; thus, it might be regulating the interplay between microglia induced neuroinflammation and NSC survival in the human brain. It is therefore indispensable to understand if and how microglia activation regulates NSC survival, proliferation and differentiation upon inflammatory stimuli.
Here we aim to recapitulate *in vitro* the microenvironment of the human neurovascular unit (NVU) using human induced pluripotent stem cell derived (hiPSC) brain microvascular endothelial cells (BMVEC), long-term neuroepithelial stem cells (lt-NES) and microglia to study the impact of neuroinflammation on NSC survival and differentiation. Our NVU-on-a-chip xeno-

free co-culture system aims to utilize microfluidics and novel materials to mimic the 3D *in vivo* state in an elegant *in vitro* setup. This may pave the way towards a better understanding of the capacity of the human brain to repair itself as well as towards the development of novel agents for effective therapeutics in neurodegenerative diseases.

Disclosures: P. Nikolakopoulou: None. **D. Voulgaris:** None. **I. Matthiesen:** None. **T.E. Winkler:** None. **A. Herland:** None.

Poster

656. Neurotoxicity, Inflammation, and Neuroprotective Mechanisms: Preclinical

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 656.11/F23

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: TCVGH-HK1078004

Title: The inflammatory responses in aging brain of rats

Authors: *J.-Y. WANG[1], C.-L. CHEN[2], S.-Y. CHEN[1];
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Abstract: Alzheimer's disease (AD) is the most common neurodegenerative disorder in central nerve system (CNS). The prevalence of AD increasing with age and life expectancy is constantly increasing in civilized countries. It will become more important in health problems in the future. Some characteristic lesions in brain of AD: extracellular deposits of β-amyloid peptides (Aβ), so called neuritic or senile plaques (NP or SP), and the intracellular neurofibrillary tangles (NFT) of hyperphosphorylated tau protein. It is known that the intracellular Aβ load in the onset of cognitive dysfunction. Furthermore, Aβ may promote neurodegernation by activation of glial cells. In response to neurogenerative events, astrocytes and microglial cells release variety of inflammatory mediators including cytokines (such as TNF-α), free radicals and nitric oxide (NO), all of which can contribute to neuronal dysfunction and cell death, ultimately creating a vicious cycle. Aβ stimulates a nuclear factor κB (NFκB)-dependent pathway that is required for cytokine gene transcription and induces the inducible NO synthase (iNOS). It indicates that neuroinflammatory response may play a key role and an initial step in pathological mechanisms of AD. The activated astrocytes in aged brain may be acting as a positive feedback loop of chronic inflammation, astrocyte activated, and further inflammation. But the other evidence had shown an astrocyte-mediated protective effect over Aβ-induced damage and modulation of the activation of microglial cells. As far the roles of astrocytes and microglial cells in Aβ-induced injury is still not clear. In this study, we want to investigate the inflammatory responses in aging brain. Aβ1-42 is the major subtype deposited in the brain as an efficient stimulator to induce

neuroinflammatory response in AD. The rat cortical mixed neuronal-glial cultures will be subjected to various experiments. Cell density and morphology will be observed by phase-contrast microscopy. Cell injury will be assessed by 3-(4,5-Dimethyl thianol-2-yl) 2,5 di-phenyltetrazolium bromide (MTT) reduction. The production of NO will be measured to estimate the inflammatory responses. The aging rats (18-22 months) were sacrificed and prepared brain section for immunocytostaining. Our results indicated that Aβ1-42 (5 μM) treated for 24 hr significantly decreased MTT reduction and increased the nitrite accumulation in mixed neuronal-glial cultures. And the results of immunocytostaining of brain revealed that the number of neurons decreased significantly in prefrontal cortex and hippocampus (CA1); however, the activation of microglial cells and iNOS were increased.

Disclosures: **J. Wang:** None. **C. Chen:** None. **S. Chen:** None.

Poster

656. Neurotoxicity, Inflammation, and Neuroprotective Mechanisms: Preclinical

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 656.12/DP03/F24

ControlExtraData.DynamicPosterDisplay:
Dynamic Poster
Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: DZNE and Helmholtz Association, DFG (KI1524/6, KI1524/10 and KI1524/11)

Title: TNF decreases GFAP+ human neural stem cells and upregulates inflammasome component AIM2 in 3D hydrogel cultures

Authors: *H. CELIKKAYA[1,2], M. I. COSACAK[1,2], U. FREUDENBERG[2,3], C. WERNER[2,3], C. KIZIL[1,2];
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Abstract: Neuroinflammatory cytokines such as TNF are implicated in neuropathologies and their effects on human neural stem cell (NSC) plasticity require further elucidation. We investigated the impact of TNF treatment on human NSCs cultured in 3D cell instructive starPEG-heparin hydrogels. TNF led to a 4-fold reduction in GFAP+ NSC number. The neuronal networks that formed in the presence of TNF treatment displayed morphological differences from control cells such as having lean connected paths with few side branches and cells with elongated nuclei. Stem cell markers were downregulated, while cortical markers remained either unchanged or were downregulated except for cortical layer I marker reelin that was upregulated more than 50-fold as demonstrated by whole transcriptome analysis. Additionally, reactive

astrocyte markers and NFκB pathway were markedly upregulated in the presence of TNF. Interestingly, these changes were accompanied by an upregulation of inflammasome component AIM2. Our results indicate that TNF may negatively affect human NSC plasticity by depleting the GFAP+ neurogenic cells, limiting stem cell and cortical layer marker expression, and promoting reactive astrocyte activation. We suggest that the aforementioned TNF effects on human NSCs may be exerted by AIM2 inflammasome activation.

Disclosures: **H. Celikkaya:** None. **M.I. Cosacak:** None. **U. Freudenberg:** None. **C. Werner:** None. **C. Kizil:** None.

Poster

656. Neurotoxicity, Inflammation, and Neuroprotective Mechanisms: Preclinical

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 656.13/F25

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: Geroscience Center for Brain Health and Metabolism (FONDAP-15150012)
Fondecyt de Postdoctorado Project Nº 3180313
Fondo Nacional de Desarrollo Científico y Tecnológico (FONDECYT, No. 1150766)

Title: Necroptosis activation and low-grade chronic inflammation in age-associated neurodegeneration

Authors: *M. S. ARRÁZOLA, F. COURT;
Ctr. for Integrative Biol., Univ. Mayor, Santiago, Chile

Abstract: Brain aging is associated with a decrease in brain function as result of progressive neurodegeneration and increased neuro-inflammation. In addition, low-grade inflammation during aging has been implicated in the pathogenesis of several age-related neurodegenerative diseases. Collective evidence indicates that systemic pro-inflammatory status of an aged organism could affect brain function. We recently demonstrated thatnecroptosis, a regulated necrotic-like cell death pathway that participates in the pathogenesis of several neurodegenerative diseases, regulates axonal degeneration. In this study, we aim to determine whether age-progressive neurodegeneration is mediated by necroptosis activation and potentiated by low-grade chronic and systemic inflammation. Mice of different ages: young (6 month), mild-aged (12-15 month) and old (more than 24 month), were injected (i.p.) with low doses of LPS twice a week during 1 month to induce inflammation. After treatment, animals were subjected to several brain-associated behavioral tests. Microglia and necroptosis activation was evaluated by flow cytometry and immunocytochemistry in different brain areas. The progression of neurodegeneration was assessed with FluoroJade C staining in brain sections. Microglia numbers

($CD45^{low}$/$Cd11b^{+}$) increased in hippocampus, cortex and striatum of young mice after systemic inflammation, accompanied by a morphological change associated with steady-state microglia. Activation state of microglia was confirmed evaluating the percentage of pro-inflammatory M1 Microglia (CD206-/CD16CD32+) over reparative M2 Microglia (CD206+/CD16CD32+). LPS decreased microglial activation in all brain regions analyzed, corroborating our morphological results and suggesting that our model of low-grade and chronic inflammation silence brain immune response, which might favor neurodegeneration.Necroptosis activation, analyzed by pMLKL and pRIPK3 levels, was evidenced only in the striatum of young mice after LPS, suggesting a susceptibility of striatal neurons to undergo necroptosis under chronic inflammation. Degeneration was also observed in striatal terminals. Throughout aging, neurons of the hippocampus progressively degenerate. LPS potentiated hippocampal degeneration in young mice. Hippocampal-dependent memory function was assessed by the Novel Object Recognition test. Only young mice were capable to identify the new object, and LPS inhibited this memory performance, suggesting that systemic inflammation promotes degeneration of neurons in different areas of the aging brain, affecting their functions.

Disclosures: **M.S. Arrázola:** None. **F. Court:** None.

Poster

656. Neurotoxicity, Inflammation, and Neuroprotective Mechanisms: Preclinical

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 656.14/F26

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: Capes-Cofecub program [Me928/19]
FAPESP fellowship to MDSP [2018/03482-0]
Program Investissements d'Avenir [ANR-10-IAIHU-06]
Translational Research Infrastructure for Biotherapies in Neurosciences [ANR-11-INBS-0011-NeurATRIS]

Title: Cannabidiol prevents microglial inflammatory-type reactions by inhibiting ROS-dependent NF-kB activation and glucose consumption

Authors: ***P. P. MICHEL**[1], M. DOS-SANTOS-PEREIRA[1,2], F. S. GUIMARÃES[3], E. DEL-BEL[2], R. RAISMAN-VOZARI[1];
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Abstract: We studied, here, the anti-inflammatory potential of cannabidiol (CBD), the major non-psychoactive component of cannabis. For that, we used microglial cells in culture that were

isolated from post-natal mouse brain through a procedure that relies on the adhesion preference of these cells to the polycation polyethyleneimine (Sepulveda-Diaz et al, Glia, 2016; dos-Santos Pereira et al, Glia, 2018). We established that CBD (1-10 μM) was highly efficient in reducing inflammatory-type responses triggered by the Toll-like receptor4 (TLR4) agonist, lipopolysaccharide (LPS, 10 ng/ml). In particular, CBD strongly reduced the release of two pro-inflammatory cytokines TNF-α and IL-1β and that of glutamate, a non-cytokine mediator of inflammation. Interestingly, CBD was also highly effective against other inflammatory signaling molecules, the TLR-2 agonist Pam3CSK-4 and the P2X7 agonist BzATP, indicating that CBD inhibitory effects were not restricted to a particular inflammatory pathway. The effects of CBD were predominantly receptor-independent; they were only marginally blunted by SCH336, a selective antagonist/inverse agonist at CB2 receptors and insensitive to antagonists of CB1 receptors and PPAR-γ. Additional experiments revealed that CBD had the capacity to restrain LPS-induced inflammatory events by interfering with a signaling cascade involving the ROS producing enzyme NADPH oxidase and subsequently NF-κB-dependent signaling. Importantly, we noticed that NF-κB inhibition by either CBD (1, 10 μM) or TPCA-1, an IκB kinase inhibitor counteracted the rise in glucose uptake that is observed after exposure of microglial cells to LPS, suggesting that CBD occluded pro-inflammatory events by lowering glucose consumption. Comforting this view, CBD anti-inflammatory effects were mimicked by 2-deoxy-D-glucose (2-DG), a synthetic, non-metabolizable glucose analog. Interestingly, CBD and 2-DG led to a reduction of glucose-derived NADPH, a requisite factor for ROS production by NADPH oxidase. Altogether, our findings suggest that CBD possesses potent anti-inflammatory effects towards microglial cells through an antioxidant mechanism that restrains glucose utilization and NADPH synthesis. Present data also further confirm that CBD may have a therapeutic interest in conditions where neuro-inflammatory processes are prominent.

Disclosures: P.P. Michel: None. **M. dos-Santos-Pereira:** None. **F.S. Guimarães:** None. **E. Del-Bel:** None. **R. Raisman-Vozari:** None.

Poster

656. Neurotoxicity, Inflammation, and Neuroprotective Mechanisms: Preclinical

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 656.15/F27

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: PhD scholarship (Deakin University/Australian Federal Government)

Title: Production of purified fractions from garcinia mangostana l. (mangosteen) pericarp containing bioactive compounds and testing in anti-inflammatory cellular *in-vitro* assays (C8-B4 cell line)

Authors: *A. LEUNG[1], C. BARROW[2], M. BERK[3], O. DEAN[3], A. NEALE[3], C. BORTOLASCI[3], K. WALDER[3], S. DODD[3], B. HARVEY[4];
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Abstract: Over the last 15+ years there has been a dearth of new successful pharmaceutical treatments for mental health conditions such as bipolar and schizophrenia. Existing pharmaceutical treatments for these conditions have a wide variability of effectiveness and also have significant negative side effects. Mangosteen pericarp is the rind from the mangosteen fruit, longed used in traditional South East Asian medicine. Constituents of the mangosteen pericarp including alpha-Mangostin and some of the other xanthone compounds have been investigated for their effect in other medical conditions including their potential cytotoxic, anti-microbial and metabolic pathway modulating behaviour. Previously, extracts have been used anecdotally by the general population for minor skin conditions and gastrointestinal illness. Mangosteen pericarp extract is being used by a Deakin University (AUS) clinical research group in large-scale randomised placebo-controlled clinical trials. In particular, the mangosteen pericarp extract is being investigated for its bioactive compounds in relation to oxidative and inflammatory mechanisms and their role in psychiatric disorders such as bipolar, schizophrenia and depression. It has only been in more recent decades that research has been undertaken to investigate inflammatory cytokines possible effect in causing neurocognitive changes and neuropsychiatric diseases, with previous research predominantly focusing on their actions and effect on the immune and metabolic systems.
Our objective was to prepare a number of different Mangosteen extracts and purified fractions derived from these extracts in order to test their anti-inflammatory nature. We investigated methods and processes that resulted in the isolation of bioactive compounds for the use in LPS stimulated C8-B4 cell line assays. We undertook cellular assays using different mangosteen pericarp extracts and purified fractions derived from these extracts. We observed changes in TNF-alpha levels in some of the assays at certain concentration levels. These results will prompt further cell line assays and zebra fish assays to investigate the anti-inflammatory effect of Mangosteen bioactive compounds in more detail.

Disclosures: A. Leung: None. **C. Barrow:** None. **M. Berk:** None. **O. Dean:** None. **A. Neale:** None. **C. Bortolasci:** None. **K. Walder:** None. **S. Dodd:** None. **B. Harvey:** None.

Poster

656. Neurotoxicity, Inflammation, and Neuroprotective Mechanisms: Preclinical

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 656.16/F28

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: MH110550
MH101874

Title: Anti-neuroinflammation effects of neurosteroids

Authors: *S. J. MENNERICK[1], M. KEISER[2], A. BENZ[3], D. COVERY[3], C. ZORUMSKI[3], **H. SHU**[3];
[1]Psychiatry, Washington Univ. Sch. of Med., St Louis, MO; [2]Psychiatry, [3]Washington Univ. in St Louis, Saint Louis, MO

Abstract: Depression is one of the most common psychiatric disorders and affects patients throughout the lifespan. Existing treatments are good but have drawbacks including side effects, slow onset, and low efficacy in some patients. Neurosteroids have captured recent attention as rapidly acting antidepressants. Their best-known action is that of positive modulation of $GABA_A$ receptors. However, other $GABA_A$ modulators, as far as known, do not exhibit antidepressant actions. We hypothesize that neurosteroids may have anti-inflammatory actions that participate in antidepressant effects. Here we began to evaluate structural attributes important for anti-inflammatory effects. We challenged the microglial BV2 cell line with lipopolysaccharide (LPS). As expected, transcripts for pro-inflammatory cytokines IL-1β, IL-6 and TNF-α increased with 6 h LPS treatment. The neurosteroid allopregnanolone decreased LPS-induced proinflammatory transcription in a concentration-dependent fashion. Surprisingly, and unlike $GABA_A$ receptor effects, the enantiomer of allopregnanolone also decreased pro-inflammatory cytokines at similar concentrations. Pre-administration of neurosteroids did not increase the effectiveness or potency. Our results are consistent with a different structure-activity profile for neurosteroids than that exhibited for $GABA_A$ receptor modulation. Thus, our results may suggest a structure-activity profile that selectively engages neuroinflammation.

Disclosures: S.J. Mennerick: None. **M. Keiser:** None. **A. Benz:** None. **D. Covery:** None. **C. Zorumski:** None. **H. Shu:** None.

Poster

656. Neurotoxicity, Inflammation, and Neuroprotective Mechanisms: Preclinical

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 656.17/F29

Topic: F.03. Neuroendocrine Processes

Support: FAPESP (2016/07803-0)

Title: Inhibition of microglial activation differently affects hormone secretion during sepsis

Authors: *L. H. A. COSTA[1], N. N. SANTOS-JUNIOR[1], C. H. R. CATALÃO[1], M. J. A. ROCHA[2];

[1]Ribeirao Preto Med. School, Univ. of Sao Paulo, Ribeirao Preto, Brazil; [2]Sch. of Dent. of Ribeirao Preto, Univ. of Sao Paulo, Ribeirao Preto, Brazil

Abstract: Sepsis, a dysregulated inflammatory response to an infection, promotes deleterious consequences on brain function, including alterations in the neuroendocrine system. The increased production of inflammatory mediators in the hypothalamus, the major central area of hormonal control, could be involved in the complex pathophysiology of sepsis-associated brain dysfunction. Given the essential contribution of microglia, brain innate immune system cells, on neuropathologic conditions, our objective was to access the effect of the activation of these cells on hormone secretion during sepsis. Male Wistar rats (300-350g) received a single intracerebroventricular injection of minocycline (100μg), an inhibitor of microglial activation, or vehicle just before sepsis induction by cecal ligation and puncture (CLP) surgery (10 punctures, 16-gaude needle). Six and 24 hours after the surgery, the animals were decapitated and blood and hypothalamus were collected for hormone and cytokines analysis (ELISA) and protein expression (western blot). A second group was perfused for immunohistochemical processing. Sepsis differently affected endocrine secretion in the acute (6 hours) or late phase (24 hours) of the disease, with decreased (ACTH, prolactin), increased (corticosterone), or a dual response (vasopressin, oxytocin) depending on the hormone. It was accompanied by neuroinflammation and increased markers of hypothalamic apoptosis. Minocycline diminished microglial activation in the hypothalamus, reduced central inflammatory mediators, and prevented cell death, notably at 24 hours. At 6 hours, the inhibition of microglial activation decreased plasma oxytocin and increased corticosterone and vasopressin levels, while in the late phase it diminished oxytocin and increased ACTH and corticosterone. Prolactin secretion was not affected by minocycline administration at any timepoint. We conclude that the activation of microglial cells promotes differential effects on the secretion of different hormones during sepsis.

Disclosures: L.H.A. Costa: None. **N.N. Santos-Junior:** None. **C.H.R. Catalão:** None. **M.J.A. Rocha:** None.

Poster

657. Stroke III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 657.01/DP04/F30

ControlExtraData.DynamicPosterDisplay:
Dynamic Poster
Topic: C.09.Stroke

Support: CIHR MOP 106662
NSERC Grant 2017-04829

Title: Impaired visuomotor adaptation following stroke

Authors: *R. T. MOORE[1], S. P. DUKELOW[2], T. CLUFF[3];
[1]Med., [2]Clin. Neurosciences, [3]Fac. of Kinesiology, Hotchkiss Brain Inst., Univ. of Calgary, Calgary, AB, Canada

Abstract: It is estimated that over 700,000 Canadians are living with stroke-related disability. Previous research suggests that up to 70% of stroke survivors have sensory and/or motor impairments. Many of these individuals participate in neurorehabilitation to improve sensory and motor function. While it is widely accepted that motor learning is critical for neurorehabilitation, comparatively little is known about how stroke impacts motor learning. Here we compare how healthy adults and adult stroke survivors adapt to a novel visuomotor rotation while performing goal-directed reaching movements. We recruited 30 stroke survivors [median age (IQR): 57.5 (14.75); 10 female; median time since stroke (IQR): 58 (553); median Fugl-Meyer upper-limb score (IQR): 60 (17)] and 30 healthy adults [median age (IQR): 59 (12); 14 female]. Experiments were performed with a KINARM exoskeleton robot. The robot supported the participant's arms while they interacted with a virtual reality system through the movement of their arms. The position of their fingertip was displayed in real time using a white cursor (0.8 cm diameter). Direct vision of the arm and hand were occluded throughout the experiment. We instructed subjects to reach back-and-forth between two targets (2 cm diameter) positioned 10-cm apart. Subjects first completed 25 movements with true feedback of their hand position. We then introduced a 30-degree counter-clockwise rotation so that the hand-aligned feedback cursor traveled 30-degrees leftward when making straight movements. Participants adapted to the rotated hand feedback over the course of 125 trials. We then unexpectedly removed the rotation and participants performed another 25 movements with true hand feedback. For each trial, we calculated the angular deviation of the hand's path from a straight trajectory between the targets at 150 ms after the onset of movement. We then fit each participant's hand path deviations to exponential models to determine the overall amount and rate they adapted their movements. We found that stroke survivors adapted their movements less than healthy adults ($p < 0.05$). Stroke survivors also adapted at slower rates ($p < 0.05$) and required more trials to adapt to the rotation ($p < 0.05$). Notably, stroke survivors with more severe motor impairments, as measured by the Functional Independence Measure, also learned to a lesser extent ($r = 0.4852$; $p < 0.05$). Our results suggest that stroke survivors adapt more slowly and to a lesser extent than healthy age-matched adults. Understanding the processes underlying motor learning may be important for designing novel rehabilitation programs that may enhance sensorimotor recovery after stroke.

Disclosures: R.T. Moore: None. **S.P. Dukelow:** None. **T. Cluff:** None.

Poster

657. Stroke III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 657.02/F31

Topic: C.09.Stroke

Support: NIH Grant F32HD094527
NIH Grant R01DC008149
NIH Grant R01DC014358
NIH Grant R37CA225608

Title: Voluntary activation deficits contribute to post stroke lingual weakness in a rat model

Authors: *M. J. CULLINS, J. A. RUSSELL, N. P. CONNOR;
Univ. of Wisconsin Madison, Madson, WI

Abstract: Lingual weakness after stroke is associated with dysphagia and is often targeted by exercise interventions. Chronic weakness after stroke is attributed to both impaired ability to centrally activate target muscles and reduced force generating capacity within muscles. However, how these factors contribute to lingual weakness after stroke is not known. We used middle cerebral artery occlusion (MCAO) to model lingual weakness and deficits in swallowing function in rats after stroke. Our hypotheses were both reduced muscle force generating capacity (maximum *stimulated* force) and reduced ability to activate the muscle (Percent Voluntary Activation) contribute to lingual weakness (maximum *voluntary* force). Six-week-old male Sprague-Dawley rats were randomly assigned to MCAO (N = 14) or sham (N = 12) surgeries and trained to press an instrumented disk with the tongue for a water reward. Maximum voluntary tongue force was determined prior to MCAO and 8 weeks post-surgery. Bilateral stimulation of the medial hypoglossal nerve was used to determine maximum protrusive force generating capacity, muscle twitch properties, and a force-frequency curve. Maximum stimulated force was not significantly different between groups (MCAO = 394.2 ± 149.4 mN, Sham = 345.8 ± 105.9 mN, p = 0.182). Voluntary Activation (voluntary force/stimulated force) was significantly reduced with MCAO (MCAO = 23.7 ± 14.8 %, Sham = 37.8 ± 11.2 %, p = 0.007) and moderately correlated with mean bolus area (*Pearson's r* = 0.602, p = 0.002), a measure of swallowing function previously found to be reduced in the MCAO model. No significant differences between groups were found for muscle twitch properties, cross sectional area of the lingual genioglossus muscle, or force-frequency curves. These data suggest that the primary cause of chronic lingual weakness after stroke is an impairment in central control of muscle activation rather than a deficit of force generating capacity in lingual muscles. Percent Voluntary Activation deficits in the absence of muscle force deficits have also been reported in select hand and leg muscles.

Disclosures: **M.J. Cullins:** None. **N.P. Connor:** None. **J.A. Russell:** None.

Poster

657. Stroke III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 657.03/F32

Topic: C.09.Stroke

Support: R01 HD039343
R01 NS105759

Title: Quantifying the effect of trunk postural control deficits on arm reaching in hemiparetic stroke

Authors: *K. C. SUVADA, J. DEOL, A. ACOSTA, J. P. A. DEWALD;
Physical Therapy and Human Movement Sci., Northwestern Univ., Evanston, IL

Abstract: Our trunk provides a stable base of support during movement to facilitate not only gait but also reaching movement to interact with the environment. When this stable base is compromised due to stroke, trunk and arm coordination during reaching is impaired. Activities that were achievable are now difficult because the trunk cannot counteract the forces imposed by the limbs.

Both arm and trunk motor control is impaired in individuals with hemiparetic stroke. In the arm, this is expressed as weakness, hyperactive stretch reflexes and involuntary coupling of shoulder abduction with elbow, wrist, and finger flexion, commonly known as the flexion synergy. In the trunk, previous studies have shown earlier and excessive trunk movement during reaching with the paretic limb and larger sway area when sitting upright compared to controls. While these studies show that trunk motor control is impacted following stroke, little is known about how these trunk deficits affect reaching or whether trunk function is also impacted by the flexion synergy. Furthermore, since the flexion synergy has only been studied with the trunk restrained, the interaction between trunk and arm movement remains unknown.

The goal of this study is to measure the effect of trunk impairments arising from a stroke on reaching ability during various shoulder abduction loading conditions. I hypothesize that when the trunk is unrestrained there will be a negative impact on reaching for both arms and the impact will be amplified with shoulder abduction loading.

Participants will sit in a chair with their pelvis restrained and their hips in slight extension using a cushion. The arm will be placed in a haptic device that allows motion on a horizontal plane while applying vertical loads. The position of the hand, trunk, and shoulders will be tracked using a motion tracking system. Participants will be asked to reach as far as possible while maintaining the trunk posture with simultaneous feedback of the position of the hand on a computer monitor. Participants will receive feedback after the trial if the trunk was outside of preset circular bounds.

The effect of trunk restraint, shoulder abduction loading and limb on reaching distance will be tested via a three factor repeated measures ANOVA. We expect to find an effect of trunk restraint on reaching distance with reduced reaching ability in the unrestrained conditions across shoulder abduction load levels for both limbs. However, we expect shoulder abduction load will only affect reaching distance of the paretic limb due to the flexion synergy.
The results from this study will further our understanding of the effect of stroke on trunk motor control and its effect on reaching ability.

Disclosures: **K.C. Suvada:** None. **J. Deol:** None. **A. Acosta:** None. **J.P.A. Dewald:** None.

Poster

657. Stroke III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 657.04/F33

Topic: C.09.Stroke

Support: NIH Grant NS085568
NIH Grant NS091585

Title: Cognitive impairments mediated by the non-injured hippocampus after focal cortical ischemic stroke in mice

Authors: ***W. ZHONG**[1,2], Y. YUAN[1], X. GU[1], M. QU[1], M. R. MCCRARY[1], A. WU[1], L. WEI[1], S. YU[1,2];
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Abstract: Stroke is a serious threat to human life and health in the US and around the world. Around 8 million people in the US and 15 million people worldwide experience a stroke each year. Among them, 30%-60% of survivors suffer from cognitive impairment in the first year after stroke. However, the pathophysiology of post-stroke cognitive impairment remains unclear. In the present investigation, we tested the development of post-stroke psychological disorders in a focal ischemic stroke mouse model with select damages in the sensorimotor cortex. These stroke animals showed significant sensorimotor deficits soon after stroke followed by a gradual spontaneous recovery within 2-4 weeks after the ischemic insult. Besides the ischemic cortical damage, no TUNNEL-positive cells were detected acutely or chronically in the hippocampus, indicating that this brain region was not primarily damaged by the ischemic insult. Meanwhile, significantly enhanced neurogenic activities were observed in the sub-granule zone (SGZ) starting from 2-3 weeks after stroke. However, in the Morris Water Maze test, the hippocampus-dependent working memory was significantly impaired at 3 weeks post stroke and the deficit maintained at least till 6 weeks after stroke. Electrophysiology assays revealed functional deficits of the long-term potentiation (LTP) and pair-pulse ratio (PPF) in the CA1 region at 3-6 weeks

poststroke, suggesting a long-lasting impairment of synaptic plasticity. Our data demonstrate that a focal cortical ischemic insult may cause functional deficits in a remote non-injured region such as the hippocampus. Interestingly, the observed SGZ neurogenesis showed no functional benefits while it is possible that, based on some previous observations, stroke evoked aberrant SGZ neurogenesis might contribute to the cognitive impairment.

Disclosures: W. Zhong: None. **Y. Yuan:** None. **X. Gu:** None. **M. Qu:** None. **M.R. McCrary:** None. **A. Wu:** None. **L. Wei:** None. **S. Yu:** None.

Poster

657. Stroke III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 657.05/F34

Topic: C.09.Stroke

Title: Monoaminergic drive modulates post-stroke flexion synergy expression

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Abstract: The role of descending monoaminergic drive in human motor control, particularly in disease states such as chronic stroke, is still largely unknown. Animal work indicates that monoamines modulate the gain of spinal motoneurons. Evidence suggests that following a stroke-induced loss of cortical inputs to the cord, a subsequent increase in monoaminergic drive may increase the gain of diffuse reticulospinal inputs to compensate for voluntary motor control. The diffuse innervation of the reticulospinal tract is suggested to contribute to the flexion synergy, a prominent impairment in chronic stroke in which lifting up at the shoulder of the paretic arm coactivates elbow, wrist, and finger flexors, pulling the arm in as the individual lifts up. Thus, an increase in monoaminergic drive post-stroke may negatively contribute to reaching function. The goal of this preliminary research is to determine the role of descending monoaminergic drive in post-stroke motor control by pharmacologically manipulating norepinephrine supply to spinal motoneurons and measuring resulting reaching function. Three individuals with chronic hemiparetic stroke participated in 1) pre-medication measures of reaching function followed by 2) the administration a single oral dose of 4mg Tizanidine, followed by 3) on-medication measures of reaching function. Tizanidine is a selective noradrenergic alpha-2 (spinal action) and imidazoline (brainstem action) agonist demonstrated to decrease norepinephrine release. Individuals were instructed to ballistically reach towards a virtual target while lifting their paretic upper limb at the shoulder under varying levels of robot assisted limb support. Medication administration resulted in significant increases in reaching distance in conditions when participants had to actively support their paretic arm and significant

increases in reaching velocity in all conditions. These preliminary results suggest that Tizanidine reduces the flexion synergy post-stroke, and that monoaminergic drive modulates the gain of the reticulospinal tract in voluntary motor control post-stroke. A supraspinal reduction in monoaminergic drive may reduce the expression of the flexion synergy and improve reaching function for individuals with chronic hemiparetic stroke.

Disclosures: J.R. Patterson: None. **C. Heckman:** None. **J.P. Dewald:** None.

Poster

657. Stroke III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 657.06/F35

Topic: C.09.Stroke

Title: Transcutaneous cranial nerve stimulus in individuals with a chronic hemiparetic stroke

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Abstract: Chronic stroke induced limitations in upper extremity motor function are commonly manifested as the emergence of hyperactive stretch reflexes (spasticity) and a loss of independent joint control, such as the abnormal coupling between shoulder abduction with elbow, wrist and finger flexion (flexion synergy). Evidence suggests these motor impairments can be attributed to a loss of corticofugal projections, inciting a greater dependence on contralesional corticobulbospinal tracts and an increased monoaminergic drive. This is believed to increase spinal motoneuron excitability, generating the observed spasticity and amplifying the diffuse descending commands postulated to be responsible for the flexion synergy expression. This yields a potential avenue, whereby modulating monoaminergic drive (norepinephrine) may causally manipulate spinal motoneuron excitability and flexion synergy expression in this population. We therefore hypothesize that use of non-invasive transcutaneous cranial nerve stimulation via the trigeminal or auricular branch of the vagal nerves to modulate monoaminergic brainstem areas, such as the locus coeruleus (LC) and raphe nuclei (RN), will alter motoneuron excitability in individuals with a chronic hemiparetic stroke. Thus, we recruited four individuals with moderate to severe upper extremity impairment at least one-year post stroke. Motoneuron excitability was quantified via the tonic vibration reflex in the biceps brachii of an individual's paretic limb following both sham and real transcutaneous ophthalmic trigeminal nerve stimulation (TNS; 100 Hz, 300μs, avg: 4.5mA). Specifically, participants were instructed to generate and maintain 15% of maximum voluntary elbow flexion torque for 20s, with vibratory stimulus (128 Hz) applied to the paretic biceps brachii muscle from 10-15s. The reflexively generated elbow flexion torque during this vibratory stimulus was then assessed before, during, and after one hour of TNS. Compared to an active sham stimulus, TNS applied

bilaterally to the supraorbital nerve elicited greater decreases in reflexively generated elbow flexion torque in all four participants. This was observed as a significant decrease in reflexively generated elbow flexion torque between the sham and TNS conditions. This suggests that greater monoaminergic drive may increase spinal motoneuron excitability in this population. Further work to understand the effects of TNS on spasticity and flexion synergy in individuals with a stroke will be conducted.

Disclosures: J.A. Beauchamp: None. **J. Yao:** None. **J.P.A. Dewald:** None.

Poster

657. Stroke III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 657.07/F36

Topic: C.09.Stroke

Title: Silent stroke to the medial dorsal nucleus of the thalamus impairs olfactory circuitry

Authors: H. VAN DER GIESSEN[1], D. BARWICK[1], ***A. N. CLARKSON**[2];
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Abstract: Introduction: Olfactory impairments are common and have been reported to affect up to 43% of chronic stroke patients, however, the mechanisms associated with olfactory impairments remain poorly understood. Several human clinical studies have shown stroke to the MDNT results in olfactory deficits. Therefore, we aimed to establish a model of stroke targeting the MDNT in mice to investigate connections between the orbitofrontal cortex and piriform cortex; and whether disruptions in these circuits alter olfactory behavior. **Methods:** Young C57BL/6 mice (2-3 month old, n=20) received either an injection of the vasoconstrictor N5-(1-iminoethyl)-L-ornithine (L-NIO: 2.50µl; infused at 0.3ul/min, n=10) to induce a stroke or saline (n=10) as sham controls. Behavioral assessments, both buried food and odor discrimination, were undertaken on weeks one and four post-stroke. On the final day of behavior, the retrograde tracer Cholera Toxin subunit B (CTB-488; 200nl infused at 0.125µl/min) was injected into the orbitofrontal cortex and the anterograde tracer Biotinylated Dextran Amine (BDA; 300nl infused at 0.125µl/min) was injected into the piriform cortex to assess changes in olfactory circuitry. Infarct volume and differences in reactive astrogliosis were assessed histologically and immunohistochemically. **Results:** Histological assessments revealed no overt signs of an infarct, whereas assessment of GFAP-labeling revealed extensive reactive astrogliosis in the MDNT ($p=0.0178$) 5-weeks post-stroke indicating widespread injury compared to sham controls. Assessment of tract-tracing studies revealed injury to the MDNT results in a significant loss of connections between the orbitofrontal cortex and piriform cortex ($p=0.0396$), indicating olfactory function could potentially be compromised. **Discussion:** To the best of our knowledge, we believe the current study is the first to report a model that could represent silent stroke that when

induced in the MDNT disrupts olfactory circuitry (connections), which could underpin the development of a behavioral deficit.

Disclosures: H. Van der Giessen: None. **D. Barwick:** None. **A.N. Clarkson:** None.

Poster

657. Stroke III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 657.08/F37

Topic: C.09.Stroke

Support: NIH Grant F31NS095706

Title: Examining the interplay between movement control and resting posture after stroke

Authors: *A. M. HADJIOSIF[1], S. T. ALBERT[2], K. KITA[1], R. SHADMEHR[2], J. W. KRAKAUER[1];
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Abstract: A common characteristic of the post-stroke motor phenotype is abnormal coupling of muscles that move different joints - such as shoulder vs. elbow - a coupling which disrupts movement. These *synergies* define the motor phenotype to the point that breaking out of them is widely considered a recovery milestone, as described in Twitchell's seminal work and used in scales of post-stroke motor impairment such as the Fugl-Meyer. In addition, patients often have abnormal arm postures and heightened stretch reflexes at rest, i.e., when they are not trying to make a voluntary movement.
Here, we aim to examine the interplay between such resting abnormalities and the control of reaching and holding by measuring both in the same workspace. We hypothesize that deficits in the motor control of reaching may be, to a degree, explained by the abnormal muscle contraction patterns that stroke patients produce at rest. For example, the direction and amount of resting postural forces on a position may explain why and how movements to that target may be impaired.
We first evaluated movement control during reaching and holding. Stroke patients (so far N=14) and healthy controls (so far N=5) made repeated, arm-supported 2D reaches between 5 different targets. Patients' (unperturbed) movements were impaired compared to the non-paretic arm and controls: they were slower and took a longer path to reach the target. Since postural abnormalities may differentially affect regular movement vs. responses to perturbations, we also examined patients' responses to perturbing forces applied during reaching and/or holding. During a fraction of reaches, force-pulses pushed the arm lateral to the ideal trajectory; during some hold-on-target periods, forces pulled the arm away from the target. Patients exhibited deficits in responding to both perturbation types, taking longer times and/or longer paths to

stabilize the arm.
To evaluate postural abnormalities in these patients, we built upon previous work (Simo et al *SfN 2013*) and measured resting postural forces by passively moving the arm to different locations in the same workspace where movement control was assessed. We found that stroke patients displayed remarkably stronger resting postural force biases in their paretic arm compared to the non-paretic arm and controls, and that these resting force biases were even greater when measured without weight-bearing arm support.
We will proceed to relate these resting postural forces to the quality of reaching and holding control within the same workspace. This will enable as to assess the degree to which abnormal resting postural forces explain the post-stroke motor control phenotype for the arm.

Disclosures: A.M. Hadjiosif: None. **S.T. Albert:** None. **K. Kita:** None. **R. Shadmehr:** None. **J.W. Krakauer:** None.

Poster

657. Stroke III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 657.09/F38

Topic: C.09.Stroke

Support: NWO (STW grant 14904)

Title: Passive ankle joint stiffness compensation by a novel ankle-foot-orthosis: Improving spastic paretic ankle motor control after stroke

Authors: *K. E. RODRIGUEZ[1], J. H. DE GROOT[2], F. BAAS[3], M. STJINTJES[2,4], F. C. VAN DER HELM[4], H. VAN DER KOOIJ[4], W. MUGGE[4];
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Abstract: Patients with spastic paresis of the lower leg have lost neuromuscular control of the ankle joint due to affected active and passive components. Muscle paresis and increased passive joint stiffness (~100%, mainly originating from calf muscles) substantially reduce (~30%) the active range of motion (aROM) of the ankle[1], which impairs gait causing disability. Although standard Ankle-Foot-Orthoses (AFOs) for spastic paresis show clinical relevant improvements of gait parameters, their designs limit the aROM even more due to the additional stiffness they add to the joint. We propose a (non-powered) AFO with negative stiffness (nAFO) that aims to compensate for the pathologically increased passive ankle joint stiffness in spastic paresis. A spring- loaded CAM follower mechanism generates the negative stiffness that can be adjusted to the user's passive torque-angle characteristic modelled as an exponential curve with 3 parameters

($T=c_1e^{c2(\theta-c3)}$) where T is the passive torque and θ is the ankle angle. We hypothesize that compensating the passive ankle joint stiffness would 'augment' the patient's muscle capabilities to achieve a higher aROM. The first nAFO design proved the principle and walking-ability in a healthy subject. In this study, a redesign of the nAFO attains important improvements in adaptability, weight, hysteresis and range of motion of the orthosis. The brace of the nAFO has a modular design: the foot and calf parts are exchangeable to fit the user's lower leg. The weight of the nAFO is below 1.0kg (max foot size 42). Results of technical tests show a maximum negative stiffness of 1.4Nm/° at 10 ° dorsiflexion (DF) (patients up to 1.5Nm/deg[1], knee extended) with energy loss of 10% (hysteresis) throughout its range of motion of 60° (50° plantarflexion to 10° DF). Pilot tests in 3 healthy male subjects (~25 years) show that the nAFO can (over)compensate their passive ankle joint stiffness up to 170% between 0° and 10° DF (knee 30° flexed). We conclude that the current nAFO is a promising design to compensate for high passive ankle joint stiffness of multiple patients with spastic paresis. We have started a clinical trial in which the aROM is assessed at joint level (ankle rotations applied by an ankle manipulator while sitting) and at activity level (during walking on an instrumented treadmill). We expect patients to use their remaining (mainly dorsiflexion) muscle force to enlarge the aROM at both single joint and activity level.

1. Gao, F., Grant, T. H., Roth, E. J. & Zhang, L.-Q. Changes in Passive Mechanical Properties of the Gastrocnemius Muscle at the Muscle Fascicle and Joint Levels in Stroke Survivors. *Arch. Phys. Med. Rehabil.* 90, 819-826 (2009).

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Poster

657. Stroke III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 657.10/F39

Topic: C.09.Stroke

Support: R01: 5R01HD053793-12
P&K Pühringer Foundation

Title: Reinforcement motor learning is impaired in acute stroke patients

Authors: M. BRANSCHEIDT[1,2], A. M. HADJIOSIF[3], M. A. ANAYA[2], J. KELLER[4], K. D. RUNNALLS[2], M. WIDMER[5], A. R. LUFT[1,5], J. W. KRAKAUER[3], A. J. BASTIAN[4], *P. A. CELNIK[2];
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Johns Hopkins Univ., Baltimore, MD; [4]Kennedy Krieger Inst., Baltimore, MD; [5]Cereneo Advanced Rehabil. Inst. (CARINg), Vitznau, Switzerland

Abstract: It has been argued that reduction of motor impairment mainly occurs within a 'sensitive period' early after a stroke. The mechanisms underlying the behavioral gains are unclear, but mouse models suggest a causal link to a peri-ischemic milieu of heightened plasticity that lasts ~3weeks (Wahl et al. 2014). Since humans also experience a period of rapid motor recovery in the upper extremity in first 3months after stroke, we ask whether the capacity for motor learning is also increased during this period, perhaps mediated by the heightened plasticity described in animal models. In a cross-sectional study, we tested the ability of patients with supratentorial strokes to learn two motor tasks during the acute (<2months; n=22) vs. chronic recovery stage (>6months; n=29), and in healthy controls (n = 11). Across these groups, we compared learning of a reinforcement-based motor task that likely predominantly relies on corticomotor-basal ganglia loops with a visuomotor adaptation task that relies mostly on error-based processes driven by cerebellar plasticity. We hypothesized that if a peri-ischemic hyperplastic state indeed promotes learning, patients in the acute stage will experience higher rates of reinforcement motor learning relative to patients in the chronic stage and controls, with no group differences in adaptation. To assess learning, participants sat in a Kinarm robot and made 10cm reaching movements from a start position through a visual target. During learning, (both tasks were designed to shift movement directions by the same 15°) the adaptation task by gradually imposing a visuomotor rotation upon the cursor, and the reinforcement task by hiding the cursor and providing binary, endpoint feedback that rewarded movements directed closer and closer to a 15° shift. Total learning was defined as changes in reach angles from baseline to late perturbation. Preliminary results show that while adaptation learning was not affected by time after stroke, learning in the reinforcement task was reduced in the acute stroke group relative to the chronic and healthy controls.Further, reinforcement learning was also reduced compared to adaptation in the acute group. Importantly, these differences were not explained by execution abnormalities in baseline point-to-point reaches, reinforcement rate, the severity of motor and cognitive impairment, or age. Our findings are opposite to the original prediction, showing impaired rather than enhanced reinforcement learning in the acute stage. This suggests that if there is heightened plasticity in humans, it might not be engaged in motor learning, which has important implications for rehabilitation training strategies.

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Poster

657. Stroke III

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Topic: C.09.Stroke

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NIH Grant R01HD039343
NIH Grant T32EB009406
NIH Grant R01NS098509

Title: The relationship between stroke-induced changes in motor unit firing behavior and the expression of motor deficits

Authors: *A. S. HASSAN[1], M. Q. CUMMINGS[1], C. K. THOMPSON[3], F. NEGRO[4], R. K. POWERS[5], C. HECKMAN[2], L. M. MCPHERSON[6,7], J. P. DEWALD[1];
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Abstract: Over half of stroke survivors experience long-term motor deficits in the upper extremity. Previous studies have shown that following a stroke there is a reduction in individual motor unit firing rates, impaired motor unit firing rate modulation, and atypical motor unit recruitment order. However, the relationship between the change in motor unit firing patterns and movement disabilities in individuals with stroke has not been thoroughly investigated. One possible explanation for the reduced motor unit firing rates and motor unit firing rate modulation may be a reduction in direct drive from corticospinal pathways, which has been partly replaced by activation of reticulospinal pathways, leading to abnormal muscle synergies and less efficient activation of motor units. Using a quantitative metric (change in firing rate (pps) as a function of % increase in maximum voluntary torque), our preliminary results show that motor unit firing rate modulation decreases as impairment level increases in individuals with stroke. However, the relation between this impaired modulation and specific motor impairments is still unknown. This work utilizes high-density surface EMG and a blind source separation algorithm to identify firing patterns of tens of motor units from multiple muscles, simultaneously. We sought to determine the relationship between motor unit firing rate modulation and interlimb weakness in individuals with chronic hemiparetic stroke across impairment levels. In preliminary data from 3 stroke subjects, we have found a positive correlation between elbow extension strength ratio and the motor unit firing rate modulation of the paretic triceps. We also aimed to identify differences in motor unit rate modulation between voluntary and synergy-driven contractions, in individuals expressing the prevalent flexion synergy following chronic hemiparetic stroke. In 38 motor units discriminated from 2 moderately impaired chronic stroke subjects, we found a reduced firing rate modulation of -0.31 ± 0.072 pps/%MVT during synergy-driven contractions, compared to 0.16 ± 0.161 pps/%MVT during voluntary contractions. These results show not only a reduction in rate modulation linked to losses of the corticospinal system (weakness) but further reductions when indirect corticoreticulospinal systems are increasingly being used such as during the expression of the flexion synergy.

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Poster

657. Stroke III

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Topic: C.09.Stroke

Support: NIH Grant R01NS058667
NIH Grant T32EB009406
American Heart Association Predoctoral Fellowship 18PRE33960466
Foundation for Physical Therapy PODS II

Title: Characterization of reaching distance and velocity in individuals with childhood-onset hemiplegia

Authors: *N. M. HILL[1], J. P. A. DEWALD[2];
[1]Biomed. Engin., [2]Physical Therapy and Human Movement Sci., Northwestern Univ., Chicago, IL

Abstract: Introduction: Children use their arms to complete several tasks over the course of a typical day. A unilateral injury to the brain resulting from a diagnosis of cerebral palsy or pediatric stroke can markedly impair the ability to use one arm, making routine tasks difficult or impossible. Previous work in this population has demonstrated that in isometric conditions, individuals with later injuries have decreased ability to isolate shoulder abduction torque generation from elbow, wrist, and finger torque generation. In contrast, individuals with earlier injuries are more similar to typically developing controls in being successful in isolating torque generation across joints. The purpose of this study was to investigate the ability of the brain to selectively control the shoulder and elbow joints during a high effort, ballistic reaching task in individuals with childhood-onset hemiplegia and determine if there are differences based on injury timing during a dynamic task. Methods: Participants were seated in a Biodex chair and cued to reach ballistically to a virtual target on a screen. The arm was rigidly attached to an admittance controlled robotic device that allows movement in the X, Y, and Z planes and is able to modulate the amount of shoulder abduction torque required to lift the arm off of the haptic table. Participants were instructed to reach with the arm fully supported on the haptic table or while lifting a percentage of their maximum torque effort (up to 80%). Reaching distance and velocity was measured for each condition tested. Results: A total of 18 participants ages 6-19 years old completed the reaching tasks on the non-dominant arm for typically developing controls and paretic arm for participants with hemiplegia. Reach distance is normalized to maximum distance achieved across all trials for comparison between participants. Reaching

results show a trend towards decreased reach distance at higher shoulder abduction torques in individuals with later injuries compared to earlier injuries and typically developing controls. Overall velocity results show slower reaching velocities for individuals with hemiplegia compared to typically developing controls and a greater effect of shoulder abduction torque on reaching velocity in individuals with later injuries compared to earlier injuries.

Disclosures: N.M. Hill: None. **J.P.A. Dewald:** None.

Poster

657. Stroke III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 657.13/F42

Topic: C.09.Stroke

Support: NIH Grant 5R01HD089952-03

Title: Asymmetry of reflex thresholds between contralateral limbs in hemispheric stroke survivors and dominant limbs in neurologically intact individuals

Authors: T. AFZAL[1], M. K. CHARDON[4], N. L. SURESH[2], *W. Z. RYMER[3];
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[4]Physiol., Northwestern Univ., Chicago, IL

Abstract: Spasticity, characterized by increased stretch reflex excitability, is a major consequence of stroke. One possible cause of hyperreflexia in chronic stroke survivors is increased motoneuron (MN) excitability. Based on findings from animal studies, there are multiple potential sources of increased spinal MN excitability after a stroke, including increased vestibulospinal and/or reticulospinal (RS) drive, potentially due to disruption of cortico-bulbar inhibitory pathways projecting to these brainstem nuclei. Spasticity, as clinically assessed in stroke survivors is highly lateralized, thus the involvement of the vestibulospinal tract is obviously relevant. On the other hand, RS nuclei project bilaterally to the spinal cord, thus RS contributions to lateralized spasticity, are difficult to reconcile. We hypothesize that after hemispheric stroke, alterations in the excitability of the RS tract affect both sides of the spinally innervated musculature and thereby contribute to hyperexcitability of reflex pathways on both sides of stroke survivors (as compared to neurologically intact subjects). In this work, we report on stretch reflex threshold measurements in biceps brachii muscles of hemispheric stroke, as well as in controls. Thresholds were obtained using progressive indentation of the biceps tendon using a linear motor. We tested spastic and contralateral limbs and dominant limbs of four hemispheric stroke survivors (2 males, 2 females) and in four age and gender matched intact subjects. We recorded surface EMG from the biceps (and triceps) muscle. The reflex threshold was identified as the indentation level where the rectified-integrated EMG in a 50 ms window, measured 20 ms

after the tap, increased above mean + 3SD of the pre-tap EMG. For consistency across subjects, we indented the biceps distal tendon up to a depth of 25 mm. The mean reflex threshold in the stroke survivors was 14.5 (4.7) mm on the contralateral limb. For intact subjects, the mean threshold was 24.3(1.0) mm. The difference between the reflex thresholds was statistically significant ($p < 0.05$). Our findings, i.e., a reduction of reflex threshold on the contralateral limb with respect to intact controls, supports our contention that the disruptions in the RS tract subsequent to stroke-induced lesions increases MN excitability in both affected and contralateral muscles of stroke survivors. Indeed, there is a high correlation between the (individual) reflex thresholds measured on both sides of our stroke participants.

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Poster

657. Stroke III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 657.14/F43

Topic: C.09.Stroke

Title: Event related cortical activity during simple motor task post stroke

Authors: *P. BALASUBRAMANIAN[1], S. Z. ALQAHTANI[2], A. S. HYNGSTROM[2], B. D. SCHMIT[1];
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Abstract: Introduction: In this study, we examined the ability of stroke survivors to modulate brain activity in a cued fingertap task. Event related desynchronization (ERD), a measure of cortical activity during a motor task, has reduced signal strength and somatotopic organization during self-paced fingertap in people with stroke. Our study identified changes in magnitude, spatial distribution, and time course of beta ERD during a cued task, which also distinguishes cortical modulation during a motor task.
Methods: Six stroke (mean age 69.5 ±12.4, 1 male and 5 females) and six healthy adults (mean age 24 ±1.2, 3 males and 3 females) made fingertap movements using their paretic/dominant index finger, to visual cues on a computer screen. Cues lasted 500ms and the cue interval randomly varied between 5-7 s. EEG signals were recorded using 64 active electrodes, arranged on the ACTi Cap (Brain Products GmbH) EEG cap, set in the conventional 10-20 international system of electrodes. The signals, sampled at 1000Hz, were band pass filtered (0.3 and 200Hz), notch filtered (60Hz), and amplified using the Scan 4.5 software and a Synamps 2 EEG system (Compumedics™ Neuroscan™). EEGLab and Fieldtrip toolboxes were used to epoch, filter, and artifact clear the EEG data, to compute changes in the power of the signals in beta (13-26 Hz) frequency band.
Results: Cortical activation measured using beta ERD indicated lateralized reduction in power in

healthy adults, at movement onset. Their beta ERD was at 30% below baseline for <1s, followed by resynchronization up to 20%. In stroke survivors, reduction in power measured as beta ERD was larger (45% below baseline) and the cortical activation was longer (about 2s) before returning to baseline. Spatially, beta ERD was seen in medial central sensorimotor areas in people with stroke, compared to lateralized activity in controls. In addition, stroke survivors lacked resynchronization post movement, which typically denotes end of cortical processing. **Conclusion**: Increased and sustained beta ERD with the absence of resynchronization in stroke adults showed their reduced ability to modulate cortical activity during a motor task.
References: G. Pfurtscheller and F. H. Lopes Da Silva, "Event-related EEG/MEG synchronization and desynchronization: Basic principles," *Clinical Neurophysiology*, vol. 110, no. 11. pp. 1842–1857, 1999.

Disclosures: P. Balasubramanian: None. **S.Z. Alqahtani:** None. **A.S. Hyngstrom:** None. **B.D. Schmit:** None.

Poster

657. Stroke III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 657.15/F44

Topic: C.09.Stroke

Support: NS056839

Title: Coordinated asymmetrical bimanual reaching strategies used by C57/BL6 mice in a novel bimanual skilled reaching task

Authors: *D. MIRANDA-SOHRABJI[1], S. KUMAR[2], E. NUDI[1], N. DONLAN[2], T. A. JONES[3];
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Abstract: The synapse to circuit level plasticity involved in unimanual skill learning has received a wealth of attention, but that of bimanual skill learning has not. This project was motivated by a need to better understand how the two may vary in the context of stroke recovery. Upper limb hemiparesis after stroke leads to compensatory reliance on the other hand, exacerbating disuse and dysfunction in the paretic side. Prior findings in rodents with unilateral motor cortical infarcts indicate that learning new unimanual skills with the nonparetic hand is particularly maladaptive for the paretic side. This is in contrast to bimanual skill training (BiT). After motor cortical infarcts, training rats in a novel skilled bimanual reaching task (the popcorn retrieval task) improved unimanual performance with the paretic side. Mouse models would be advantageous for investigating distinctions in synaptic structural correlates of bimanual vs.

unimanual skill learning effects on paretic forelimb function, but no suitable mouse BiT tasks were available for the purpose. Thus, we developed a new one, the Puff Retrieval Task, and characterized performance strategies across a 2 month period in mature adult male C57/BL6 mice. In this task, both paws reach through a window to grasp and retrieve a food reward (a shaped piece of puffed wheat, Quaker Oats Co.). Wheat puffs were chosen as a suitably large and motivating reward of low caloric density, avoiding satiety. Food reward size and the resistance created by anchoring the puff on a pin encouraged use of both paws. Mice were found to use coordinated asymmetrical bimanual reaching and grasping strategies to perform the task. The majority of successful bimanual retrievals were initiated by extending and contacting the puff with one forepaw followed by the other, after which the puff was pulled from the pin with both paws for retrieval. Adjustments in contact position(s) with one or both limbs after initial contact were common. Most mice had a preferred limb (left or right) for reach initiation. Work is ongoing to refine the behavioral analysis approach for characterizing task acquisition, and to assess reliability across experimenters and across video vs. real time measures. Assuming replication of prior findings in rats of beneficial effects of post-stroke BiT, the new BiT task will then be extended to the question of the synaptic structural correlates of its post-stroke influence on paretic forelimb function.

Disclosures: D. Miranda-Sohrabji: None. **S. Kumar:** None. **E. Nudi:** None. **N. Donlan:** None. **T.A. Jones:** None.

Poster

657. Stroke III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 657.16/F45

Topic: C.09.Stroke

Support: SEAMO
CTAQ
Brain Canada
CIHR CGSD

Title: Robotic assessment of upper limb function in a nonhuman primate model of chronic stroke

Authors: *Y. CHEN[1], M. C. POOLE[1], J. Y. NASHED[1], A. CHAMPAGNE[1], D. J. COOK[2]; [1]Ctr. for Neurosci. Studies, [2]Neurosurg., Queen's Univ., Kingston, ON, Canada

Abstract: Stroke is a leading cause of death and disability worldwide and survivors are frequently left with long-term disabilities that diminish their autonomy and result in the need for chronic care. There is an urgent need for the development of therapies that improve stroke recovery, as well as accurate and quantitative tools to measure function. Nonhuman primates

closely resemble humans in neuroanatomy and upper limb function, and may be crucial in randomized pre-clinical trials for testing the efficacy of stroke therapies. In this study, two cynomolgus macaques were trained to perform a visually guided reaching task and were assessed in a passive stretch task on the Kinesiological Instrument for Normal and Altered Reaching Movements robot. Strokes were then induced in these animals by transiently occluding the middle cerebral artery and their motor performance on the same tasks was assessed after recovery. Relative to pre-stroke, post-stroke hand movements of the affected limb became slower and less accurate, similar to motor deficits revealed in the same task in human stroke patients. Regression analyses reveal both recovered and compensatory movements to complete movements to different areas in space. Lastly, we note decreased range of motion in the elbow joint of the affected limb post-stroke associated with spasticity. Taken together, these studies highlight that sensorimotor deficits in reaching movements following stroke in cynomolgus macaques resemble those in human patients and validate the use of robotic assessment tools in a nonhuman primate model of stroke for identifying and characterizing such deficits.

Disclosures: Y. Chen: None. **M.C. Poole:** None. **J.Y. Nashed:** None. **A. Champagne:** None. **D.J. Cook:** None.

Poster

657. Stroke III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 657.17/F46

Topic: C.09.Stroke

Title: Entrainment of stepping frequency to vertical motion of walking surface in stroke and age-matched controls

Authors: *D. GOBESKI[1], B. ROBERTSON-DICK[3], T. ONUSHKO[1], S. C. RAAB[2], L. RIEM[1], N. GREGG[1], A. S. HYNGSTROM[2], B. D. SCHMIT[1];
[1]Biomed. Engin., [2]Physical Therapy, Marquette Univ., Milwaukee, WI; [3]Physical Med. and Rehabil., Med. Col. of Wisconsin, Milwaukee, WI

Abstract: Introduction: Gait entrainment to external stimuli is used as a rehabilitative technique in different neurologically-injured populations. Previous research has focused on repetitive sensory stimuli, e.g. auditory and tactile, and has shown that individuals can synchronize their stepping frequency to the stimulus, with less work done on the effects of entrainment to walking surface motion. As walking surface motion interacts directly with an individual's gait dynamics, synchronization of the gait cycle to the walking surface motion is expected to be readily attainable as the motion cannot be passively ignored and filtering out its effects on gait would require additional effort. In this study, the walking surface was oscillated up and down while research participants walked on it. Participants were chronic stroke survivors

and age-matched controls.
Methods: All trials were performed while a participant walked on a motion base: a split-belt treadmill mounted on a platform capable of six degree of freedom motion (x-, y-, and z-translation, yaw, pitch, and roll). Kinematics data was obtained using the Helen Hayes marker set and a multiple-camera OptiTrack motion capture system. Kinetics data was obtained using single-axis force transducers mounted beneath the treadmill belts. EMG was obtained for 4 muscles on each leg. Gait parameters were calculated from the marker and force data during post-processing.
Each 4minute trial started with ~1 minute of the motion base stationary, then 2 minutes of sinusoidal vertical oscillations (ztranslation only; no rotation), then ~1 minute of the motion base stationary. The vertical oscillations were set to 90/100/110/180/200/220 percent of the participant's preferred stepping frequency, and the order of the 6 trials was randomized separately for each participant.
Results: Vertical oscillation of the motion base resulted in varying amounts of gait entrainment, with no oscillation frequency consistently showing best or worst results across all individuals. When averaged across trials and participants, the stroke and control groups spent comparable amounts of time entrained during the oscillations (53% for stroke, 57% for control). The two groups experienced similar reductions in step length asymmetry [100% x ABSOLUTE VALUE of (RIGHT STEP LENGTH – LEFT STEP LENGTH) / (RIGHT STEP LENGTH + LEFT STEP LENGTH)] when comparing the section of each trial immediately before and after the oscillations (-12% for stroke, -16% for control).
Conclusion: Control and chronic stroke participants both exhibit gait entrainment and accompanying reductions in step length asymmetry, with the exact results being individual-specific.

Disclosures: D. Gobeski: None. **B. Robertson-Dick:** None. **T. Onushko:** None. **S.C. Raab:** None. **L. Riem:** None. **N. Gregg:** None. **A.S. Hyngstrom:** None. **B.D. Schmit:** None.

Poster

657. Stroke III

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Program #/Poster #: 657.18/G1

Topic: C.09.Stroke

Support: NIH Grant
AHA Postdoc Fellowship 18POST33970007

Title: An *in vivo* model of microglia phagocytosis of aged red blood cells in the mouse brain

Authors: *J. WAN[1], J. WANG[2];
[1]Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [2]Anesthesiology/Critical Care Med., Johns Hopkins Univ., Baltimore, MD

Abstract: Intracerebral haemorrhage (ICH) is a devastating subtype of stroke associated with high mortality and morbidity, however lacks effective treatment to date. Initial brain injury occurs in the first few hours after ICH as a result of mass effect by hematoma formation. Microglia represents the primary phagocytic function to mediate hematoma clearance, which has not been well studied. In this project, we obtained red blood cells (RBCs) from UBC-GFP mouse (C57BL/6J background) and artificially aged them by raising intracellular calcium concentration to stimulate microglia phagocytosis; we observed microglia engulfment in an *ex vivo* organotypic slice cultures of the mouse striatum model, and in *in vivo* aged RBCs-induced, normal RBCs-induced, and whole blood-induced ICH models at different time points after injury. We found aged RBCs enhanced microglia phagocytosis *ex vivo* and *in vivo* when compared with those of normal RBCs. Moreover, in aged RBCs-induced ICH model, the hematoma size increased to peak at 3 days post injury and neurological deficits outcomes were more severe at 1 and 3 days post injury and tended to recover at 7 days post injury, which were similar to those of whole blood-induced ICH model, a more clinically relevant model. We further observed microglia activation and phagocytosis increased and reached to peak at 5 days after aged RBCs-induced ICH, which were significantly more prominent in comparison to normal RBCs-induced ICH model. Our experiments establish an *in vivo* mouse model to observe microglia phagocytosis, demonstrate that aged RBCs enhanced microglia phagocytosis both *ex vivo* and *in vivo*, and provide new strategies for studying microglia functions and hematoma clearance after ICH.

Disclosures: J. Wan: None. **J. Wang:** None.

Poster

657. Stroke III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 657.19/G2

Topic: C.09.Stroke

Support: NSFC 81870935 to WJ

Title: Inhibition of NBCs activity protects hippocampus CA1 delayed neuronal death induced bytransient global cerebral ischemia in gerbils

Authors: M. JIA[1,2,3], W. SHAN[1], S. LIU[4], N. CHEN[4], A. GUO[1], Q. WANG[1], Y. WANG[1], *J. WU[1,2,3,4];
[1]Beijing Tiantan Hospital, Captial Med. Univ., Beijing City, China; [2]Beijing Advanced Innovation Ctr. for Human Brain Protection, Beijing Med. Univ., Beijing, China; [3]China Natl.

Clin. Res. Ctr. for Neurolog. Dis., Beijing, China; [4]Wuhan Univ. of Technol. Sch. of Chemistry 、 Chem. Engin. and Life Sci., Wuhan, China

Abstract: Metabolic acidosis plays key role in ischemia reperfusion (I/R) induced hippocampus delayed neuronal death, the underlying mechanism remains obscure. Sodium bicarbonate co-transporters (NBCs) contribute cellular acid-base homeostasis in pathophysiological processes, and may lead to intracellular sodium over influx and calcium dyshomeostasis during I/R hippocampus injury. We speculated that blockage of NBCs activities would be beneficial for neuronal surviving during I/R injury. Using an well established gerbils transient global cerebral ischemia model, we examined the protective effect of S0859, a NBCs specific inhibitor, on the hippocampus delayed neuronal death and animal behavior alterations induced by I/R. Compared with the sham-operated group, ischemia-operated group animals exhibited hyperactivity in open field which tested at 3d post-ischemia; Histological study confirmed that I/R selectively impaired hippocampal CA1 pyramidal neurons; TUNEL positive neurons(apoptosis) were not detected in all the hippocampal subregions including CA1 region in the sham-operated group, but could be observed in the stratum pyramidal of the CA1 region as early as 12h, which peaked at 3d and declined at 7d post-ischemia, the later might be due to the neuronal loss in hippocampal regions. Pretreatment of ischemia-operated animals with S0859 (300ug/Kg, *i.p* , 3d before I/R) attenuated markedly I/R induced hyperactivity and hippocampus delayed neuronal death. Apoptosis neurons were significantly reduced in S0859 pretreated group, compared with that in no-treated group. The result indicated that NBCs activation during I/R induced a “pH regulation dependent sodium influx and calcium dyshomeostasis” ,which in turn lead to neuronal apoptosis and neuronal death. S0859 protects hippocampus CA1 pyramidal neurons delayed death through an anti-apoptosis mechanism (Supported by NSFC 81870935 to WJ).

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Poster

657. Stroke III

Location: Hall A

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Program #/Poster #: 657.20/G3

Topic: C.09.Stroke

Title: Investigating the molecular and cellular basis of moyamoya disease using patient derived induced pluripotent stem cells

Authors: *S. P. RAO, Q. ZHANG, H. UCHINO, A. PENDHARKAR, M. Y. CHENG, G. K. STEINBERG;
Neurosurg., Stanford Univ., Palo Alto, CA

Abstract: Background: Moyamoya disease (MMD) is a progressive steno- occlusive disease affecting terminal regions of the cerebral internal carotid artery (ICA), leading to stroke. Revascularization surgery is the only treatment option. Analysis of the affected arteries showed thickening of the intima, depletion of the elastic lamina as well as the media, indicating a dysfunction of the vascular smooth muscle cells (VSMCs) and endothelial cells (ECs). However the pathogenesis of the disease is still unclear. We aim to address this gap in knowledge and determine the cellular and molecular mechanisms underlying MMD by using patient derived induced pluripotent stem cells (iPSCs), to generate VSMCs and ECs.
Methods: Peripheral blood mononuclear cells (PBMCs) from controls and MMD patients (n=3 per group) were utilized for generating iPSCs. Immunocytochemistry and qPCR confirmed the expression of pluripotency markers, SSEA4, TRA1-60, OCT4 and NANOG in all iPSC samples. iPSCs were induced to differentiate into neuro-ectoderm (NE) derived VSMCs. BrDU incorporation within the cells was measured to assess cell proliferation. Scratch and transwell migration assays were performed to measure cell migration. VSMCs were exposed to either normoxia or hypoxia model (1%O_2) to investigate how cells respond to the insult. HIF1α activation was determined using western blot.
Results: Control and MMD VSMCs were characterized by immunocytochemistry, qPCR and flow cytometry analysis, to confirm the expression of VSMC specific proteins CNN1, TAGLN and MYH11. Pluripotency markers were undetectable. Under normoxia MMD VSMC's proliferated and migrated to a lesser extent, while being more contractile compared to controls. Western blot analysis showed that hypoxia inducible factor 1α (HIF1α) protein expression was already elevated in normoxic MMD VSMC and hypoxia caused a further increase.
Conclusions: Our preliminary results indicate that MMD VSMCs are dysfunctional and may be related to the elevated basal expression of HIF1α, possibly contributing to MMD pathology. We are currently determining the angiogenic properties of MMD ECs followed by co-culturing the cells and transcriptome analysis, which will provide a better understanding of the cellular and molecular mechanisms underlying MMD.

Disclosures: S.P. Rao: None. **Q. Zhang:** None. **H. Uchino:** None. **A. Pendharkar:** None. **M.Y. Cheng:** None. **G.K. Steinberg:** None.

Poster

657. Stroke III

Location: Hall A

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Program #/Poster #: 657.21/G4

Topic: C.09.Stroke

Support: NIH Grant R01NS093057

Title: Automated assessment of motor deficits after experimental stroke using Erasmus Ladder

Authors: *T. C. CHIANG, S. HARVEY, A. PENDHARKAR, Z. CAO, M. Y. CHENG, G. K. STEINBERG;
Stanford Univ., Stanford, CA

Abstract: Background: Traditional behavior assessment of motor deficits using manual scoring can be subjective and labor intensive. The bias between individuals can lead to incorrect and inconsistent assessment, resulting in variability and non-reproducible data. Here we demonstrate the feasibility of an automated motor behavior assessment in adult mice via two experimental stroke models. Methods: Adult male C57Bl6 mice (11-13 weeks) were subjected to transient middle cerebral artery occlusion (tMCAO, n=15) or distal middle cerebral artery occlusion (dMCAO, n=10). Naïve mice (n=10) were prepared as no stroke control. Brains were collected at PD 30 and sections were processed for immunostaining using antibodies targeting neurons (MAP2) or activated microglia/macrophage (CD68). Mice with infarcts in both cortex and striatum were included in the study. Mice behavior were evaluated by Erasmus Ladder at pre-stroke baseline (4 unperturbed and 4 perturbed sessions) and post-stroke days (PD) 7, 14, 21 and 28 (all perturbed sessions). Mice were grouped via assessment of several parameters recorded by Erasmus Ladder: trial time, pre-perturbed time, post-perturbed time, and HH-long step percentage. Results: In the tMCAO model, stroked mice show a significant deficit in pre- and post-perturbed times and various step types after stroke. While significant changes were altered in many step types between PD7-14 after tMCAO, only HH-long step and reaction time to perturbation were significantly different when compared to control. Specifically, we observed a sustained decline in the usage of affected limb over unaffected limb until PD28. This imbalance in limb use is also observed in the dMCAO model, however, other step types and reaction times were not altered in the dMCAO model. Interestingly, in both models the stroke mice exhibit lower trial time when compared to control mice, indicating a faster completion of each trial despite the limb deficit. Conclusions: Our results indicate that the Erasmus Ladder can provide automated, unbiased assessment of motor deficit in mice after stroke, at least until post-stroke day28. Furthermore, Erasmus Ladder allows tracking of the affected and non-affected limb use after stroke. Greater motor variable differences were detected in the tMCAO versus dMCAO model. Ongoing studies are elucidating the Erasmus Ladder's capability to detect recovery in mice treated with therapeutic interventions such as optogenetic stimulation.

Disclosures: T.C. Chiang: None. **S. Harvey:** None. **A. Pendharkar:** None. **Z. Cao:** None. **M.Y. Cheng:** None. **G.K. Steinberg:** None.

Poster

657. Stroke III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 657.22/G5

Topic: C.09.Stroke

Title: Center of mass fluctuations in stroke survivors as a response to unexpected lateral support surface perturbations during gait

Authors: *S. C. RAAB[1], L. I. RIEM[2], T. ONUSHKO[2], N. GREGG[2], D. GOBESKI[2], A. S. HYNGSTROM[1], B. D. SCHMIT[2];
[1]Physical Therapy, [2]Biomed. Engin., Marquette Univ., Milwaukee, WI

Abstract: High fall risk during walking is a common problem for many individuals post-stroke. Balance responses during walking are not well described, particularly when the support surface is providing the perturbation. The ability to control the excursion of center of mass (COM) within the base of support (BOS) is central to the maintenance of an upright posture when a perturbation is delivered. Although previous research supports that stroke survivors have greater excursion of COM both in quiet stance and during gait without perturbations, less COM excursion in response to an unexpected perturbation suggests a more rigid and simpler control strategy that is not optimal for maintaining reactive posture. In the present study, 4 chronic stroke survivors and 4 healthy age- and gender-matched controls walked at self-selected walking speeds on a treadmill system that is programmed to medially/laterally shift 2.5 cm immediately after initial heel strike. Spatial and temporal changes to medial lateral (ML) COM movement during the first 5 COM fluctuations in response to lateral destabilizing perturbations of the treadmill were quantified. Perturbations were randomized between the side of heel contact and direction of perturbation. As a group, stroke survivors' COM fluctuations exhibited less reactive change in amplitude and timing between COM shifts when compared to the control group. Amplitude fluctuations increased from a mean of 8.0 cm to 10.84 cm during the last step before perturbation delivery and the first step after perturbation delivery in the stroke group, but decreases in the control group from 6.41 cm to 3.65 cm. Temporally, stroke survivors' fluctuations in COM decreased by 0.036 s while controls' fluctuations decreased by 0.200 seconds. These results combined with future research elucidate post-stroke COM control during gait and will contribute to developments of therapy techniques to improve dynamic balance in response to perturbations.

Disclosures: S.C. Raab: None. **L.I. Riem:** None. **T. Onushko:** None. **N. Gregg:** None. **D. Gobeski:** None. **A.S. Hyngstrom:** None. **B.D. Schmit:** None.

Poster

657. Stroke III

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Topic: C.09.Stroke

Support: American Heart Association grant #17AIREA33700076 to Zahoor A. Shah

Daniyah Almarghalani was supported by Taif University, Saudi Arabia and Higher Committee for Education Development of Saudi Arabia

Title: The role of cofilin in intracerebral hemorrhage-induced neuroinflammation

Authors: *D. A. ALMARGHALANI[1], M. AMIRA[2], D. TA[2], A. KONDAKA[2], Z. A. SHAH[2]; [1]Dept. of Pharmacol. and Exptl. Therapeut., [2]Dept. of Medicinal & Biol. Chem., Col. of Pharm. and Pharmaceut. Sciences, The Univ. of Toledo, Toledo, OH

Abstract: Intracerebral hemorrhage (ICH) is a devastating disease associated with high mortality and accounts for about 15% of all stroke cases. About 50% of patients die within the first month of attack and those who survive have a long-term disability and neurological deficit; however, only 20% of patients who survive ICH achieve functional independence after 6 months. The understanding of the pathological changes and the repair mechanisms after ICH are not clearly understood. Our previous study demonstrated a major role of the cytoskeletal protein, cofilin in ICH-induced brain injury. We reported that knockdown of cofilin in a mouse model of collagenase induced-ICH improved neurobehavioral deficits and decreased hemorrhagic volume as well as blood-brain barrier disruption (BBB) and microglia activation. In the present study, we aimed to determine the cofilin signaling and glial activation up to 14 days following ICH. Therefore, we subjected different cohorts of mice to intrastriatal collagenase injection-induced ICH and mice were sacrificed at different time-points of 1, 3, 7, and 14 days. Using Western blotting (WB), we observed a significant upregulation of cofilin protein levels in the ipsilateral striatum on day 3 and then a decreasing trend was observed from day 7 to day 14. Mice suffered from severe neurobehavioral deficits immediately after ICH which lasted for 7 days and then a gradual improvement was observed in motor deficits. Using immunohistochemistry analysis, activated microglia were observed to be increased after ICH from day 1, especially around the hematoma and lasted until day 7 and there was a gradual decrease observed at day 14. Activated microglia were associated with morphological changes from ramified into an amoeboid shape particularly around the hematoma from day 1 up to day 14. Astrocyte activation observed by WB showed a gradual increase in GFAP protein expression from day 1 and lasted until day 14. In conclusion, we believe that cofilin overactivation plays an important role in the activation of microglia and astrocytes subsequently leading to neuroinflammation and motor deficits following ICH. Developing therapies against cofilin might provide novel alternatives for ICH therapy.

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Poster

657. Stroke III

Location: Hall A

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Program #/Poster #: 657.24/G7

Topic: C.09.Stroke

Support: JES Edwards Foundation

Title: Effect of genistein on age-dependent differences in cerebral ischemia in ovariectomized rats

Authors: *A. OPPONG-GYEBI[1], D. METZGER[1], N. SUMIEN[2], D. A. SCHREIHOFER[3]; [2]Pharmacol. & Neurosci., [1]Univ. of North Texas Hlth. Sci. Ctr., Fort Worth, TX; [3]Dept. of Pharmacol. and Neurosci., Univ. of North Texas Hlth. Sci. Ctr. At, Fort Worth, TX

Abstract: Background: Advancing age increases women's susceptibility to stroke compared to men, especially after the menopausal transition, which has been attributed mainly to a drastic drop in estrogen post-menopause. However, time-dependent mixed beneficial and detrimental effects of estrogen therapy for prevention of stroke and cardiovascular diseases after menopause have contributed to widespread mistrust of estrogen use. This has led to the use of other agents like soy isoflavones including genistein as alternatives to hormone therapy. In this study, we investigated genistein's effect on age-dependent differences in cerebral ischemia in ovariectomized rats. **Hypothesis**: We hypothesized that the neuroprotective effects of genistein, a soy isoflavone, on cerebral ischemia are less sensitive to the aging and duration of hormone deprivation. **Method**: To test this, young (3-4 months old) and retired proven breeder rats (9 months old) were ovariectomized (OVX), grouped into two ovarian hormone deprivation time points (2weeks= short-term and 12 weeks= long-term) and treated with isoflavone-free diet (IF) or genistein diet (GEN). Estrogen (E2) pellet-treated group was added as a control for hormone supplementation post OVX. Animals underwent middle cerebral artery occlusion (MCAO) or sham surgery for 60 mins followed by reperfusion and behavioral tests to assess neurological, motor and cognitive deficits. The extent of brain injury was quantified with immunohistochemical stains of activated calcium-binding protein (Iba1) and glial fibrillary acidic protein (GFAP). **Results**: We observed no effect of GEN on neurological assessment and motor learning ($p>0.05$) across stroked groups. The retired breeder stroked rats performed worse than the young adults ($p<0.05$) revealing an effect of age. Long-term estrogen deprivation in retired breeders worsened gait performance showing a duration effect ($p<0.05$).GEN had no effect on the histological extent of injury ($p>0.05$). GEN, however, improved cognitive flexibility in retired breeder stroked groups compared with IF and E2 groups ($p<0.05$). **Conclusion**: Our results suggests that increasing age increases neurological, motor and cognitive deficits after cerebral ischemia. Long-term estrogen deprivation increases motor deficits. GEN

had little effect on the sensorimotor outcomes, but may improve certain aspects of cognitive function post-stroke.

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Poster

657. Stroke III

Location: Hall A

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Program #/Poster #: 657.25/G8

Topic: C.09.Stroke

Title: The role of microglia cell-specific estrogen receptor alpha (ERα) signaling in an ischemic stroke model

Authors: *T. RODRIGUEZ[1,3], J. KYLE[2], C. MELIAN[1], A. HO[2], S. TSYRKA[2], M. ACOSTA-MARTÍNEZ[1];
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Abstract: Stroke is a sexually dimorphic disease, with very strong sex and age interactions affecting risk, pathophysiology and outcomes. For example, stroke is uncommon among premenopausal women; however after menopause the incidence of stroke increases, and women experience worst stroke outcomes compared to men. This protection in the female brain has been attributed to the anti-inflammatory and neuroprotective effects of estradiol (E_2). However the cell types and intracellular mechanisms underlying E_2 anti-inflammatory actions after ischemic injury are poorly understood. Activation of microglia cells is a key component of the post ischemic inflammatory response that contributes to the extent of brain injury. Even though estrogen receptor alpha (ERα) is the primary mediator of E_2 anti-inflammatory actions, evidence of direct regulation of microglia function by E_2-ERα signaling is missing. Therefore, we investigated the contribution of macrophage/microglia cell-specific ERα signaling in the inflammatory response to ischemic injury. Mice with macrophage/microglia-cell specific deletion of ERα were generated by mating floxed ERα mice and Csf1R-Cre animals. Focal ischemia was pharmacologically induced in WT ($ER\alpha^{flx/flx}$) and Csf1R-1-$ER\alpha^{flx/flx}$ mice by intracortical injection of the vasoconstrictive peptide endothelin-1 (ET-1); infarct volume, ERα and microglia (Iba-1) expression was evaluated 24 hours after injection. Infusion of ET-1 resulted in significant cortical infarcts in both genotypes, however compared to WT, Csf1R-1-$ER\alpha^{flx/flx}$ females showed a larger infarct volume (1.18% vs. 2.1 %, WT and Csf1R-1-$ER\alpha^{flx/flx}$ respectively, $p<0.01$). An increase in microglia cell numbers (Iba-1 staining) as well as ERα protein expression was observed in the peri infarct area of male and female mice of both genotypes. However, no genotype effect on Iba-1 or ERα expression was observed. We also tested the

susceptibility of microglia isolated from neonatal WT and KO females to *in vitro* ischemia. Microglia were exposed to oxygen-glucose deprivation for 2 hours followed by 16 of reperfusion (OGD/R) and the effect on microglia activity was assessed by phagocytosis assay. Compared to normal treatment, OGD/R increased the % of phagocytic microglia cells from female mice, regardless of genotype (WT: 15% vs. 32%, normal vs. OGD/R; KO: 15% vs. 48%, normal vs. OGD/R). Our data suggests that the loss of ERα in microglia/macrophage cells leads to deregulation of post-ischemic stroke inflammatory responses and higher vulnerability to ischemic stroke in the female brain.

Disclosures: T. Rodriguez: None. **J. Kyle:** None. **C. Melian:** None. **A. Ho:** None. **S. Tsyrka:** None. **M. Acosta-Martínez:** None.

Poster

657. Stroke III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 657.26/G9

Topic: C.09.Stroke

Support: 19PRE34380992

Title: Pathophysiological characterization of stroke-induced skeletal muscle injury

Authors: *M. BALCH, H. HARRIS, D. CHUGH, W. ARNOLD, C. L. RINK;
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Abstract: Ischemic stroke is a leading cause of long-term disability in the United States. Rehabilitation offers therapeutic benefit, but best practices are unclear. Despite the need for evidence-based therapies, less than 3% of ischemic stroke literature over the past decade has addressed the state of skeletal muscle in response to stroke. Previous work identified acute changes in skeletal muscle within 2 weeks of the stroke event, far earlier than chronic manifestations typically noted with stroke disability. Here, we present a detailed characterization of acute skeletal muscle injury following stroke.
Ischemic stroke was induced in male Wistar rats via transient middle cerebral artery occlusion and confirmed using MRI. Animals were followed out to various acute timepoints (post-stroke day (PSD) 3, PSD7, PSD14), after which skeletal muscle from both stroke-affected and contralateral hindlimbs was collected. Tissue analysis included study of neuromuscular junction (NMJ) morphology, fiber phenotype, fetal programming markers, and mediators of satellite cell activity, all compared to naïve healthy controls. An additional cohort of stroke/sham rats underwent *in vivo* muscle contractility and electrophysiology testing at pre-stroke, PSD7, PSD14, and PSD21 timepoints.
To characterize the stroke-induced response of skeletal muscle tissue, we reviewed markers of

skeletal muscle repair after injury. A significant increase in Pax7+ cells and Embryonic Myosin Heavy Chain+ cells was observed at PSD7, suggesting heightened satellite cell renewal and regenerative re-expression of a developmental marker respectively. NADH-TR staining, indicative of mitochondrial distribution, presented a shift in fiber phenotype to more fatigable, fast-twitch isoforms. Electrophysiological study of muscle contractility and motor unit functionality demonstrated a decrease in motor unit number estimation and tetanic force at PSD14 and PSD21. We propose further analysis will present maladaptive changes at the NMJs - to include morphological adaptations and potential polyneuronal innervation - which prompt the fiber type shift and the ensuing cascade of compensatory myogenic activity.
Taken together, this work provides a novel characterization of the stroke-induced physiological response in skeletal muscle tissue. Disruptions to the neuromuscular unit initiate a compensatory response of potentially maladaptive proportions, all contributing to functional loss and motor deficit. Harnessing such understanding will inform tailored, optimized therapeutic paradigms to maximize recovery benefit in stroke survivors.

Disclosures: **M. Balch:** None. **H. Harris:** None. **D. Chugh:** None. **W. Arnold:** None. **C.L. Rink:** None.

Poster

657. Stroke III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 657.27/G10

Topic: C.09.Stroke

Support: NIH R01HD075813

Title: The stroke paradox: Hypertonicity with weakness

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Abstract: Weakness, especially of the distal upper extremity, is a hallmark of impairment following stroke. While the sources of this weakness remain a matter of some debate, neurological factors undoubtedly contribute. To address potential mechanisms, we examined voluntary and reflexive muscle activation in 90 stroke survivors participating in a longitudinal intervention trial. Participants had chronic, severe hand impairment, rated as Stage of Hand 2-3 on the Chedoke-McMaster Stroke Assessment (Fugl-Meyer upper extremity scores ranged from 0 to 33). Participants were at least 6 months post-stroke (mean ± standard deviation of 6.7±6.6

years post-incident) and ranged in age from 21 to 80 years old (57.9±11.5 years). All participants signed an IRB approved, written informed consent. Substantial hand weakness was confirmed in all participants. Grip strength in the paretic hand was only 12.2%±9.8 of the force generated with the less impaired hand. Metacarpophalangeal (MCP) flexion torque generated across all four fingers was measured with a custom apparatus to be 2.1±1.4 Nm, much less than the 10.4±2.8 Nm typically produced by neurologically intact individuals. MCP extension torque, also measured with the same apparatus, was largely non-existent (only 7/90 participants generated extension torque), with maximum values of only 1.02Nm across all participants. Despite the weakness, we observed hypertonicity of the long finger flexors. Imposed stretch of the finger flexors through externally controlled MCP rotation resulted in a spastic reflex response in a majority of the subjects (reflex torque = 0.89±0.57 Nm). Hypertonicity was further confirmed by the significantly prolonged time required to relax the finger flexor muscles once activated. EMG recordings from flexor digitorum superficialis (FDS) revealed that stroke survivors required 3.8±3.7 seconds to terminate FDS activity following creation of a maximal flexion force. In contrast, neurologically intact individuals in a prior study required only 0.24±0.11 seconds to terminate activity, or 15% of the time needed by stroke survivors. While this hypertonicity was apparent, stroke survivors appeared to have difficulty in voluntarily activating muscles. In fact, for 17 subjects, MCP reflex torque induced by passive stretch was greater than the voluntary MCP torque that could be produced by the subject. Furthermore, a total of 16 subjects exhibited greater reflex FDS activation than they could generate voluntarily. These results confirm that following stroke, externally applied stretch can generate greater flexor muscle activity and torque than during voluntary activation.

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Poster

657. Stroke III

Location: Hall A

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Program #/Poster #: 657.28/G11

Topic: C.09.Stroke

Support: NIH Grant P30GM103400
New Mexico BBHI Mini Grant BBHI 2017-1006

Title: Endogenous zinc proroporphyrin formation critically contributes to hemorrhagic stroke-induced brain damage

Authors: *R. PAN[1], G. TIMMINS[2], Y. YANG[2], X. ZHOU[2], K. LIU[2];
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Abstract: Hemorrhagic stroke is a leading cause of death in the U.S. with a survival rate being only around 27%. The causes of intracerebral hemorrhage (ICH)-induced brain damage are thought to include lysis of red blood cells, hemin release and iron overload. However, these mechanisms have not proven very amenable to therapeutic intervention, and so other mechanistic targets are being sought. Here, we report that accumulation of endogenously formed zinc protoporphyrin (ZnPP) also critically contributes to ICH-induced brain damage. ICH caused a significant accumulation of ZnPP in surrounding brain tissue, as evidenced by fluorescence microscopy of ZnPP, and further confirmed by fluorescence spectroscopy and supercritical fluid chromatography-mass spectrometry. ZnPP accumulation was dependent upon both ICH-induced hypoxia, and an increase in free zinc accumulation. Notably, inhibiting ferrochelatase, which catalyzes insertion of zinc into protoporphyrin, greatly decreased ICH-induced endogenous ZnPP generation. Moreover, a significant decrease in brain damage was observed upon ferrochelatase inhibition, suggesting that endogenous ZnPP contributes to the damage in ICH. Thus, our findings reveal a novel mechanism of ICH-induced brain damage through ferrochelatase-mediated formation of ZnPP in ICH tissue. Since ferrochelatase can be readily inhibited by small molecules, this may provide a new and druggable target for ICH therapy.

Disclosures: R. Pan: None. **G. Timmins:** None. **Y. Yang:** None. **X. Zhou:** None. **K. Liu:** None.

Poster

657. Stroke III

Location: Hall A

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Program #/Poster #: 657.29/G12

Topic: C.09.Stroke

Support: NIH RO1 HD089999
NIH RO1 GM098308

Title: Critical role of formyl peptide receptor 1 on activated splenocytes in brain ischemic injury

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Abstract: Background: Formyl peptide receptor 1(FPR1), identified by their ability to bind N-formyl peptides, has been shown to mediate the leukocyte recruitment after ischemia-reperfusion injury. We have synthesized the peptide cinnamoyl-phenylalanine–(D) leucine-phenylalanine-

(D) leucine-phenylalanine (cFLFLF), an FPR1 specific antagonist. This peptide has been shown to be excellent in labeling inflammatory foci in the peripheral tissues but its molecular and biological effects after antagonizing FPR1 are not well studied. We hypothesize that cFLFLF may provide neuroprotection by inhibiting the migration of peripheral immune cells including splenocytes into the brain and reducing the neuroinflammation after stroke.
Methods: Eight-week-old CD-1 male mice weighing 28-32 g were randomly assigned to the following groups: 1) sham, 2) 0 h reperfusion, 3) 4 h reperfusion, 4) 24 h reperfusion, 5) 28 d reperfusion, 6) 0.5 mg/kg cFLFLF treatment +4 h reperfusion, 7) 5.0 mg/kg cFLFLF treatment + 4 h reperfusion, 8) 0.5 mg/kg cFLFLF treatment +24 h reperfusion, 9) 5.0 mg/kg cFLFLF treatment+24 h reperfusion, and 10) 5.0 mg/kg for three days+28 d reperfusion. Brain ischemia was a 90-minutes left middle cerebral artery occlusion (MCAO) that was achieved by an intraluminal filament method. Neurological outcome including neurological deficit scores, motor coordination, brain infarct volume, and spleen weight was evaluated at the corresponding times. Some mice were used for immunofluorescent staining and biochemical analysis. FPR1 knockout mice were used to defy the role of FPR1 in cFLFLF induced neuroprotection.
Results: cFLFLF improved neurological outcomes after MCAO and attenuated MCAO-induced decrease of spleen weights. cFLFLF inhibited the activation and migration of splenocytes as shown by the significant decrease of pro-inflammatory cytokine expression *in vivo* and mitigated chemoattractive movement *in vitro*. The phosphorylated nuclear factor(NF)-κB and chemokine C-C motif ligand 2 (CCL2) were reduced after cFLFLF treatment in the tissues of brain and spleen after MCAO, which may be the molecular mechanisms for cFLFLF-induced neuroprotection. Both phosphorylated NF-κB and CCL2 were reduced in FPR1 knockout mice with or without MCAO.
Conclusions: cFLFLF inhibites the migration and infiltration of splenocytes into the brain, attenuates neuroinflammation and improves neurological outcome after ischemic stroke in mice. Reducing phosphorylated NF-κB and CCL2 expression via a FPR1 dependent inflammatory pathway may contribute to the neuroprotection induced by cFLFLF.

Disclosures: **J. Li:** None. **M. Chordia:** None. **D. Pan:** None. **Z. Zuo:** None.

Poster

657. Stroke III

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Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 657.30/G13

Topic: C.09.Stroke

Support: NIH Grant 1R21HD090453-01A1

Title: Muscle spasticity and motor performance after botulinum neurotoxin injection in stroke subjects with spastic hemiplegia

Authors: *Y.-T. CHEN[1], C. ZHANG[2], E. MAGAT[1], M. VERDUZCO-GUTIERREZ[1], P. ZHOU[1], Y. ZHANG[2], S. LI[1];
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Abstract: There are approximately 20-40% of stroke survivors who suffer from muscle spasticity. Botulinum neurotoxin (BTX) is the first-line treatment for spasticity management. BTX injection is able to effectively reduce spasticity, but at the same time it causes muscle weakness. It is known that a weaker muscle has worse performance in force control. The purpose of this study was to quantify the effect of BTX injection on the spasticity, strength and motor performance of the spastic muscle in stroke survivors. Seven stroke subjects (Age: 52.9 ± 11.8 yrs; 2 women) who received 100 units of onabotulinumtoxinA (Botox) or incobotulinumtoxinA (Xeomin) injection on biceps brachii muscle were recruited. Subjects were assessed within one week before (baseline) and 3 weeks after (3-wks) BTX injection. The spasticity, maximum voluntary contraction (MVC), and motor performance of the spastic biceps muscle were evaluated. MVC and motor performance were also collected from the contralateral non-affected side. Spasticity of elbow flexors was quantified as reflex torque using a computerized passive stretch equipment. Motor performance was quantified as the coefficient of variation (CV) during isometric elbow flexion tasks at 10%, 30%, and 50% of MVC. On average, the MVC (baseline: 12.6 ± 2.5 N-m; 3-wks: 10.6 ± 1.6 N-m; $p = 0.04$), and reflex torque (baseline: 3.8 ± 0.8 N-m; 3-wks: 2.6 ± 0.6 N-m; $p = 0.02$) of the spastic biceps muscle were reduced after BTX injection compared to the baseline. However, motor performance remained unchanged after BTX injection (no significant differences between baseline and 3-wks; all $p > 0.05$). Nonetheless, all the parameters from the non-paretic sides had no significant differences between baseline and 3-wks visits (all $p > 0.05$). Our results provide evidence that BTX injection reduces muscle spasticity of the spastic biceps muscle. Though the spastic biceps muscle became weaker after BTX injection, no reduction in motor performance was observed. Collectively, BTX injection is able to reduce spasticity, while maintaining the motor performance of the weakened spastic muscle.

Disclosures: Y. Chen: None. **C. Zhang:** None. **E. Magat:** None. **M. Verduzco-Gutierrez:** None. **P. Zhou:** None. **Y. Zhang:** None. **S. Li:** None.

Poster

658. Traumatic Brain Injury: Biomarkers

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 658.01/G14

Topic: C.10. Brain Injury and Trauma

Support: National Institute of Health, Eunice Kennedy Shriver National Institute of Child Health and Human Development, Predicting Outcomes in Children with Mild Traumatic Brain Injury, 1R01HD076885-01

Title: Post-acute white matter diffusion predicts post-concussive symptom severity at six-months following mild traumatic brain injury in children

Authors: *A. L. WARE[1], A. SHUKLA[1], N. GOODRICH-HUNSAKER[2], E. A. WILDE[2], T. J. ABILDSKOV[2], E. D. BIGLER[3], D. COHEN[4], L. K. MIHALOV[4], A. BRAVEVICE[5], B. A. BANGERT[5], H. G. TAYLOR[4], K. O. YEATES[1];
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Abstract: INTRODUCTION: Mild traumatic brain injury (mTBI) is a global public health concern that affects millions of children annually. Mild TBI results in subtle and diffuse alterations in brain tissue, challenging accurate clinical detection and prognostication. The results of studies using advanced MRI techniques like diffusion-weighted imaging (DWI) have been promising but inconsistent. This likely reflects the broadly differing age ranges, injury phases, comparison groups, and brain regions examined. The current study addressed these limitations by comparing post-acute white matter diffusivity in children with mTBI versus a mild orthopedic injury (OI), and by determining whether post-acute white matter diffusivity correlated with post-acute and chronic post-concussive symptoms (PCS). **METHODS:** Data were drawn from a two-site study of pediatric mTBI. Children aged 8-16.99 years with mTBI (*n*=135) or mild OI (*n*=69) were recruited from emergency departments (ED) at two children's hospitals. Injuries and acute signs and symptoms were assessed during the initial ED visit, during which parents also rated pre-injury symptoms; participants also completed a post-acute (<2 weeks post-injury) assessment, which included a 3T MRI, and 3- and 6-months post-injury assessments. Parent-proxy ratings of PCS were obtained at each assessment. Diffusion metrics were derived from DWI using Automatic Fiber Quantification (AFQ) software. Multiple multivariable regression analyses were used to compare groups and to examine prediction of PCS, with False Discovery Rate (FDR) used to correct for multiple comparisons. **RESULTS:** Demographic characteristics did not differ between the groups or sites. No significant group differences were found in any of the 28 fibers. Significant main effects were found for age in a number of regions, and there was a significant covariate effect of site. No group, age, and sex interactions were significant. Time post-injury of MRI did not relate to DTI metrics. Post-acute and 3-month PCS ratings were not significantly associated with diffusion metrics in any region. However, significant interactions between group and diffusion metrics were found for 6-month PCS ratings; post-acute diffusivity in posterior regions of the corpus callosum was (negatively for FA and positively for MD) associated with chronic PCS in the mTBI, but not in the OI group. **CONCLUSIONS:** Post-acute diffusion metrics did not differ for children with mTBI versus OI. However, post-acute diffusion characteristics were predictive of chronic PCS in children with mTBI but not OI. This result implies that brain diffusivity may moderate the long-term impact of pediatric mTBI.

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Poster

658. Traumatic Brain Injury: Biomarkers

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 658.02/G15

Topic: C.10. Brain Injury and Trauma

Title: Ocular motor abnormalities and shortened telomeres in collision sport athletes

Authors: *S. R. SHULTZ[1], G. FULLER SYMONS[1], R. M. MYCHASIUK[2];
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Abstract: Mild brain injuries associated with collision sport participation have been linked to a range of neurological consequences, with evidence suggesting that these athletes are more vulnerable to developing neurological syndromes later in life. Consequently, there is a need to understand how potential neurological changes manifest and whether abnormalities are specific to concussion history or whether sub-concussive impacts also contribute. With female participation in collision sports rising, there is also further need to determine whether changes manifest differently between sexes. This study investigated the neurological implications of collision sport participation in male (n=72) and female (n= 28) amateur Australian rules footballers, with and without a history of concussion, in comparison to male (n=29) and female (n=21) non-collision sport control athletes. Effects of collision sport participation was investigated in two ways: (1) ocular motor assessment, a demonstrated sensitive marker of brain and namely cognitive functioning in a range of collision sports; (2) telomere length, found to be reduced in rodents given mild brain injuries. Overall, footballers exhibited reduced spatial accuracy to a remembered location on an ocular motor memory guided task ($p < 0.01$), and reduced telomere length ($p < 0.05$) in comparison to controls; both findings were independent of concussion history and sex. Notably, shortened telomere length was associated with shortened memory guided latencies among Australian rules footballers ($p < 0.001$). These finding suggest that, even at the amateur level, Australian rules footballers have demonstrable neurological abnormalities relative to non-collision sport control athletes. Importantly, these changes are measurable through both ocular motor assessment and analysis of telomere length, suggesting these methodologies might be sensitive biomarkers to monitor long-term neurological health of collision sport athletes.

Disclosures: **S.R. Shultz:** None. **G. Fuller Symons:** None. **R.M. Mychasiuk:** None.

Poster

658. Traumatic Brain Injury: Biomarkers

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 658.03/G16

Topic: C.10. Brain Injury and Trauma

Support: Understanding Disease RFA, La Trobe University.

Title: Circulating microRNAs as biomarkers of concussion in amateur Australian rules footballers

Authors: *W. T. O'BRIEN[1], C. J. TAYLOR[2], G. A. NEOCLEOUS[2], G. H. FULLER SYMONS[1], A. A. HARDIKAR[3], M. V. JOGLEKAR[3], S. R. SHULTZ[1], S. J. MCDONALD[1,2]; [1]Dept. of Neurosci., Monash Univ., Melbourne, Australia; [2]Dept. of Physiology, Anat. and Microbiology, La Trobe Univ., Melbourne, Australia; [3]NHMRC Clin. Trials Centre, Fac. of Med., The Univ. of Sydney, Sydney, Australia

Abstract: Background: Concussion is a mild traumatic brain injury that is highly prevalent in collision sports such as Australian rules football. Currently the diagnosis and management of concussion involves objective measures such as clinical symptomology. As such, there is a need for an objective biomarker that can guide the diagnosis, and recovery from concussion. One possible class of molecules is microRNAs (miRNAs). MiRNAs have shown much promise as circulating indicators of various neurological disorders, including schizophrenia and depression. Little is known, however, about the temporal profile of circulating miRNAs following concussion. Methods: Here we aimed to compare the expression of plasma miRNAs in amateur Australian rules footballers at baseline and three time points post-concussion. Blood was collected from nine male Australian rules footballers during the 2017 pre-season, at 24-48 hours, 6- and 13-days post-concussion. Five controls were also included from sex-, age-, and education-matched athletes without a history of concussion, or previous involvement in collision sport. Blood from a further five male and four female footballers, at baseline and three post-concussion time points, as well as nine matched controls was collected during 2018. Plasma miRNA expression of 754 known miRNAs was analysed using OpenArray. Results: Preliminary findings from the 2017 samples showed that the levels of a number of miRNAs were significantly altered at 24-48 hours post-concussion when compared to baseline. These findings were validated with low throughput RT-PCR using a different normalization technique. Of particular interest, the plasma expression of miR-328 significantly correlated with both concussion symptom number and severity at 24-48 hours post-concussion. The miRNA analysis from these additional participants is currently ongoing and will be completed with the additional analysis of the concussion associated miRNA pathways, prior to the Society for Neuroscience annual meeting in

October 2019. Conclusion: The initial findings from amateur Australian rules footballers suggest that miRNAs may have the potential to indicate the occurrence of sports-related concussion.

Disclosures: W.T. O'Brien: None. **C.J. Taylor:** None. **G.A. Neocleous:** None. **G.H. Fuller Symons:** None. **A.A. Hardikar:** None. **M.V. Joglekar:** None. **S.R. Shultz:** None. **S.J. McDonald:** None.

Poster

658. Traumatic Brain Injury: Biomarkers

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 658.04/G17

Topic: C.10. Brain Injury and Trauma

Support: Air Force Contract No. FA8702-15-D-0001

Title: Investigation of the relationship of vocal, eye-tracking, and fMRI ROI time-series measures with preclinical mild traumatic brain injury

Authors: *D. E. STURIM[1], T. F. QUATIERI[1], H. M. RAO[2], J. WILLIAMSON[1], A. LAMMERT[1], T. TALAVAGE[3];
[2]Bioengineering Systems and Technologies, [1]MIT Lincoln Lab., Lexington, MA; [3]Sch. of Electrical and Computer Engin., Purdue Univ., West Lafayette, IN

Abstract: In this work, we are examining correlations between vocal articulatory features, ocular smooth pursuit measures, and features from the fMRI BOLD response in regions of interest (ROI) time series in a high school athlete population susceptible to repeated head impact within a sports season. Initial results have indicated relationships between vocal features and brain ROIs that may show which components of the neural speech networks effected are effected by preclinical mild mTBI.
The data used for this study was collected by Purdue University on 32 high school athletes over the entirety of a sports season (Helfer, 2014), and includes fMRI measurements made pre-season, in-season, and postseason. The Immediate Post-Concussion Assessment and Cognitive Testing suite (ImPACT) was used as a means of assessing cognitive performance (Broglio, 2007). The test is made up of six sections, which measure verbal memory, visual memory, visual motor speed, reaction time, impulse control, and a total symptom composite. Using each test, a threshold is set for a change in cognitive performance. The threshold for each test is defined as a decline from baseline that exceeds one standard deviation, where the standard deviation is computed over the change from baseline across all subjects' test scores.
Speech features were extracted from audio recordings of the Grandfather Passage, which provided phonetically balanced speech. Oculomotor testing included two experimental conditions. In the smooth pursuit condition, a single target moving circularly, at constant speed.

In the saccade condition, a target was jumped between one of three location along the horizontal midline of the screen. The fMRI features are derived from the bold time-series data from resting state fMRI scans of the subjects. The pre-processing of the resting state fMRI and accompanying structural MRI data (for Atlas registration) was performed with the toolkit CONN (Whitfield-Gabrieli 2012). Functional connectivity was generated using cortical and sub-cortical atlas registrations. This investigation will explores correlations between these three modalities and a cognitive performance assessment.
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Disclosures: D.E. Sturim: None. **T.F. Quatieri:** None. **H.M. Rao:** None. **J. Williamson:** None. **A. Lammert:** None. **T. Talavage:** None.

Poster

658. Traumatic Brain Injury: Biomarkers

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 658.05/G18

Topic: C.10. Brain Injury and Trauma

Title: Monitoring axonal damage in neurological disorders: detection and quantification of neurofilaments light and heavy chain (NF-L/ pNF-H) as potential biomarkers of neurodegeneration

Authors: *Y. NOAM[1], T. A. LIBERMANN[2], S. T. DILLON[2], V. SHEEN[2], S. KARUMANCHI[3], E. SCHOELL[1], D. PERREGAUX[1], T. MUNN[4], P. YOUNGE[4], I. O'BRIEN[4], N. STEERE[4], M. ANDERSON[4];
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Abstract: Axonal damage is a hallmark of neurodegenerative disorders. In various neuropathologies, injured or degenerated axons release their intracellular components into the extracellular space, resulting in circulation of these molecules in the cerebrospinal fluid (CSF) and peripheral blood. Consequently, monitoring the levels of these molecules in biological fluids can serve as a potent biomarker for the diagnosis, prognosis, and evaluation of treatment in neurodegenerative diseases.
Of the various axonal molecules, neurofilaments are major structural components of the cytoskeleton. There are three distinct axonal neurofilament subunits: light (NF-L, ~68 kDa),

medium (NF-M, ~145 kDa), and heavy/phosphorylated (pNF-H, ~200 kDa). In recent years, neurofilaments (and in particular NF-L and NF-H) have emerged as promising biomarkers across a wide range of neurological disorders, including neurodegenerative dementia, multiple sclerosis, Parkinson's disease, traumatic brain injury, stroke, and amyotrophic lateral sclerosis (ALS). The ability to detect neurofilaments not only in CSF but also in blood is important in order to allow minimally-invasive diagnosis and monitoring of disease progression. However, whereas neurofilaments are readily detected in the CSF, their substantially lower levels in blood pose a challenge for standard immunoassay-based methods.
Here, we employed the Ella^{TM} platform to establish a novel, microfluidics-based assay for detecting and quantifying NF-L and pNF-H in CSF and blood samples. The automated nature of the assay facilitated a high degree of precision and reproducibility across trials, while requiring $\leq$ 25 ul of sample per measurement. Applying our assay to a physiologically-relevant context, we first studied the role of neurofilaments in aging by assessing NF-L and pNF-H in blood and CSF samples of healthy controls across ages. We next applied our assay to evaluate the potential of NF-L/ pNF-H as non-invasive bio-markers by measuring their levels in blood samples of patients diagnosed with neurodegenerative diseases. Taken together, our results support a role for neurofilaments as valuable markers of neurodegeneration and provide a novel and efficient platform for their detection in various biological samples.

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Poster

658. Traumatic Brain Injury: Biomarkers

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 658.06/G19

Topic: C.10. Brain Injury and Trauma

Support: NIH Grant HD51912
The James S. McDonnell Foundation
The Jerold B. Katz Foundation

Title: Eeg evidence of phonemic processing is severely brain-injured patients

Authors: *P. JAIN[1], M. M. CONTE[2], J. D. VICTOR[2], N. D. SCHIFF[2];
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Abstract: Assessment of cognitive function in severely brain-injured patients is critical to long-term recovery and rehabilitation. However, many patients with profound motor deficits lack the

ability to demonstrate reliable overt behaviors indicative of consciousness or speech comprehension. In these patients, EEG has been used to assess language processing at the level of command following, but the level of phonemic processing has not been explored. It has been previously reported that, in normal subjects, the EEG responses to natural speech encode distinct phonetic features (Khalighinejad, et al, 2017). Here, we determined whether a similar EEG signature of phonemic processing is present in severely brain-injured patients. We studied a cohort of 15 severely brain-injured patients (13 traumatic, 2 anoxic; 10 M) and nine healthy controls. Patients were assessed for motor function and overt cognitive function via the Coma Recovery Scale - Revised (CRS-R); scores ranged from 5 to 23. EEG was recorded using an augmented 10-20 montage (250 Hz, 37 electrodes; impedances ≤ 5kOhms), during presentation of a 148-sec audio clip of *Alice in Wonderland*. EEG responses to consonant phoneme classes (approximants, fricatives, nasals, and plosives) were extracted by averaging the EEG (60 Hz notch; 2-15 Hz bandpass filtered) with respect to time markers placed using PRAAT (Boersman, et al, 2002). We focused on the period from 200 ms prior to phoneme onset to 500 ms afterwards. Since the number of fricatives and plosives within the audio clip was twice that of the nasals and approximants, analyses were performed for only plosives and fricatives. In all healthy controls (HCs), we found phoneme class-specific responses to fricatives and plosives. Preliminary results show significant differences between the responses to plosives and fricatives 200-400 ms after phoneme onset, in agreement with previous reports (Khalighinejad, et al, 2017). The majority of significant responses were lateralized to left centroparietal, posterior-occipital and posterior mid-line channels. Patients emerged from minimally conscious state (eMCS) (CRS-R = 23) had responses that closely resembled those of HCs, whereas EEG responses in patients categorized as low MCS (CRS-R = 6-7) showed more variable differences between phoneme classes. Patients with cognitive-motor dissociation (fMRI and/or EEG evidence of command-following but no motor responses, n = 11) had responses that were similar to those of HCs and eMCS. These results support the claim that preserved phonemic processing, a necessity for language processing, can be assessed by EEG.

Disclosures: P. Jain: None. **M.M. Conte:** None. **J.D. Victor:** None. **N.D. Schiff:** None.

Poster

658. Traumatic Brain Injury: Biomarkers

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 658.07/G20

Topic: C.10. Brain Injury and Trauma

Title: Osteopathic manipulative treatment changes cerebral blood flow after concussion injury

Authors: *L. D. HENDERSON[1,4], R. KALKAT[1], S. K. GILL[1], D. J. GORBET[2,1,3], L. E. SERGIO[2,1,3], L. M. HYNES[1,3,2];**

[1]Sch. Kinesiol & Hlth. Sci., [2]Ctr. for Vision Res., [3]York Univ. Sport Med. Team, York Univ., Toronto, ON, Canada; [4]Canadian Col. of Osteopathy, Toronto, ON, Canada

Abstract: Altered cerebral blood flow (CBF), is seen in both animal[1-2] and human[3] models of concussion and represents one of the longest lasting biomarkers of concussion injury. Current research in humans has shown a significant decrease in CBF at 8-days post-concussion relative to 24h,[4] and others have found decreases in CBF in the dorsal midinsular cortex up to 1 month post-concussion[3], supporting the potential use of CBF as a biomarker for concussion recovery. Colour duplex-doppler ultrasongraphy (CDU) is a comparable CBF measure to phase contrast magnetic resonance imaging (PC-MRI)[5] making it a cost-effective and accessible evaluation tool. Concussion symptomology has been strongly associated with CBF[6], leading to our hypothesis that targeted therapy will cause a change in one or more factors associated with CBF (blood flow velocity or vessel cross-sectional area) and symptom severity. In the current study, we used CDU to measure blood flow velocity and volume of the right and left internal carotid (ICA) and vertebral arteries (VA) to measure CBF[5] and evaluate changes in concussion symptoms after osteopathic manipulative treatment (OMT). We recruited 11 healthy participants (mean age 27.3 yrs, n= 6 female) and 13 symptomatic concussed participants (mean age 27.5 yrs, n= 7 female) who were screened using a health questionnaire and the Standardized Concussion Assessment Tool, version 5 (SCAT5). CDU measurements were taken before receiving treatment at two different timepoints; first at the time of enrollment in the study and then 1-2 weeks later. Participants completed the SCAT5 and CDU evaluation again at the start of the next visit before the second treatment was provided. Final SCAT5 and CDU measurements were collected 5-6 weeks post enrollment in the study to evaluate if the effects of treatment were maintained. Preliminary analyses show that osteopathic manipulative treatment elicited a statistically significantly decrease in CBF velocity (76.5cm/s to 65.7cm/s; p= 0.002) in symptomatic concussed participants while demonstrating no significant changes in the healthy group. These results provide support that OMT may provide benefit to individuals who have sustained a concussion by improving blood vessel compliance.
References: 1. Giza & Hovda et al. 2014, Neurosurgery. 75(4):S24-S33; 2. Pasco et al. 2007, Journal of neurotrauma. 72(5):530-38; 3. Meier et al. 2015, JAMA neurology. 24(8):1321-30; 4. Wang et. al. 2016, Journal of neurotrauma. 33(13):1227-36; 5. Khan et al. 2017, Journal of cerebral blood flow. 37(2):541-49; 6. Albawali et al. 2017, Journal of neurotrauma 34:2700-2705.

Disclosures: L.D. Henderson: None. **R. Kalkat:** None. **S.K. Gill:** None. **D.J. Gorbet:** None. **L.M. Hynes:** None. **L.E. Sergio:** None.

Poster

658. Traumatic Brain Injury: Biomarkers

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 658.08/G21

Topic: C.10. Brain Injury and Trauma

Support: CRC to AJN

Title: An exploration of biological markers of post-concussion syndrome using transcranial magnetic stimulation

Authors: *M. B. LOCKE[1], S. L. TOEPP[1], C. V. TURCO[1], D. HARASYM[2], M. P. RATHBONE[3], M. D. NOSEWORTHY[2], A. J. NELSON[1];
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Abstract: Post-concussion syndrome (PCS) affects ~15-30 % of adults who incur a concussion, yet no objective marker of PCS has been identified in humans. Identifying a neurological marker of PCS development may enhance our ability to identify those whom are vulnerable to secondary injury long-term, and further our understanding of the underlying pathophysiology of PCS. This study sought to identify a physiological marker of PCS using transcranial magnetic stimulation (TMS) over motor cortex (M1) of adults with PCS (n = 15, 4 male; mean age = 28.8 ± 8.7 years) compared to healthy adults with no history of concussion (n = 13, 3 male; mean age = 26.8 ± 7.7 years). A single session featuring symptom measures (post-concussion symptom scale (PCSS) and Beck's Depression Inventory (BDI-II)) and multiple TMS measures related to excitability (resting motor threshold, active motor threshold, motor evoked potentials, intracortical facilitation), intracortical inhibition (short-interval intracortical inhibition, cortical silent period (CSP)), and transcallosal inhibition (ipsilateral silent period, interhemispheric inhibition) were acquired. A between-group difference was found in CSP ($p = 0.021$, $g = 0.960$), suggesting reduced intracortical $GABA_B$ receptor activity in the PCS group. All other measures, including measures of intracortical $GABA_A$ and glutamate receptor activity, were similar between groups. No significant differences in transcallosal inhibition were found. Secondary regression analyses tested the predictive value of symptom scales (PCSS, BDI-II) for all outcome measures. Interestingly, greater scores on BDI-II were related to reduced CSP length, while PCSS scores did not significantly predict CSP length. While this study did expose differences in cortical function in those with PCS, these changes may in fact be due to existing depressive symptoms rather than concussion symptoms. Further investigation is warranted to determine whether measures of cortical $GABA_B$ function provide a useful biomarker for PCS development.

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Poster

658. Traumatic Brain Injury: Biomarkers

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 658.09/G22

Topic: C.10. Brain Injury and Trauma

Support: National Institute of Nursing Research Intramural Research Program
Defense and Veterans Brain Injury Center, US Army Medical Research and Material Command (USAMRMC)

Title: Exosomal and plasma biomarkers relate to chronic symptoms in veterans with history of mild traumatic brain injury

Authors: *V. DE ALVARENGA GUEDES[1], C. LAI[1], C. DEVOTO[1], B.-X. QU[2], K. KENNEY[2], J. M. GILL[1];
[1]NIH, Bethesda, MD; [2]Uniformed Services Univ. of the Hlth. Sci., Bethesda, MD

Abstract: Individuals who sustained a mild traumatic brain injury (mTBI) are at increased risk of developing chronic neurobehavioral symptoms. Posttraumatic stress disorder (PTSD), depression, and post-concussive (PCS) are highly prevalent in military populations and frequently occur comorbidly with TBI, resulting in substantial health risks. This study examined associations among chronic mTBI, peripheral blood biomarkers, including exosomal proteins, and symptoms of PTSD, depression, and PCS. Exosomal and plasma levels of neurofilament light (NFL), tau, p-tau, amyloid beta (Aβ)-40, Aβ-42, interleukin (IL)-6, IL-10, tumor necrosis factor (TNF)-alpha, and vascular endothelial growth factor (VEGF) were measured using an ultrasensitive assay in a cohort of 195 Veterans, enrolled in the Chronic Effects of Neurotrauma Consortium (CENC) Longitudinal Study. PTSD, depression and PCS were evaluated using PTSD Checklist Military Version (PCL), patient health questionnaire-9 (PHQ-9), and neurobehavioral symptom inventory (NSI), respectively. Individuals with history of TBI reported significantly worse PTSD ($p = 0.0002$), depression ($p =0.0002$) and PCS ($p<0.0001$) symptoms than controls. Biomarker levels were compared among those with no TBI (controls), 1-2 mTBIs and repetitive (3 or more) mTBIs. Higher levels of exosomal ($p = 0.0105$) and plasma ($p = 0.0024$) NFL were observed in individuals with repetitive mTBIs than in those with 1-2 TBIs. In individuals with TBI, PCL scores were correlated with exosomal ($r= 0.497$, $p<0.0001$) and plasma ($r= 0.2955$, $p= 0.0004$) NFL, and plasma TNF-alpha ($r= -0.2267$, $p= 0.0255$). PHQ9 was positively correlated with exosome ($r= 0.4368$, $p<0.0002$) and plasma ($r= 0.2041$, $p<0.0156$) NFL, and plasma Tau ($r = 0.1858$, $p = 0.0266$). NSI scores were correlated with exosomal ($r = 0.5516$, $p<0.0001$) and plasma ($r = 0.3425$, $p<0.0001$) NFL, and plasma TNF-alpha ($r = -0.2328$, $p = 0.0211$). Our results suggest that elevations in NFL, Tau and TNF-alpha levels are associated with symptom severity in individuals with history of mTBI, while increased levels of NFL are elevated in those with multiple head injuries.

Disclosures: V. De Alvarenga Guedes: None. **C. Lai:** None. **C. Devoto:** None. **B. Qu:** None. **K. Kenney:** None. **J.M. Gill:** None.

Poster

658. Traumatic Brain Injury: Biomarkers

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 658.10/G23

Topic: C.10. Brain Injury and Trauma

Support: Innovative Seed Grant Program (ISGP)

Title: Cognition, mood, and cortisol circadian profiles following mild traumatic brain injury in college students: Confirmation of subjective reports of impairment with objective cognitive measures

Authors: *E. VILLEGAS, Jr[1], B. ABEN[2], M. J. HARTSOCK[1], M. VALDEZ[1], M. MCQUEEN[1], R. L. SPENCER[3], T. D. HERNANDEZ[3];
[2]Psychology and Neurosci., [1]Univ. of Colorado Boulder, Boulder, CO; [3]Psychology and Neurosci., Univ. of Colorado at Boulder, Boulder, CO

Abstract: Mild Traumatic Brain Injury (mTBI) is the most common form of TBI accounting for approximately 80% of the annual (2.8M) TBI cases. More importantly, this number is likely an underestimation as it does not include the number of individuals who sustain mTBI and do not seek medical care or are inaccurately diagnosed. An additional obstacle to effective assessment and treatment is that there are often no readily observable signs through commonly used neuroimaging techniques and symptom presentation may vary from person to person. Still, the most common mTBI symptoms reported include those related to cognition, mood and sleep. However, no prior studies have systematically used objective cognitive and circadian measures to assess the severity of these symptoms over the first several weeks following the occurrence of mTBI. The present study was designed to assess the presence and time-course of these symptoms acutely after mTBI in a sample of otherwise young healthy adults (college student sample). To this end, the Automated Neuropsychological Assessment Metric (ANAM) and the Brief Assessment of Mood (BAM) were used in addition to circadian cortisol sampling. Measurements were obtained in students who sustained a recent mTBI (n=46) and in healthy controls (n=44) at baseline and at a one-week follow-up timepoint. The main findings include overall significant differences between the mTBI and control group on several cognitive measures including simple reaction time, procedural reaction time, and code substitution. Furthermore, the mTBI group reported significantly higher mood disturbance at baseline followed by a significant decrease in mood disturbance at the one-week follow-up when compared to controls. Additional findings from the study will be discussed including the relationship of circadian function to cognitive function and mood disturbance, and their changes over time.

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Poster

658. Traumatic Brain Injury: Biomarkers

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 658.11/G24

Topic: C.10. Brain Injury and Trauma

Support: NIH Grant R21NS099789
DOD Grant W81XWH-14-1-0561

Title: Acute effects of sport-related concussion on neuroactive kynurenine pathway metabolites and their association with post-concussion mood symptoms

Authors: *T. B. MEIER[1,2,3], M. E. NITTA[1,5], T. K. TEAGUE[6,7,8], J. B. HOELZLE[5], L. D. NELSON[1,4], M. A. MCCREA[1,4], J. SAVITZ[9,10];
[1]Neurosurg., [2]Cell Biology, Neurobio. and Anat., [3]Biomed. Engin., [4]Neurol., Med. Col. of Wisconsin, Milwaukee, WI; [5]Psychology, Marquette Univ., Milwaukee, WI; [6]Surgery and Psychiatry, Univ. of Oklahoma Sch. of Community Med., Tulsa, OK; [7]Pharmaceut. Sci., Univ. of Oklahoma Col. of Pharm., Tulsa, OK; [8]Biochem. and Microbiology, Oklahoma State Univ. Ctr. for Hlth. Sci., Tulsa, OK; [9]Laureate Inst. for Brain Res., Tulsa, OK; [10]Community Med., Univ. of Tulsa, Tulsa, OK

Abstract: There is great interest in identifying objective biomarkers to assist in the diagnosis and prognosis of sport-related concussion (SRC). Previous work has demonstrated that an imbalance in neuroactive kynurenine pathway (KP) metabolites measured in serum is associated with mood dysregulation in a variety of psychiatric diseases and potentially SRC. Here, we tested the hypothesis that neurotoxic KP metabolites (3-hydroxykynurenine [3HK] and quinolinic acid [quinA]) are elevated relative to neuroprotective metabolites (kynurenic acid [kynA]) following SRC and are associated with post-injury mood symptoms. Blood was collected at preseason and at 6 hours, 48 hours, and 8, 15, and 45 days post-concussion in high school and collegiate football players (N=63, age=18.00±1.56 years). Matched, non-injured football players were recruited as controls and completed similar visits (N=60, age=18.22±1.71 years). Mood symptoms were assessed using the Brief Symptom Inventory 18 (BSI-18) somatization, depression, and anxiety subscales at each visit except at 6 hours post-injury. KP metabolites were quantified in serum by high-performance liquid chromatography with tandem mass spectrometry, blind to diagnosis, and subsequently natural-log transformed. Linear mixed effects models were used to assess changes across visits with the effect of group and the interaction of group by visit, with participant modeled as a random effect. Generalized linear models were used to determine the relationship between KP metabolites and BSI-18 subscales in concussed athletes, covarying preseason biomarker levels and BSI-18 scores. SRC had elevated anxiety, depression, and somatization symptoms at 48 hours post-injury relative to other post-injury visits

and relative to controls (ps<0.05), while somatization and depression symptoms were still elevated relative to controls at 8 days (ps<0.05). There was a significant group by visit interaction for the ratio of kynA to 3HK (p=0.03). Follow-up tests showed that kynA/3HK was significantly higher in SRC at 6 hours relative to preseason and 8, 15 and 45 days post-injury as well as relative to contact controls (ps<0.05). In addition, kynA/3HK levels in SRC at 45 days post-concussion were significantly lower relative to all other visit (ps<0.05). Higher kynA/3HK at 6 hours post-concussion predicted lower depression scores at 48 hours (p<0.05). This relationship was driven by a positive association between 3HK at 6 hours post-concussion and depression scores at 48 hours (p<0.05). These findings suggest that SRC results in an acute increase in the neuroprotective kynA/3HK ratio that may attenuate post-concussion depressive symptoms.

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Poster

658. Traumatic Brain Injury: Biomarkers

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 658.12/G25

Topic: C.10. Brain Injury and Trauma

Title: Measurement of inflammatory cytokines and neurodegenerative/injury biomarkers in acute concussion/mild traumatic brain injury (c/mTBI) serum and saliva samples

Authors: *A. CHENNA, C. J. PETROPOULOS, J. W. WINSLOW;
Monogram Biosci. Inc/Labcorp, South San Francisco, CA

Abstract: An estimated 1.6 to 3.8 million recreational and competitive athletes in the US incur/experience a concussion each year. Elevations in certain central nervous system (CNS) proteins (t-Tau, NF-L, GFAP and UCH-L1) and inflammatory cytokines (IL-6, IL-10, TNFα) in blood and CSF samples have been associated with c/mTBI, representing candidate diagnostic and prognostic biomarkers. Recently the FDA approved GFAP and UCH-L1 as diagnostic biomarkers of TBI. Characterizing the timing and fluctuation in CNS and inflammatory biomarkers following c/mTBI could improve diagnostic and prognostic utility. The SIMOA Neurology 4-plex A and Cytokine 3-plex A immunoassays (Quanterix) were used to measure t-Tau, NF-L, GFAP, UCH-L1 and IL-6, IL-10, TNF-α, respectively. Blood samples were collected from study subjects (n= 30 each) within 1-4 hr and 8-16 hr post-c/mTBI injury, as well as 30 healthy controls. Matching saliva samples were also collected from the 8-16 hr post-c/mTBI subgroup (n= 30). IL-6, IL-10 and TNFα were significantly elevated in the 1-4 hr and 8-16 hr post-c/mTBI serum samples relative to healthy controls (p <0.0001). Receiving Operating Characteristic (ROC) curve analysis indicates that each of the 3 cytokines is highly

discriminatory for c/mTBI patients vs healthy controls (AUC = 0.86-0.99). Cytokine levels were significantly correlated across the 1-4hr and 8-16 hr time groups, with the exception of IL-6 in the 8-16 hr time group, which trended toward significance. With the exception of IL-6, cytokine levels in most saliva samples were near or below the lower limit of quantitation. Median levels of GFAP, NF-L, UCH-L1 and t-Tau were significantly elevated in matched 1-4 hr and 8-16 hr post-c/mTBI serum samples relative to healthy controls. ROC analysis of neuronal biomarkers indicate moderate discriminatory ability for c/mTBI vs controls (AUC = 0.7-0.76), relative to the cytokine 3-plex proteins (AUC=0.86-0.99). The combination of CNS proteins and inflammatory cytokines as biomarkers of c/mTBI may enhance diagnostic capability as well as prognosis with regards to the severity and outcome of brain injuries. Based on our initial findings using a single processing approach, these 3 saliva cytokines may not represent useful biomarkers for concussion patients.

Disclosures: **A. Chenna:** A. Employment/Salary (full or part-time):; Monogram Biosciences Inc. **C.J. Petropoulos:** A. Employment/Salary (full or part-time):; Monogram Biosciences Inc. **J.W. Winslow:** A. Employment/Salary (full or part-time):; Monogram Biosciences Inc.

Poster

658. Traumatic Brain Injury: Biomarkers

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 658.13/G26

Topic: C.10. Brain Injury and Trauma

Title: Auditory sensory processing is impaired following mild traumatic brain injury

Authors: *M. C. DUGGINS, Y. KIM, J. DAVIS, K. PAULSON, R. THOMA, J. D. LEWINE; The Mind Res. Network, Albuquerque, NM

Abstract: Following mild traumatic brain injury, many subjects complain of persistent auditory processing problems, such as difficulties tracking conversations in noisy environments (e.g., restaurants). To better understand the relevant neurobiology, a paired-tone auditory evoked response paradigm was used to examine basic auditory processing, rapid auditory processing, and sensory-gating in 70 neurotypical control subjects (45 males, ages 8-74) and 60 patients with persistent (>6 months) post-concussive symptoms following a mild traumatic brain injury (39 males, ages 9-72). Stimuli consisted of single 1 or 2 kHz pure tone pips (to measure basic auditory processing); paired discrepant tone pips (1kHz-2kHz, 2kHz-1kHz, 300 msec inter-tone-interval, to measure rapid auditory processing); and paired identical tone pips (1kHz-1kHz, 2kHz-2kHz, 300 msec inter-tone-interval, to measure sensory gating). For paired conditions, an N100 gating ratio was calculated as the amplitude of the response to the second tone divided by the amplitude of the response to the first tone. No significant differences were seen between the control and mTBI groups on measures of basic auditory processing or rapid auditory processing.

For the sensory gating condition, the average gating ratio for control subjects was 0.38. In contrast, the average gating ratio for TBI subjects was 0.64. A high gating ratio indicates a failure in the normal suppression/gating of brain activity evoked by the second redundant stimulus in a pair of rapidly presented identical stimuli. This difference was highly significant, $F(1,129)=84.32$, $p<0.001$. Using a cutoff gating ratio of 0.05, 84% of all subjects were correctly classified as coming from control versus TBI groups. Thirty-four of the TBI patients also completed the SCAN-III, a behavioral evaluation of central auditory processing abilities. The r-squared correlation coefficient between the sensory gating ratio and SCAN-III score was -0.49, an indication that gating impairments (high S2/S1 ratios) were associated with poor auditory processing abilities. The data demonstrate that mild traumatic brain injury is associated with correlated deficits in central auditory processing as measured by both behavioral and electrophysiological methods.

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Poster

658. Traumatic Brain Injury: Biomarkers

Location: Hall A

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Program #/Poster #: 658.14/G27

Topic: C.10. Brain Injury and Trauma

Support: Ministry of Science and Technology, Taiwan, Grant MOST106-2314-B-010-058-MY2
Ministry of Science and Technology, Taiwan, Grant MOST107-2634-F-038 -001

Title: Anxiety-related alterations of resting-state networks in mild traumatic brain injury

Authors: Y.-T. LEE[1], C.-F. LU[2], N.-C. CHEN[1], L.-C. HSIEH[1,3,4], S.-J. CHENG[1,3], Y.-C. J. KAO[1,4,5], C.-Y. CHEN[1,3,4];
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Abstract: PURPOSE
The causes of increased anxiety level after mild traumatic brain injury (mTBI) are complicated and may involve the abnormality in different brain regions. We aim to compare the functional connectivity between mTBI and healthy control (HC) groups to identify the anxiety-related alterations during resting state.
MATERIALS AND METHODS

In total 68 Chinese participants were enrolled in this study, including HC (N=27, 7 males, aged of 33.04), high-anxiety mTBI with scores of Beck Anxiety Inventory larger than 7 (HmTBI, N=18, 3 males, aged of 33.00), low-anxiety mTBI (LmTBI, N=23, 9 males, aged of 35.83) groups. There's no sex difference between groups. Resting-state fMRI and 3D T1-weighted images were acquired using a Siemens Prisma 3T scanner. After standard preprocessing steps, the independent component analysis was performed to extract 27 resting-state networks (RSNs) using GIFT toolbox.

RESULTS

Significant group differences were presented in 6 RSNs (Fig.1). In comparison with the HC, several results were found: a) In default mode network, the LmTBI group has higher connectivity in right superior frontal and middle temporal gyri, and lower connectivity in right calcarine; b) In posterior executive network, the HmTBI group exhibits lower connectivity in right superior frontal gyrus and left calcarine; c) In anterior executive network, the LmTBI group shows higher connectivity in right inferior frontal gyrus, and the HmTBI group shows higher connectivity in left precuneus and lower connectivity in posterior cingulate cortex; d) In frontal-parietal network, the HmTBI group has higher connectivity in right precuneus/posterior cingulate cortex and lower connectivity in right superior frontal gyrus and left cerebellum; e) In visual network, the HmTBI group has higher connectivity in right superior frontal cortex; f) In motor network, the HmTBI group shows higher connectivity in left superior frontal cortex and lower connectivity in left supramarginal gyrus.

CONCLUSION

Increased anxiety level after mTBI involves the changes of functional connectivity in several RSNs.

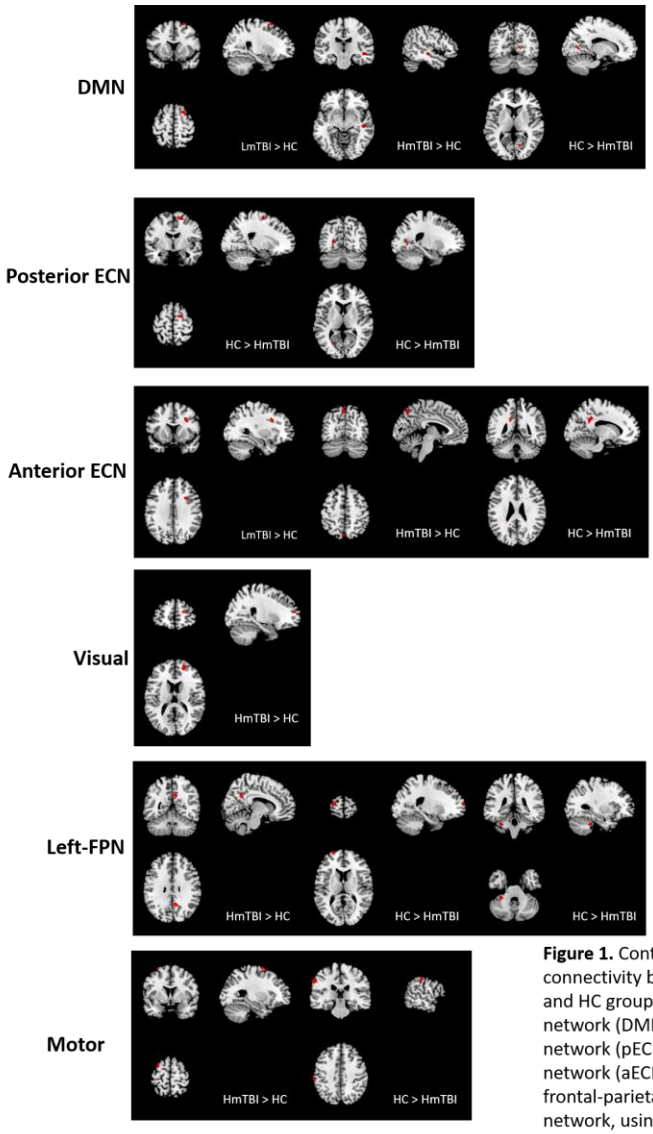

Figure 1. Contrast functional connectivity between HmTBI, LmTBI, and HC group on default mode network (DMN), posterior executive network (pECN), anterior executive network (aECN), visual network, left frontal-parietal network, and motor network, using uncorrected p <0.001 with cluster size >10 as threshold.

Disclosures: Y. Lee: None. **C. Lu:** None. **N. Chen:** None. **L. Hsieh:** None. **S. Cheng:** None. **Y.J. Kao:** None. **C. Chen:** None.

Poster

658. Traumatic Brain Injury: Biomarkers

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 658.15/G28

Topic: C.10. Brain Injury and Trauma

Support: NIMH Grant 1 P50 MH094258
McDonnell Foundation Collaborative Award 220020387
NIA at NIH Grant R37 AG025667; R43AG047722; R21AG048170
AMBI

Title: Functional connectivity patterns of the lesioned default mode network

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Abstract: The Default Mode Network (DMN) is involved in crucial processes for autobiographical memory and is susceptible to aging and mental disorders such as Alzheimer's (Damoiseaux et al., 2007; Grecius et al., 2004). It has been proposed to consist of Core regions that interact with a dorsomedial prefrontal cortex (dmPFC) subsystem and a medial temporal lobe (MTL) subsystem (Andrews-Hanna et al, 2010) based on resting state functional connectivity magnetic resonance imaging (rs-fcMRI). Having a clear idea of the DMN's functional connectivity (fc) pattern is useful for understanding the relationship between severity of network disruption and subsequent reorganization and recovery. One way to address this is by studying the effect of focal lesions on DMN fc, yet this remains unclear. Here, we evaluate the consequences of damage to the proposed components of the DMN by using rs-fcMRI and the lesion method to test two predictions: when one subsystem is damaged, its fc decreases while fc of the undamaged subsystem increases; when the Core is damaged, fc between the two subsystems will decrease further. An additional exploratory analysis will be performed by creating sham lesions on the rs-fcMRI data of the demographically-matched non-lesioned participants to test whether their fc patterns remain intact; this would help elucidate the effect of physical damage on DMN fc patterns. We predict that sham lesions would cause minimal impact, since physical damage would be necessary to significantly alter fc patterns.
We gathered rs-fcMRI data of patients with stable, circumscribed lesions in different components of the DMN (N=29) and compared to rs-fcMRI data of demographically-matched non-lesioned participants (N=29) and brain-damaged controls (N=18).
A repeated measures ANOVA with one between-groups factor and one repeated factor of subsystems was performed.
Contrary to our predictions, preliminary results of patients with dmPFC-restricted lesions do not have significant group fc differences within the MTL, but do show significant changes within other DMN components compared to the non-lesioned data with no sham lesions. When all three proposed DMN components had lesions, we found significant group fc differences within and between DMN components.
These results bring further insight into DMN organization based on resting fc patterns, which could expand the characterization of memory subsystems in relation to normal aging, eventually leading to improvements in predicting clinical outcomes for neurological and psychiatric patients, and expediting the development of memory performance-improving interventions and more effective and personalized treatments.

Disclosures: A. Rivera-Dompenciel: None. **J.E. Bruss:** None. **D. Tranel:** None. **M. Voss:** None.

Poster

658. Traumatic Brain Injury: Biomarkers

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 658.16/G29

Topic: C.10. Brain Injury and Trauma

Title: Brain structural connectivity predicts cognitive performance in TBI patients

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Abstract: Traumatic brain injury (TBI) affects 2.5 million people each year and has a detrimental impact on people life. Patients often suffer from widely distributed axonal damage, named diffuse axonal injury after TBI. Although the behavioral and cognitive deficit is conspicuous in TBI patients, brain structures and networks that were disrupted by TBI are complicated and widely distributed throughout the brain. The current study aimed at examining if brain structural connectivity between different brain regions can predict TBI patients cognitive outcome in different cognitive domains. 68 TBI patients and 100 control subjects were recruited in the study. Subjects were scanned using a multi-shell protocol on a 3T Siemens Tim Trio magnet with a 32-channel head coil. Diffusion imaging data were reconstructed using Generalized Q-Sampling Imaging in the subject's DWI space and then whole-brain fiber tracking was performed by DSI studio. A whole brain structural connectivity matrix with the mean quantitative anisotropy(QA) values between each pair of brain regions as inputs was generated for each subject. We explored if brain structural connectivity can predict cognitive performance in control and TBI patients by applying the connectome based predictive modeling (Finn et al.2015; Rosenberg et al.2016). We found that brain structural connectivity between prefrontal, motor cortex to subcortical regions successfully predict individual differences in processing speed performance in TBI patients ($r=0.48$, $p<0.0001$). Structural connectivity between parietal lobes and subcortical regions successfully predict TBI patients' working memory performance ($r=0.34$,$p<0.01$). Our results highlight the role of brain structural connectivity on high-level cognitive functions and the disconnectivity and damage of different anatomical pathways could result in cognitive impairment in different cognitive domains.

Disclosures: P. Li: None. **W. Schneider:** None.

Poster

658. Traumatic Brain Injury: Biomarkers

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 658.17/G30

Topic: C.10. Brain Injury and Trauma

Support: DoD Grant MR141214

Title: Chemical and microstructural brain biomarkers of traumatic brain injury-related chronic pain

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Abstract: More than 50% of people that experience a traumatic brain injury (TBI) develop chronic pain that may interfere with their daily activities and quality of life. By identifying important changes in brain chemistry and microstructure that are associated with chronic pain after TBI, so called pain biomarkers, we will be able to understand more about the specific mechanisms of this type of pain. The long-term goal of this study is to develop a basis for treatments tailored to the specific underlying mechanisms of TBI-related chronic pain. This research combines non-invasive, whole-brain imaging techniques to investigate areas of the brain that are significantly involved in the perception and modulation of pain (i.e., the thalamus, insula, cingulate, prefrontal cortex, and hippocampus) and the associations with pain symptoms, sensory and neuropsychological assessments. This dataset focused on the comparison of magnetic resonance spectroscopy (MRS) and diffusion kurtosis imaging (DKI) measures between participants (ages 18-50) with: (1) mild to moderate TBI who experienced chronic pain for a minimum of 6 months (n=9); (2) mild to moderate TBI with no pain (n=8); and (3) pain-free controls (n=30). N-acetyl aspartate (NAA), a marker of neuronal mitochondrial activity; Myo-inositol (Ins), a glial marker involved in the volume and osmoregulation of astrocytes; and a combination of Glutamate-Glutamine (Glx) levels were quantified using a 3T-MRI scanner and compared among the three groups by one-way ANOVA-post-hoc-Tukey test. Two DKI components: axial diffusivity (Dax) and radial diffusivity (Drad), calculated by the anisotropic water diffusion in the nerves, were used to indicate microstructural integrity of neurons and glia. Subjects with TBI that experienced chronic pain exhibited significantly: higher hippocampal levels of NAA ($p<0.05$), higher mid cingulate Glx/Ins levels ($p<0.01$) and greater hippocampal and thalamic Dax ($p<0.01$) and Drad ($p<0.01$), suggesting neuronal hyperexcitability, glial proliferation, and a reduced axonal and myelin integrity in these specific brain regions involved

in pain processing. Further analysis needs to be performed in order to confirm those results and to correlate them with the pain symptoms, sensory and neuropsychological assessments.

Disclosures: L.E. Robayo: None. **V. Govind:** None. **S. Sheriff:** None. **L. Fleming:** None. **A.A. Maudsley:** None. **E. Widerstrom-Noga:** None.

Poster

658. Traumatic Brain Injury: Biomarkers

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 658.18/G31

Topic: C.10. Brain Injury and Trauma

Title: Relationship between serum-based biomarkers and MRI measures following mild traumatic brain injury in collegiate athletes post return-to-play

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Abstract: With over 1 million emergency room visits a year and 1.7 million new cases annually in the United States, traumatic brain injury (TBI) is widely prevalent. About 80% of all TBIs are classified as mild, more commonly referred to as a concussion. Despite the high prevalence of concussion there are not many studies using neuroimaging techniques to assess the post-injury phase. Magnetic resonance imaging (MRI) is a neuroimaging technique that is used to assess a variety of clinical and research needs including TBI. Recently, there has been a rise in concussion research specifically assessing the effects it may have on protein levels in serum, a derived portion of blood, between concussed and control groups. Brain derived neurotrophic factor (BDNF) has been previously linked to concussion and plays a role in the recovery of brain function. Proteins such as BDNF have been found to have altered levels in serum after TBI. However, there is limited knowledge about the relationship between serum-based biomarkers and MRI-based biomarkers in concussed athletes post return-to-play. This study aimed to bridge this gap by collecting MRI and serum samples from 28 participants across two groups. The first group (n = 14) consisted of recently cleared to return-to-play collegiate athletes after experiencing a sports-related concussion. The second group (n=14) consisted of collegiate athlete controls matched on age, sex, and sport. Neither group had experienced a concussion for at least three years prior to the study. Five ml blood samples were collected to assess the levels of BDNF. All samples were aliquoted and centrifuged for their respective times and then stored at -80 degrees Celsius until further handling. A ChemiKine BDNF sandwich Enzyme-Linked Immunosorbent Assay (ELISA) kit was used in duplicate to analyze the samples. Structural MRI measures were used for analysis. Although there was not a significant effect of group for BDNF, associations of gray matter volume and BDNF were observed in the prefrontal cortex, brainstem,

precuneus, right and left cerebellum regions between groups. In summary, these results suggest lingering effects of concussion, granting a better depiction of the post return-to-play timeframe following sports-related concussions.

Disclosures: T.R. Susa: None. **M.T. Moore:** None. **J.M. Carlson:** None.

Poster

658. Traumatic Brain Injury: Biomarkers

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 658.19/G32

Topic: C.10. Brain Injury and Trauma

Support: CONACYT GRANT 512853
CONACYT GRANT 252808

Title: Evaluation of biomarkers of oxidative stress in orbitofrontal cortex of suicide victims

Authors: *A. A. ORDUÑA[1], A. J. VÁZQUEZ HERNÁNDEZ[2], L. ARROYO GARCÍA, SR[3], R. A. VAZQUEZ, SR[4], S. DURAN[4], F. E. TAKAJASHI[5], H. TENDILLA[6], F. GARCIA-DOLORES[7], G. FLORES[8];
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Abstract: Suicide is a growing health problem. According to the World Health Organization (WHO), around one million people lose their life for this reason every year. Even though the process of suicide is not clear, several mental disorders such as schizophrenia, depression or drug addiction are thought to be related. It has been known that orbitofrontal cortex is relevant in the decision making, so any alteration in this area could lead to this radical action. The aim of this study is to know the oxidative stress in the orbitofrontal cortex of suicide victims. To reach this aim we measured oxidative stress biomarkers such as BDNF, PSD95, which are related to neuroplasticity. One as a cellular grown factor and the other one as a membrane protein associated with NMDA receptors respectively. The last biomarker that was studied was metallothionein, which is related to the kidnapping of heavy metals. The samples were separated into two principal groups: young (12-30 years) and adults (31-67 years). Having control and cases for each group and each biomarker. The cause of death, gender and age were considerate for each group as any diagnosis in neuropathologies or drug abuse. These biomarkers were measured by using immunohistochemistry staining. Then we got microphotographs which later

were analyzed by counting every reactive cell for each reactive. Our results suggest a decrease in metallothionein in the case young group, without significant changes in the adult group. This could mean that young people are more susceptible to oxidative change. In addition, the young group also showed a decrease in the levels of PSD95. On the other side, in the adult group, we found fewer levels of PSD95 in the control group suggesting a possible compensation mechanism. Finally, our results about BDNF have not been concluded yet. This could lead us to find a clearer way to understand this pathology.

Disclosures: **A.A. Orduña:** None. **A.J. Vázquez Hernández:** None. **L. Arroyo García:** None. **R.A. Vazquez:** None. **S. Duran:** None. **F.E. Takajashi:** None. **H. Tendilla:** None. **F. Garcia-Dolores:** None. **G. Flores:** None.

Poster

658. Traumatic Brain Injury: Biomarkers

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 658.20/G33

Topic: C.10. Brain Injury and Trauma

Support: Bass Connections / Brain & Society (DIBS)

Title: Anti-saccade and sub-concussive loading: Changes in initial and end gain task metrics following head impact exposure in a high school football season

Authors: ***W. J. PRITZLAFF**[1], B. M. BLASS[1], M. Z. ABRAMS[1], D. O'CONNELL[1], M. PAITHANE[1], C. HILE[1], E. HSIEH[1], K. KHYLYSTOVA[1], A. MEHLENBACHER[2], B. CAPEHART[3], C. R. BASS[1], J. F. LUCK[1];
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Abstract: An accurate and objective diagnostic tool for mild traumatic brain injury (mTBI) resulting from sub-concussive loading - described as the cumulative effects of sustained low-magnitude head impact exposure (HIE) - in pediatric populations that participate in a contact sport does not yet exist. The objective of this pilot study was to examine the relationship between HIE and eye-tracking performance using two accuracy (gain - % of target; deg/deg) based anti-saccade task metrics in varsity high school football athletes across a season to understand potential neurological deficits resulting from sub-concussive loading. Participating varsity football athletes during the 2017-2018 season (n = 31) were grouped into 10^{th} (low) and 90^{th} (high) HIE percentiles based on weekly HIE frequency scores self-reported through athletic activity/contact exposure questionnaires (AACEQ). Eye-tracking assessments were conducted at the beginning-of-season (BOS), middle-of-season (MOS) and end-of-season (EOS) for each player. Mixed-design ANOVAs were performed for anti-saccade initial and end gain. Task

performance was analyzed at BOS, MOS, and EOS (repeated measures) between low (n = 4) and high (n = 4) HIE groups (between subjects factor). The mixed-design ANOVA indicated a significant interaction between time of season and HIE group on end gain, $F(2,134) = 3.857$, $p = 0.024$, $\eta^2 = 0.053$. A repeated measures ANOVA indicated a significant effect of time of season on end gain, $F(1.536,52.232) = 3.834$, $p = 0.038$, $\omega^2 = 0.030$, in the low HIE group (Greenhouse-Geisser correction). Bonferroni-corrected post-hoc tests revealed that there was not a significant difference between pairwise comparisons at different time points throughout the season. There was not a significant effect of time of season on end gain in high HIE group, $F(2,66) = 1.073$, $p = 0.348$, $\eta^2 = 0.032$. At EOS, end gain was significantly lower in the low HIE group (89.8 ± 29.8, $p = 0.003$) compared to the high HIE group (124.4 ± 58.8). The mixed-design ANOVA omnibus test for initial gain indicated no significant interaction or main effects. These pilot results suggest that anti-saccade end gain may exhibit differences across seasonal time points and between HIE groups of varsity football athletes. However, some limitations that may have skewed true measures of low and high HIE groups include three assumptions: the AACEQ accurately stratifies HIE, the small samples are representative of true low and high HIE, and there was no learning effect. A further investigation controlling for these limitations is necessary to further our understanding of the potential role of accuracy based anti-saccade metrics as objective mTBI indicators.

Disclosures: W.J. Pritzlaff: None. **B.M. Blass:** None. **M.Z. Abrams:** None. **D. O'Connell:** None. **M. Paithane:** None. **C. Hile:** None. **E. Hsieh:** None. **K. Khylystova:** None. **A. Mehlenbacher:** None. **B. Capehart:** None. **C.R. Bass:** None. **J.F. Luck:** None.

Poster

659. Brain Injury and Trauma II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 659.01/G34

Topic: C.10. Brain Injury and Trauma

Title: The role of protein in shunt flow and obstruction

Authors: *K. BEHARRY[1], N. GORELICK[2], R. SERRA[2], B. TYLER[2], H. BREM[2], M. LUCIANO[2];
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Abstract: As Cerebrospinal fluid (CSF) surrounds every facet of the central nervous system, CSF disorders can impact neuroscientists greatly. Shunts are neurosurgical devices used in the treatment of hydrocephalus, but 85% of shunts fail within 10 years after implantation. The computer-driven model for testing may not accurately detect variability in flow rate or obstruction. Our benchtop gravity-flow system used commonly implanted valves, each equipped with antisiphon devices (ASDs). We varied position and fluid protein content in diurnal trials of

upright and supine conditions to evaluate the role of protein in flow rate and obstruction.
Within an incubator set to 37° C, saline with or without protein was filled in a reservoir of a gravity-driven apparatus that drove flow continuously via 6 catheters through valves and into their respective collecting flasks. The collecting flask heights were alternated between 28.5 cm and 2 cm below the valves for 14 and 8 hours in upright and supine trials, respectively, to mimic a patient's daily positional changes. Valves were tested in 3 saline studies: protein-free, 1 g/L protein, and 5 g/L protein for up to 30 days. For each trial, the hydrostatic pressure driving force, temperature, and fluid output were recorded for each valve to compare the effects of protein on flow rates.
When comparing the averages of all the trials of protein-free saline and low-protein saline, valve type A increased its supine position flow rates from 0.06 to 3.24 mL/hr ($p = 0.03$ E-8) and in the upright position increased their flow rates from 21.23 to 21.62 mL/hr ($p = 0.34$). Similarly, in valve type B, protein increased its supine flow rates from 0.06 mL/hr to 0.23 mL/hr ($p = 0.04$) and in the upright position the flow rates went from 20.23 mL/hr to 20.13 mL/hr ($p = 0.80$). When tested with high-protein saline, both valve types became fully obstructed after 12 days, with flow rates at 0 mL/hr for the rest of the trial.
The role of protein on flow rate throughout the system could be due to the protein acting like a detergent, possibly by decreasing surface tension and resistance, therefore increasing flow rates. We hypothesize the decrease in flow rates to 0 mL/hr in the high protein trials may be due to the protein concentration being too high, causing the protein to precipitate out of solution and aggregate in the system. The properties of protein through this system have a potential impact both in understanding the molecular fluid dynamics of CSF and in clinical testing of shunt valves and systems. Shunt failures account for more than $1 billion annually in hydrocephalus care in the United States and have devastating effects on patients' morbidity and mortality.

Disclosures: K. Beharry: None. **N. Gorelick:** None. **R. Serra:** None. **B. Tyler:** None. **H. Brem:** None. **M. Luciano:** None.

Poster

659. Brain Injury and Trauma II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 659.02/G35

Topic: C.10. Brain Injury and Trauma

Title: Intermediate-term survival of transplanted bioengineered neural tissue grafts with pharmacological intervention

Authors: B. J. GU[1], *G. MAN[1], D. JGAMADZE[1], V. LIAUDANSKAYA[2], D. KAPLAN[2], H.-C. I. CHEN[1];

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Abstract: Introduction: Neural transplantation is a promising approach to repair brain injuries. Three-dimensional constructs emulating the cytoarchitecture of native neural tissue may possess great potential as a therapeutic substrate to replace large brain defects and restore lost circuit functions. A major challenge is the suboptimal survival of neural grafts after transplantation. In a rat motor cortex injury model, we assessed the effects of different pharmacological interventions on the survival of rat embryonic cortical cells seeded on a silk sponge scaffold. Methods: Embryonic day 18 rat cortical cells were isolated and seeded on a silk sponge scaffold. Green fluorescent protein (GFP) expression in these neurons was achieved by AAV vectors. On surgery day, the constructs were embedded in fibrin hydrogel containing either 1) necrostatin-1, a necroptosis pathway blocker, 2) Y-27632, a ROCK pathway inhibitor, 3) methylprednisolone, a corticosteroid, or 4) base media with no drug. For necrostatin-1 and Y-27632 groups, the constructs were also cultured in media with the drug overnight before hydrogel embedding. After embedding, the constructs were grafted into the primary motor cortex of adult male Sprague-Dawley rats after an aspiration lesion had been created. One month after transplantation, the animals were sacrificed, the brains extracted for histological analysis. Results: Considerable survival of grafted neurons was observed, especially in necrostatin-1 group. A high degree of intra-group variability was observed. The majority of the cells and their processes within the grafts were beta-3-tubulin positive, indicating their neuronal phenotype. Glial cells (GFAP+) within the graft were primarily of host origin. The silk scaffold was still present at this time point. There was also evidence of anatomical integration between the graft and the host brain. GFP+ processes from the graft projected into the host brain in all directions but more predominantly in the anterior and posterior directions, reaching as far as 1 mm from the transplantation site.
Conclusion: We have demonstrated the feasibility of transplanting silk constructs seeded with neurons up to 1 month after transplantation in a rat model. Pharmacological intervention was a crucial part of our strategy to improve graft survival. The robust anatomical integration suggests the possibility of functional integration of the graft with the host brain. Ongoing studies are investigating the sources of intra-group variability to further optimize graft survival at longer time points. These efforts will facilitate future studies on the functional integration and behavioral impact of such grafts.

Disclosures: B.J. Gu: None. **G. Man:** None. **D. Jgamadze:** None. **V. Liaudanskaya:** None. **D. Kaplan:** None. **H.I. Chen:** None.

Poster

659. Brain Injury and Trauma II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 659.03/G36

Topic: C.10. Brain Injury and Trauma

Support: 18dk0310062j0003
16K13113
19dk0310096j0001

Title: Awareness detection in patients with unresponsive wakefulness syndrome

Authors: *Y. OKAHARA[1,2], K. TAKANO[2], M. ODAKI[3], K. KANSAKU[4,2,5];
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Abstract: Recent neuroimaging studies have revealed that some patients, who diagnosed as unresponsive wakefulness syndrome (UWS; Laureys, et al., 2010), may retain consciousness to some extent, and may be able to modulate their thoughts voluntarily (Monti, et al., 2010, Cruse, et al., 2011). Proper awareness detection in patients with UWS comes to an important issue, because it may provide applicable rehabilitation and then improve their quality of life. In this study, we performed two types of experiments, which consisted of fMRI and brain-computer interfaces using a steady-state visual evoked potential (SSVEP-BCI; Sakurada, et al., 2015). Eight UWS patients participated (4 male, mean: 50.9 years old, JFK Coma Recovery Scale-Revised range: 5-7).We used passive listening tasks in fMRI, which consisted of two different speech conditions to evaluate a level of speech comprehension. In “FN” task, to observe the whole extent of activation elicited by listening to a narrative, the narrative (80 s) was delivered during the four test epochs and no sound was delivered during the control epochs. In “FR” task, to exclude activation elicited by processing of auditory voice in general, the narrative was delivered during the test epochs and the preceding test epochs were replayed in reverse during each control epoch. Following the fMRI, we performed a SSVEP-BCI experiment using “an attention/ignorance task”, where participants are required to use attentional modulation following verbal commands such as “Attend to the LED” or “Ignore the LED”. BCI accuracy in operating the in-house BCI system was evaluated.Four out of 8 participants did not show any response to auditory stimuli, 2 participants showed activation clusters in primary auditory cortex only in FN task, and 2 participants showed significant activation in both FN and FR tasks. In the 2 participants who showed activations in fMRI tasks, reliable responses (30 trials, 80%; 41 trials, 68.2%), which crossed over upper confidence limit of chance results, were found in the BCI task.The results suggested that the combination of fMRI and BCI is effective in awareness detection in patients with unresponsive wakefulness syndrome.

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Poster

659. Brain Injury and Trauma II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 659.04/G37

Topic: C.10. Brain Injury and Trauma

Title: Hierarchical linguistic sequence processing in disorders of consciousness patients

Authors: *Y. JIANG[1], P. GUI[1], D. ZANG[2], Z. QI[2], J. TAN[2], T. HIROMI[2], J. JIANG[1], Y. WEN[1], L. XU[3], M.-M. POO[1], N. DING[4], S. DEHAENE[5], X. WU[2], L. WANG[1];
[1]Inst. of Neuroscience, CAS, Shanghai City, China; [2]Huashan Hospital, Fudan Univ., Shanghai, China; [3]Beijing Tian Tan Hospital, Capital Med. Univ., Beijing, China; [4]Zhejiang Univ., Hangzhou, China; [5]Univ. Paris Sud, Univ. Paris-Saclay, NeuroSpin center, Paris, France

Abstract: Detecting residual consciousness in unresponsive patients is a major clinical concern and a challenge for cognitive neuroscience. Comparing to studies extracting neural markers of residual consciousness from the resting period, recent neuroimaging studies have demonstrated potential approaches for informing diagnosis and prognosis in unresponsive patients. However, these imaging technologies come with considerable expense and difficulty, limiting the establishment of bedside clinical setting. Although resting electroencephalography (EEG) signals were also able to index the state of consciousness, there is still a lack of EEG study of using active paradigms for the validation of improved diagnosis and prognosis of disorders of consciousness patients. Here, using the notion that the process of auditory sequences with regularities at multiple time scales relies on different levels of conscious awareness of the auditory stimulus, we designed an exquisite language paradigm with auditory hierarchical sequences. Electrical activities were recorded from 47 healthy controls, 31 minimally conscious states (MCS) and 30 unresponsive wakeful syndrome (UWS) patients by high density EEG during hierarchal language tasks. Our findings demonstrated that EEG-derived signals, both auditory evoked activity (inter-trial phase coherence) and global dynamic pattern (microstates), in patients were significantly associated with behavioral diagnosis of consciousness and clinical outcomes. In particular, comparing to the EEG signals during the resting period, the correlations were significantly improved during the language task period. Furthermore, such correlations were notably boosted along with the incensement of the level of language hierarchy. Especially, the multiple EEG measurements in the active paradigm were robust enough for the prediction of behavioral diagnosis and future outcomes in individual patients. The predictive accuracy of at least 3-month outcome could reach 87% for positive- and 70% for negative-outcomes. Our study provides a novel approach of objective characterization of states of consciousness and tracking individual patients at bedside longitudinally in clinic.

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Poster

659. Brain Injury and Trauma II

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Program #/Poster #: 659.05/G38

Topic: C.10. Brain Injury and Trauma

Title: Colocalization of HGFR/Met and phosphorylated forms this tyrosine-kinase receptor in glioblastoma

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Abstract: Hepatocyte growth factor receptor/tyrosine-protein kinase Met (HGFR/Met) is a glycosylated receptor tyrosine kinase that plays important role in the development of cancer in different organs including liver, kidney and brain. Mature HGFR/c-Met is a disulfide-linked dimer composed of a 50 kDa extracellular alpha chain and a 145 kDa transmembrane beta chain. Interaction of HGF with HGFR/Met triggers its internalization and subsequent proteasome-dependent degradation as well as tyrosine phosphorylation in the cytoplasmic region which leads to activation of the kinase domain and expose docking sites for multiple SH_2-containing molecules. It has been found that HGFR/Met is implicated in the progression of glioblastoma which is one of the most aggressive brain tumors, and that expression of high levels of this tyrosine kinase is indicative of a shorter survival period. To investigate spatial distribution of HGFR/Met and its phosphorylated forms, we have generated antibodies against the extracellular domain and phospho-specific antibodies against Y1234/Y1235 in the intracellular kinase domain and Y1349 in the intracellular multi-substrate docking site. Multiplex immunecytochemistry and immunohistochemistry has been used to analyze co-localization of these domains in untreated and HGF-treated glioblastoma cell lines and in tissue sections of human glioblastoma. Treatment of U-251 MG, U-87 MG, U-118MG and A172 cells with recombinant HGF protein induced profound phosphorylation of HGFR/Met, and phosphorylated forms of HGFR/Met were detected in the cytoplasm and cell nuclei. We found that HGFR/Met was co-localized with either phosphorylated Y1234/Y1235 or Y1349 forms. In addition, Y1349 and Y1234/Y1235 immunoreactive profiles either overlapped or not, indicating that the action of HGF on the same cells has differential effects on the phosphorylation of tyrosines in the kinase and in docking domains. In glioblastoma tissue sections phosphorylated and non-phosphorylated forms of HGFR/Met was also detected in cell nuclei and the extent of phosphorylated Y1234/Y1235 immunoreactivity appeared higher when compared to the Y1349 form. Our data reveal that there

is a differential activation of HGFR/Met via phosphorylation at a single cell level which may underly the regulation of tumor progression.

Disclosures: **A.E. Kalyuzhny:** None. **J. Taylor:** None. **J. Hagen:** None. **A. Ptak:** None. **J. Cooper:** None. **J. Hatler:** None. **M. Levin:** None. **D. Schwartz:** None.

Poster

659. Brain Injury and Trauma II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 659.06/G39

Topic: C.10. Brain Injury and Trauma

Title: Characterization and classification of glioblastoma multiforme using the novel multiparametric cyclic immunofluorescence analysis system MACSima

Authors: *S. REISS[1], S. TOMIUK[1], J. KOLLET[1], J. DREWES[1], W. BRÜCK[2], M. JUNGBLUT[1], **A. BOSIO**[1];
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Abstract: Glioblastoma multiforme (GBM), a highly malignant, non-curative brain tumor of the primary central nervous system, has been subclassified into distinct subtypes using a multitude of analysis methods. Here, we introduce the MACSima™ imaging platform which allows for fully automated, multiparametric, cyclic immunofluorescence analysis of specimens with hundreds of antibodies. We applied this method to classify glioblastomas according to published classification schemes and identify novel glioblastoma specific markers. Glioblastoma xenografts derived from primary tumors were dissociated to single cells using the Tumor Dissociation Kit, human and the gentleMACS™ Octo Dissociator (Miltenyi Biotec). Single cells were analyzed for cell surface marker expression by flow cytometry (MACSQuant Analyzer 10) including 371 directly conjugated antibodies (MACS Marker Screen, Miltenyi Biotec). A ranking was applied according to the percentage of positive cells and the stain index, leading to a selection of 96 markers for characterization of primary glioblastoma using the MACSima™ imaging platform. Cryosections were fixed by acetone and each specimen was exposed to 96 fluorescent labeled antibodies by cycles of antibody reaction, image acquisition and erasure of signal. The 2D image stacks were analyzed for antigen quantification and pattern recognition using pixel and segmented single-cell data. The detection of previously published markers, such as PDGFRα, Olig2, p16, p53, CD44, Nestin, Podoplanin, GFAP, MET, Hes-1 and EGFR was used to subclassify the glioblastomas according to i) Motomura (Motomura et al., 2012) into Oligodendrocyte Precursor (OPC), Differentiated Oligodendrocyte (DOC), Astrocytic Mesenchymal (AsMes) or Mixed subtype, and ii) Verhaak (Verhaak et al., 2010) into Proneural, Neural, Classical, or Mesenchymal subtype. The analysis of well-established glioblastoma

marker partially already used in CAR T cell based clinical trials such as EGFRvIII, HER2, or IL-13Rα2 revealed a broad inter- and intratumor diversity of expression. Infiltrating immune cells were present in most of the tumors, but showed varying percentages. Finally, segmentation, clustering, and correlation analysis allowed for identification of new marker which might be used for a more robust classification of glioblastomas. In summary, our analysis using the MACSima™ imaging platform reveals a high heterogeneity of protein expression in glioblastomas along with the ability to deeper classify the diverse tumors and identify novel markers that allow selective detection of tumor cells for their potential use in immunotherapy.

Disclosures: S. Reiss: None. **S. Tomiuk:** None. **J. Kollet:** None. **J. Drewes:** None. **W. Brück:** None. **M. Jungblut:** None. **A. Bosio:** None.

Poster

659. Brain Injury and Trauma II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 659.07/G40

Topic: C.10. Brain Injury and Trauma

Title: Overcoming 5-FU resistance of GBM by spliceosome inhibitor Pladienolide-B

Authors: *Y.-J. LEE, D.-Y. CHANG, J.-H. JUNG, H.-G. WOO, H. SUH-KIM, S.-S. KIM; Ajou Univ. Sch. of Med., Suwon, Korea, Republic of

Abstract: Glioblastoma multiforme (GBM) is the most common and aggressive brain tumor, responds poorly to current standard therapy. The presence or development of resistance to anticancer drugs is a severe problem in GBM treatment. Recent studies suggest that alternative splicing events occur in various cancers and play a significant role in resistance to cancer therapy. Previously, we reported that cytosine deaminase-expressing mesenchymal stem cells exerted an anticancer activity with a wide therapeutic index by converting 5-fluorocytosine, a nontoxic prodrug, into 5-fluorouracil (5-FU), a potent anticancer drug. In this study, we investigated the effects of Pladienolide-β, a spliceosome inhibitor, combined or not with 5-FU on 5-FU resistance-GBM cell lines. 5-FU resistance cell line (T98FR) was developed by treatment of T98G GBM cells with moderate dose of 5-FU over passages. Microarray analysis revealed that up-regulation of spliceosome related genes in T98FR. Pladienolide-β decreased the cell proliferation of T98FR cells separately and synergically with 5-FU. Pladienolide-β treatment down regulated the expression of 5-FU metabolism related genes in T98FR cell line. Our results showed that Pladienolide-β is able to enhance 5-FU effect in 5-FU resistance cell line suggesting its potential use in 5-FU refractory cancer patients.

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Poster

659. Brain Injury and Trauma II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 659.08/G41

Topic: C.10. Brain Injury and Trauma

Support: NIH 5R01NS066905
Christopher Davidson Fund
Washington University Chancellor's Graduate Fellowship

Title: The prevalence and impact of preserved functional connectivity within glioblastoma

Authors: *A. G. DANIEL[1], K. PARK[2], J. L. ROLAND[3], D. DIERKER[4], J. GROSS[5], J. HUMPHRIES[1], C. D. HACKER[3], J. SHIMONY[4], E. C. LEUTHARDT[3];
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Abstract: Given the heterogeneous growth of glioblastoma, there is variability in its effect on the brain parenchyma. The surrounding tissue can be destroyed or displaced by the invading tumor cells resulting in a gross mass that may still contain functional tissue. In this study, we investigated the prevalence of preserved functional tissue within glioblastoma and adjacent regions using resting-state fMRI. Contrast-enhanced T1-weighted images and T2/fluid attenuation inversion recovery (FLAIR) MR images were used to identify tumor and non-tumor regions in 57 patients with newly diagnosed glioblastoma. Using resting-state functional MRI maps as inputs, a pre-validated feedforward artificial neural network algorithm probabilistically identified the network concordance of each voxel for seven canonical brain networks. The network voxels within the FLAIR hyperintensity, contrast-enhanced and necrotic regions were analyzed. For patients with reported overall survival (N = 33), the prognostic value of functionally connected regions within glioblastomas was determined. The vast majority of tumors had retained functional tissue within the contrast-enhanced boundaries (98.3%, n = 56). The amount of identified network voxels were proportional to tumor size ($r=0.788$, $P<0.001$). With the exception of the dorsal attention network, all networks showed a greater overall survival when their respective functional voxels were not found within the tumor. However, only the language network findings achieved significance ($P = 0.002$). The presence or absence of language function within tumors led to a significant median survival difference independent of demographic, clinical and genetic prognostic variables (hazard ratio: 18.67; 95% CI: 3.85 - 90.49, $P = 0.0003$). Despite the invasiveness of glioblastoma, functional tissue can be found within the tumor and adversely affect overall survival (most notably for the language network). Functional network preservation may provide a novel biomarker for glioblastoma prognosis.

Disclosures: **A.G. Daniel:** None. **K. Park:** None. **J.L. Roland:** None. **D. Dierker:** None. **J. Gross:** None. **J. Humphries:** None. **C.D. Hacker:** None. **J. Shimony:** None. **E.C. Leuthardt:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurolutions, eQuility, Immunovalent, Inner Cosmos. F. Consulting Fees (e.g., advisory boards); Monteris Medical.

Poster

659. Brain Injury and Trauma II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 659.09/G42

Topic: C.10. Brain Injury and Trauma

Title: Open science medicinal chemistry: Towards a treatment for DIPG a rare brain cancer

Authors: *C. SCHLUMBERGER[1], S. CRAMP[2], N. HAMBLIN[2], A. EDWARDS[3], O. ROBERTS[4], A. BULLOCK[5], P. BRENNAN[6], **S. ALMOND**[2];
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Abstract: Diffuse intrinsic pontine glioma DIPG is a rare, aggressive and uniformly fatal childhood brain cancer with a median survival time of 9-12 months and for which there are currently no effective drug treatments. To accelerate the drug discovery process, Meds4Kids Pharma (M4K) is pioneering an open science approach to generate an orally-available, brain-penetrant therapeutic to treat DIPG. M4K seeks to test the hypothesis that an open science framework can be successfully applied not only to accelerate basic science, using the collective knowledge of the scientific community at large, but also to take an innovative new drug candidate all the way from discovery and clinical proof-of-concept through to product registration, by making use of regulatory data protections and market incentives. Since late 2017, Charles River Early Discovery has been providing in kind drug discovery services to help progress these efforts, including medicinal and synthetic chemistry. DIPG has been shown to be associated with mutations in the ACVR1 gene (activin A receptor, type 1) also known as ALK2 kinase. Early support for the therapeutic hypothesis that an inhibitor of ALK2 kinase would have clinical benefit in DIPG, came from in vivo studies with non-selective ALK2 kinase inhibitors, which both killed DIPG cell lines harboring the ALK2 mutation and extended lifespan in xenograft mouse models. Working collaboratively with M4K and their open science partners, we have made excellent progress towards the identification of potent, selective, brain penetrant ALK2 inhibitors starting from the known inhibitor LDN-214117, previously described for FOP (fibrodysplasia ossificans progressiva). Our current lead compound has an excellent in vitro and

in vivo profile showing high oral bioavailability and brain penetration in a mouse PK study and is progressing to proof of concept studies. In addition we are progressing with the identification of a back-up series. References: 1. https://m4kpharma.com/ 2. Carvalho et. al. Neuro-Oncology, Volume 18, Issue suppl_6, 1 November 2016, Pages vi154, https://doi.org/10.1093/neuonc/now212.639 3. Mohedas et. al., J. Med Chem, 2014, 57 (19), 7900

Disclosures: **C. Schlumberger:** A. Employment/Salary (full or part-time):; Charles River Labs. **S. Cramp:** A. Employment/Salary (full or part-time):; Charles River Labs. **N. Hamblin:** A. Employment/Salary (full or part-time):; Charles River Labs. **A. Edwards:** A. Employment/Salary (full or part-time):; Chief Executive, Structural Genomics Consortium, M4KPharma, Ontario Institute of Cancer Research. **O. Roberts:** A. Employment/Salary (full or part-time):; Nobelex Biotech, M4K Pharma. **A. Bullock:** A. Employment/Salary (full or part-time):; Structural Genomics Consortium, University of Oxford, M4KPharma. **P. Brennan:** A. Employment/Salary (full or part-time):; University of Oxford. **S. Almond:** A. Employment/Salary (full or part-time):; Charles River Labs.

Poster

659. Brain Injury and Trauma II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 659.10/G43

Topic: C.10. Brain Injury and Trauma

Title: Spatial and temporal profile of intracranial vascular calcification in a mouse model with endothelial upregulation of tissue-nonspecific alkaline phosphatase

Authors: *R. L. RAMOS[1], A. UTS[2], P. SINGLA[2], E. KAMPTON[2], Y. MAYR[2], C. ROCHON[3], J. MILLAN[4], O. SAVINOVA[2];
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Abstract: Vascular calcification is an important pathophysiological factor contributing to neurodegenerative diseases such as primary familial brain calcification (PFBC). Given the essential role of tissue-nonspecific alkaline phosphatase (TNAP) in calcification, we tested the hypothesis that upregulation of TNAP activity can lead to intracranial calcification. We previously reported that overexpression of TNAP in endothelial Cre-driver mice (eTNAP mice) leads to arterial calcification. Here we analyzed intracranial calcification in this same model. eTNAP mice developed progressive intracranial calcification (0% were affected at 8 weeks, 71% at 13 weeks, and 100% at 23 weeks). At 23 weeks, calcification was associated with microvasculature in the basal ganglia, thalamus, hindbrain, and cerebellum. Calcified lesions

were accompanied by reactive astrocytes and activated microglia. Extravasation of IgG into the brain parenchyma was evident in eTNAP mice suggestive of blood-brain barrier defect. eTNAP mice displayed significant motor deficits in open-field tests (reduced ambulation, rearing, speed, and acceleration). Our results indicate that upregulation of TNAP activity can lead to intracranial vascular calcification. Given the similarities in presentation between eTNAP mice and PFBC patients, this model can advance the understanding of PFBC disease progression.

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Poster

659. Brain Injury and Trauma II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 659.11/G44

Topic: C.10. Brain Injury and Trauma

Support: Science Department, Niles West High School

Title: The effect of repeated anesthesia on learning at different ages

Authors: B. N. VENKAT[1], *C. J. DIXON[2], D. P. AKSENOV[2];
[1]Niles West High Sch., Skokie, IL; [2]Northshore Univ. Healthsystem, Evanston, IL

Abstract: General anesthetics increase the chance of Post-Operative Cognitive Disorder (POCD) in elderly patients. There is a correlation between the age of onset of Alzheimer's disease and exposure to general anesthesia before age 50. Children who had been exposed to anesthetics before age 2 developed learning disabilities and ADHD in their teens. The average American undergoes nine invasive procedures in their lifetime. Currently, there is no consensus on the effects of repeated anesthesia on cognitive function, particularly how it affects the developing and aged brains. The purpose of this study is to compare the effects of single and repetitive anesthesia on brain function at different ages. Repetitive anesthesia induces more severe learning deficit than single exposure to anesthesia and anesthesia-induced learning deficit is greater on the developing and aged brain compared to mature brain. *Caenorhabditis elegans* is a nematode that is a common model for learning in neuroscience. N2 *C. elegans* were purchased from the Caenorhabditis Genetics Center at the University of Minnesota. The standard egg wash procedure was used to control the age of the worms. *C. elegans* at 1-2 days (developing brain), 10-13 days (mature brain), and 14-17 days (aged brain) were used in this study. Each plate of *C.elegans* was treated with 20µL of an aqueous solution (0.0016%) of chloroform or isoflurane. Worms were allowed to recover from anesthesia before a second or third treatment was given. Learning was tested using tap habituation. The plates with the worms were tapped, resulting in the worms swimming in the direction opposite the tap. This is due to reflex, and the reflex

decreases with further taps, because the worms learn to ignore the tap. The number of taps a worm needs to learn to ignore the tap was measured before and after anesthesia. Anesthesia caused a greater learning impairment in aged worms compared to mature worms. Repeated anesthesia with both chloroform and isoflurane caused greater learning impairments than single exposure. Among the worms treated once with anesthetics, chloroform and isoflurane had a similar effect on aged worms, while isoflurane caused a greater impairment on mature worms than chloroform.

Disclosures: **B.N. Venkat:** None. **C.J. Dixon:** None. **D.P. Aksenov:** None.

Poster

659. Brain Injury and Trauma II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 659.12/H1

Topic: C.10. Brain Injury and Trauma

Support: NICHD Grant R01HD083001
NICHD Grant U54HD087011

Title: Sedation with brexanolone produces markedly less neurotoxicity compared to midazolam in the developing rodent brain

Authors: *J. N. HUFFMAN[1,2], K. M. KAPRAL[1,2], S. L. WILLIAMS[1], B. S. SWINEY[1], R. MORELAND[2], K. K. NOGUCHI[1];
[1]Psychiatry, Washington Univ. in St. Louis Med. Sch., Saint Louis, MO; [2]Psychological Sci., Univ. of Missouri-St. Louis, St. Louis, MO

Abstract: The developing brain is susceptible to extensive neurotoxicity following exposure to sedative/anesthetic drugs (SADs). Every year hundreds of thousands of children around the world are exposed to neurotoxic regimens of SADs without viable alternatives, and exposure widely varies as no standardized procedures guide clinical use. Allopregnanolone (ALLO) holds promising neuroprotective capabilities in the adult brain, as well as potent sedative properties in adults and neonates. ALLO and many other SADs produce their sedative/anesthetic effects through allosteric modulation of $GABA_A$ receptors, which is one of two principal mechanisms behind SAD-induced neurotoxicity. Evidence suggests ALLO has the unique capacity to regulate key apoptotic factors in adults, is critical to the development of the central nervous system, and is involved with suppressing fetal neuroapoptosis during gestation. Preclinical studies exploring the possibility of ALLO as a viable sedative/anesthetic and/or neuroprotective agent in the developing brain are virtually non-existent. Here we show a particular FDA approved formulation of ALLO, Brexanolone (BREX), can produce potent SAD-like sedation across a range of dosages in the neonatal mouse. Behavioral observation and quantification of movement

show BREX induces clinically relevant levels of sedation after a single intraperitoneal (i.p.) injection. Because fluctuations in vital signs can quickly lead to medical complications, we established dose-dependent impacts of BREX on heart rate, breath rate, pulse distention, and oxygen saturation, indicating lower doses of BREX can produce clinically applicable levels of sedation while maintaining vital signs within normal ranges. We further examined whether the neurotoxic profiles of BREX were comparable to midazolam (MIDAZ), one of the most commonly used GABAergic SADs. Equally sedative dosages of BREX and MIDAZ were administered via i.p. infusion for 6-hours, revealing markedly less neurodegeneration for BREX treated neonates compared to MIDAZ. These data supply the first evidence that BREX holds potent, clinically relevant sedative capabilities while producing strikingly low levels of apoptosis in the developing rodent brain.

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Poster

659. Brain Injury and Trauma II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 659.13/H2

Topic: C.10. Brain Injury and Trauma

Title: Unrestricted somatic stem cell (USSC) administration reduces post hemorrhagic hydrocephalus (PHH) and alters expression of aquaporin channels (AQP1 & 4) and toll-like receptor-2

Authors: *G. VINUKONDA[1], D. PUROHIT[4], Y. LIAO[2], L. IVANOVA[2], F. HU[5], D. A. FINKEL[5], S. SHAH[6], G. M. KLEINMAN[7], M. S. CAIRO[3], E. F. LAGAMMA[8];
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Abstract: Intraventricular hemorrhage (IVH) is a common complication of preterm birth where many infants develop post-hemorrhagic hydrocephalus (PHH); no effective treatment exists. PHH is associated with subependymal gliosis, fibrosis & disruption of ependymal lining (Karimy et al, 2017). Aquaporins are water channels that are associated with cerebrospinal fluid (CSF) secretion (AQP1 at choroid plexus) and absorption (AQP4 at the ependyma). Altered expression of AQP1 & AQP4 is seen in PHH and the expression pattern changes with continued injury & intervention (Verkman et al, 2017). USSCs derived from human cord blood, have anti-inflammatory and regenerative properties that along with multi-lineage differentiation (Liao et al,

2014), may be advantageous to treat PHH. We hypothesize that the intracerebral ventricular (ICV) injection of USSC will reduce inflammation associated histological changes and recover AQP1 & AQP4 expression in the ventricular system, which are associated with reduced ventricular enlargement. We used a glycerol-induced preterm rabbit model of PHH (Chua et al, 2009; Vinukonda et al, 2010). USSCs were isolated and characterized as previously described (Kogler et al, 2004; Liao et al, 2014). After ultrasound confirmation of IVH, we injected ICV $2X10^6$ USSCs & measured the ventricle area at the level of mid-septal nucleus on H&E stained coronal-section images using Image-J. Using immunofluorescence, AQP1 & AQP4 expression was evaluated in choroid plexus and ependymal lining. Total mRNA of laser/tissue dissections was used for gene expression studies. Ventricular area was significantly higher in the IVH-saline group compared to no-IVH controls whereas USSC administration in IVH pups significantly reduced ventricular volume compared to IVH-saline pups at 7 & 14d postnatal age. Histopathological evaluation of IVH pups showed ependymal denudation & loss of cilia accompanied by necrosis & inflammation, which were partially recovered in USSC treated group. Immunoreactivity & mRNA levels of AQP1 & AQP4 were reduced in PHH, whereas USSC administration recovered AQP1 & AQP4 mRNA expression & immunoreactivity by day 7. The inflammatory marker toll-like receptor-2 (TLR2) was significantly increased in IVH, whereas USSC treatment attenuated it at postnatal day 3. These findings support the possibility that USSCs: i) exert anti-inflammatory effects by reducing TLR2 ii) recover ependymal denudation, integrity and ciliary function iii) recover AQP1 & AQP4 mRNA levels which are associated with reduced ventricular volumes. Results represent a proof-of-concept for the translational potential of using USSCs to treat PHH in premature infants.

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Poster

659. Brain Injury and Trauma II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 659.14/H3

Topic: C.10. Brain Injury and Trauma

Support: Acorda Therapeutics

Title: Interhemispheric relationships in multiple sclerosis

Authors: *J. T. DAVIS[1], I. BELOVARSKI[3], C. FORD[3], K. PAULSON[2], J. LEWINE[2]; [1]Neuroimaging, [2]The Mind Res. Network, Albuquerque, NM; [3]Univ. of New Mexico, Albuquerque, NM

Abstract: Multiple sclerosis (MS) is a chronic, degenerative condition associated with inflammation and demyelination of the central nervous system (CNS). While most treatments target the autoimmune and inflammatory process that are suspected to underlie de-myelination in MS, there is growing interest in the development of treatments that directly impact axonal function and the electrophysiological consequences of the disease with respect to slowed or blocked neuronal conduction. The corpus callosum is known to be especially vulnerable to MS, so identification of inexpensive ways to measure callosal integrity might aid in tracking disease progression and the efficacy of interventions. This project therefore sought to explore the relationships between three novel biomarkers of callosal integrity: (1) Callosal fractional anisotropy [FA] derived from MRI-based diffusion tensor imaging [DTI]; (2) Interhemispheric electrophysiological coherence as derived from MEG/EEG; and (3) a novel behavioral measure of interhemispheric integration time. Eleven patients with MS (ages 25-65) and 15 neurotypical control subjects underwent MRI/DTI, MEG/EEG, and behavioral testing. The novel behavioral stimulus detection test involved presentation of left/right lateralized visual stimuli, with three response conditions - right hand only, ipsi-lateral hand, contralateral hand. The contralateral condition requires coordination of the activities for the two hemispheres, so a comparison of ipsilateral and contralateral response times provides an index of interhemispheric integration time. Compared to neurotypical controls, MS patients showed reduced callosal FA values, reduced beta-band interhemispheric coherence, and markedly increased interhemispheric integration times. Importantly, there was a high correlation between measures such that the simple behavioral measure was highly predictive of electrophysiological and structural measures of callosal integrity (correlation coefficients of -0.84 and -0.78, respectively). That is, the data suggest that simple visual-motor measures, which can be done in a clinician's office, can serve as surrogates for complex structural and functional measures of callosal disease burden.

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Poster

659. Brain Injury and Trauma II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 659.15/H4

Topic: C.10. Brain Injury and Trauma

Support: Tübitak 1001, 116S552
Tübitak 1003, 216S626

Title: Pericytes accumulate at EAE lesion sites and concurrently mediate vascular sprouting as well as fibrosis

Authors: E. SEKERDAG[1], D. ATAK[1], C. ULUSOY[3], A. B. YıLMAZ[1], S. SEYAJ[4], G. DENIZ[2], M. ZEYBEL[1], Ö. Ö. ÇAKMAK[1], A. VURAL[1], C. &. KUCUKALI[3], A. TUNCER[5], E. TÜZÜN[3], *Y. GURSOY-OZDEMIR[2];
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Abstract: Aim: Pericytes are involved in immunological responses and repair mechanisms in the central nervous system (CNS) such as scar formation, which indicate that pericytes could be the very main players in the pathophysiology of Multiple sclerosis (MS), a chronic inflammatory demyelinating disease of the CNS. This study investigated the role of pericytes in the pathophysiology of Multiple Sclerosis with a special focus on vascular pathology and pericyte differentiation. **Methods:** Experimental Autoimmune Encephalomyelitis (EAE) models were induced with MOG and PLP in C57Bl/6 and SJL mice respectively. Mice were monitored and graded daily for clinical signs of disease. At 15 days post immunization (p.i) (early EAE) and 40 days p.i. (late EAE), mice were sacrificed, blood was collected by cardiac puncture to analyze anti-MOG and anti-PLP antibodies with ELISA, and their brain and spinal cord were isolated in 4% PFA. Cryosections of spinal cord and brain areas were stained with both immunohistochemistry and immunofluorescence methods for blood-brain barrier (BBB) leakage, demyelination, inflammation, vascular pathology, pericytes, and extracellular matrix (ECM) components. All EAE groups were compared to SHAM groups. On the other hand, human brain vascular pericytes (HBVP) were cultured *in vitro* and were exposed to MS and healthy patient serum and CSF to investigate pericyte response in terms of cell differentiation and ECM secretion. **Results:** In EAE disease progression, pericyte numbers were increased at lesion sites, pericyte coverage was decreased on endothelial walls at non-lesional sites and different pericyte types were present according to co-localization studies. Vascular pathology in EAE showed an increased vascular density at lesion sites simultaneously with increased pericyte accumulation and increased extracellular matrix components such as Collagen I and IV at these areas. Pericytes *in vitro* showed also increased Collagen I and IV secretion upon exposure to MS serum and CSF compared to healthy serum and CSF. **Conclusion:** During the course of EAE/MS, pericytes are affected and they leave endothelia and migrate towards lesion sites where they high likely differentiate into myofibroblastic phenotype producing collagen and may mediate fibrosis.

Disclosures: E. Sekerdag: None. **D. Atak:** None. **C. Ulusoy:** None. **A.B. Yılmaz:** None. **S. Seyaj:** None. **G. Deniz:** None. **M. Zeybel:** None. **Ö.Ö. Çakmak:** None. **A. Vural:** None. **C.&. Kucukali:** None. **A. Tuncer:** None. **E. Tüzün:** None. **Y. Gursoy-Ozdemir:** None.

Poster

659. Brain Injury and Trauma II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 659.16/H5

Topic: C.10. Brain Injury and Trauma

Support: ONO Pharmaceuticals

Title: AAV9 gene therapy rescue of an eEF1A2 knockout mouse model

Authors: J. NG[1], H. CHU[1], M. BERTI[1], M. TIJANI[1], J. ANTINAO DIAZ[1], C. ABBOTT[3], S. SCHORGE[2], S. N. WADDINGTON[1], ***R. KARDA**[1];
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Abstract: Mutations in the eukaryotic translation elongation factor 1 alpha 2 (eEF1A2) have been associated with severe intellectual disability, autism and epilepsy. There are currently no effective treatments. We used an existing, well-characterised eEF1A2 knock out mouse (Wasted mice) to test the hypothesis that function of the protein could be restored with gene therapy. We designed an adeno-associated virus 9 (AAV9) using a pan neuronal promoter, human Synapsin, to drive expression of the human eEF1A2 cDNA (hSyn-eEF1A2). We interrogated its bio-distribution after single intravenous or intracerebroventricular injections to new born mice. We found widespread transgene expression in the CNS after both routes of administration from injection of a GFP marker gene. Following this we treated cohorts of mice in a randomised, blinded trial with AAV9-hSyn-eEF1A2. Mice with combined intracerebroventricular and intravenous neonatal administration (n=4), or intracerebroventricular (n=3) only were completely rescued by AAV9 hSyn-eEF1A2. Behavioural studies, rota-rod and inverted grid, further validated the efficacy of the treatment. Both treated groups showed no significant difference compared to wild-type controls and survived until the experiment was terminated when the entire cohort had reached 72 days of development. We present for the first time a successful gene therapy approach for the eEF1A2 wasted mice, which raises the potential for a new treatment approach for children affected by mutations in this gene.

Disclosures: J. Ng: None. **H. Chu:** None. **M. Berti:** None. **M. Tijani:** None. **J. Antinao Diaz:** None. **C. Abbott:** None. **S. Schorge:** None. **S.N. Waddington:** None. **R. Karda:** None.

Poster

660. Spinal Cord Injury III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 660.01/H6

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Craig H. Neilsen Grant 460361
NIH R01HD081274

Title: Effects of a single sequence of acute intermittent hypoxia (AIH) on motor function in healthy able-bodied persons

Authors: *A. Q. TAN[1,2], A. N. CORSTEN[1,2], S. A. BARTH[1,2], R. D. TRUMBOWER[1,2]; [1]Physical Med. and Rehabil., Harvard Med. Sch., Boston, MA; [2]Spaulding Res. Inst., Boston, MA

Abstract: Neural plasticity is a major contributor to functional recovery after spinal cord injury (SCI). Mild breathing bouts of low O_2 (acute intermittent hypoxia; AIH) is known to induced spinal plasticity, triggering a BDNF-dependent signaling cascade that leads to respiratory and non-respiratory motor recovery in rat SCI models. Previous studies also demonstrated that AIH improves ankle torque generation and walking ability in persons with iSCI. While prior studies suggest similar motoneuron potentiation occurs in rodents without SCI, no studies have addressed this possibility in able-bodied humans. The purpose of this study was to determine if a change in neuromotor excitability is present in the lower limb of neurotypical persons in response to a single sequence of AIH.

Healthy, neurotypical adult humans participated in a single sequence of AIH treatment. During treatment, participants were secured to a semi-reclined seat with the right leg positions and knee constrained in slight flexion and the neutral ankle attached to a single degree-of-freedom rotatory motor system. AIH consisted of fifteen 90-second bouts of hypoxia (FIO_2=0.10) at 60-second intervals. Biomechanical measurements of isometric ankle plantar flexion torque, as well as, electromyograms (EMG) were recorded from 3 major muscles of ankle torque production. Repeated measurements were taken at baseline and immediately post AIH treatment. Blood oxygen saturation, blood pressure, and heart rate were continuously monitored.

In contrast with previous reports in iSCI, we found no differences in maximum plantar or dorsiflexion torque following AIH. Furthermore, we observe small yet inconsistent changes in the mechanically induced soleus stretch reflex amplitude following AIH during the passive and active plantarflexion conditions. These findings suggest that AIH does not induce any discernible bias in excitatory drive to ankle extensors in neurotypical participants. Moreover, the small changes in stretch reflex excitability implies that AIH may modulate Ia afferent transmission in able-bodied person. While the current results provide important mechanistic controls, future work will determine if gains in strength maybe decoupled from reflex excitability following AIH.

Disclosures: A.Q. Tan: None. **A.N. Corsten:** None. **S.A. Barth:** None. **R.D. Trumbower:** None.

Poster

660. Spinal Cord Injury III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 660.02/H7

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH R01 NS052741
Neilsen Foundation
The Minnesota SCI and TBI Research Grant Program
Mayo Clinic Center for Biomedical Discovery

Title: Western diet drives CNS insulin resistance and impairs recovery after spinal cord injury

Authors: *H. N. KIM[1,2], M. LANGLEY[1,2], H. YOON[1,2], L. KLEPPE[1], A. MATVEYENKO[2], I. A. SCARISBRICK[1,2,3];
[1]Physical Med. and Rehabil., [2]Rehabil. Med. Res. Center, Dept. of Physiol. and Biomed. Engin., [3]Mayo Clin. Grad. Sch. of Biomed. Sci., Mayo Clin., Rochester, MN

Abstract: A Western diet promotes systemic metabolic dysfunction and is a risk factor for neurodegenerative conditions, but there is limited information regarding mechanisms of action in the intact or injured CNS. To address this gap, we investigated the influence of systemic insulin resistance triggered by consumption of a diet high in fat and sucrose on neuropathophysiological outcomes in an experimental murine model of spinal cord injury (SCI). Ten-week-old female C57BL6 mice were provided a regular diet (RD) or a diet high in fat and sucrose (HFHS) for 7 wk prior to incomplete compression SCI. Our findings show that even without SCI, consumption of a HFHS diet reduced insulin-like growth factor 1 and its receptor in the spinal cord, impaired tricarboxylic acid cycle function, and promoted signs of astrogliosis including enhanced expression of glial fibrillary acidic protein (GFAP). After SCI, mice consuming HFHS experienced impaired sensorimotor recovery compared to those consuming a RD, in addition to increased signs of microgliosis and reductions in markers of myelin and synaptic recovery. To determine mechanisms, HFHS conditions were modeled *in vitro*, with astrocytes demonstrating parallel reductions in insulin signaling intermediates, and increases in GFAP and the pro-inflammatory cytokine interleukin 6. Each of these effects were completely prevented by the insulin sensitizing agent Metformin. Moreover, conditioned media from astrocytes grown under HFHS conditions reduced expression of myelin proteins when applied to cultures of oligodendroglia. However, when astrocytes were also treated with Metformin, the HFHS-astrocyte-driven oligotoxic effects were no longer observed. Together these findings suggest that HFHS impairs insulin signaling and energy homeostasis in the CNS resulting in increases in pro-inflammatory astrocytes and impaired recovery after neural injury. These studies also highlight insulin sensitizing agents such as Metformin as a new intervention to prevent neural injury exacerbated by HFHS and to improve mechanisms underpinning neural repair and functional recovery.

Disclosures: H.N. Kim: None. **M. Langley:** None. **H. Yoon:** None. **L. Kleppe:** None. **A. Matveyenko:** None. **I.A. Scarisbrick:** None.

Poster

660. Spinal Cord Injury III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 660.03/H8

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Shriners Hospital for Pediatric Research grants SHC 84051
Neurological Disorders and Stroke R01 R01NS103481
Department of Defense (SC140089)

Title: Spinal cord injury in neonatal rats: Understanding the pathways that facilitate spontaneous recovery of forelimb function

Authors: *R. D. SMIT, T. J. CAMPION, J. B. MADRAK, G. M. SMITH;
Shriners Hosp. Pediatric Res. Ctr., Temple Univesity Sch. of Med., Philadelphia, PA

Abstract: Injury to the cervical spinal cord can result in severe paralysis, and presents a permanent disability that requires immense logistical foresight. A hallmark found across most mammalian species is that neonates recover more notably from spinal cord injury (SCI) compared to adults. Research in rodents indicates that the superior recovery is owed to the more robust regeneration of corticospinal neurons (CST) across the injury site. In the absence of intrinsic axonal regrowth, the older animals are more reliant on sprouting from uninjured subcortical populations i.e. propriospinal neurons (PN), reticulospinal neurons (RN), and rubrospinal neurons (RST). Despite this consensus, few studies have simultaneously analyzed the anatomical discontinuation of axonal regeneration with aging and how each pathway's response post-injury translates to functional outcomes. Using a multimodal study, we investigated the exact neuronal pathways (CST, RST, PN, and RN) responsible for recovery following cervical SCI at different post-natal ages (P5, 14, 21, 60). We employ a two-virus vector system to deliver DREADDs (Designer Receptors Exclusively Activated by Designer Drugs) and precisely silence the C3/C4 PN, RN, RST, or CST. We use recombinant virus (Lenti or rAAV) to deliver inhibitory DREADDs (hM4Di) caudal to the lesion, after which we individually silence the appropriate pathway by introducing a transactivator (AAV/Tet-On) at the location of neuronal soma. To map the subcortical populations, we use a retrograde transportable lentivirus (HiRet/Lenti/GFP). To label the descending CST, we inject adeno-associated virus (AAV/mCherry) into the somatomotor cortex. Behavioral assays consist of isometric pull strength, grooming, IBB (Irvine, Beattie, Bresnahan), and single pellet reach. We hypothesize that there is a critical age where intrinsic corticospinal regrowth is no longer viable and any recovery becomes dependent on interneuron plasticity (i.e. PN). In addition, by reproducing functional deficits with DREADDs, we validate the individual contribution of each neuronal pathway in promoting recovery. Our data illustrates that in P5 neonatal rats there is enhanced

axonal regeneration, increased sprouting of supplementary pathways, and superior functional recovery, when compared to the older age groups.

Disclosures: R.D. Smit: None. **T.J. Campion:** None. **J.B. Madrak:** None. **G.M. Smith:** None.

Poster

660. Spinal Cord Injury III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 660.04/H9

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Modulation of integrin signaling in the hydrogel-induced extracellular matrix to facilitate axonal ingrowth following spinal cord injury

Authors: *H. PARK, D. HWANG, Y. OH, H. KIM, B. KIM;
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Abstract: Axon regeneration failure beyond lesion site following central nervous system (CNS) injuries is hampered by fluid-filled cystic cavities formed at the lesion epicenter. Previously, we demonstrated that injection of imidazole-poly (organophosphazene) (I-5), a hydrogel with thermosensitive sol-gel transition behavior, prevented cystic cavity formation by promoting extracellular matrix (ECM) remodeling. However, the extent of axonal ingrowth into the hydrogel-induced ECM was limited. We hypothesized that inhospitable microenvironment in newly deposited ECM provides inhibitory influence to regenerating axons and that modifying the ECM environment can facilitate axonal growth into the ECM. I-5 injection results in the formation of fibrotic matrix filled with type I collagen surrounded by highly reactive astrocytes, reminiscent of the fibrotic scar. It has been reported that interaction between collagen in the ECM and integrin expressed in reactive astrocytes drives formation of glial scars, a potent inhibitory factor for axon regeneration. The present study aimed to modify microenvironment of I-5 induced ECM by modulating integrin signaling. Activated integrin beta1 immunoreactivity was observed in migrating astrocytes intermingled with ECM 1 week after I-5 injection. By 4 weeks, integrin immunoreactivity was diminished but still found at the border between reactive astrocytes and collagen-rich ECM. To suppress integrin activation, I-5 hydrogel mixed with integrin beta1 functional blocking antibody was injected 1 week after spinal cord injury in rats. Our data showed that I-5 mixed with integrin beta1 functional blocking antibody increased the extent of 5-HT (serotonin) axonal growth into fibrotic matrix. This study suggests that integrin signaling can be targeted to facilitate axonal growth in the hydrogel-induced matrix following spinal cord injury.

Disclosures: H. Park: None. **D. Hwang:** None. **Y. Oh:** None. **H. Kim:** None. **B. Kim:** None.

Poster

660. Spinal Cord Injury III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 660.05/H10

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Craig H. Neilsen Foundation 316282
NIH R21HD082808
F31 NS096921

Title: Lasting disruption of eccentric neural control after human spinal cord injury

Authors: *D. BASSO[1], K. O'BRIEN[5], T. FAW[2], S. JANSE[3], G. BROCK[3], L. WORTHEN-CHAUDHARI[4], J. SCHMIEDELER[5];
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Abstract: Spinal cord injury (SCI) causes life-long disability even with advances leading to less neuropathology and more aggressive rehabilitation. We postulate that long-standing impairments result from dysregulation between descending supraspinal drive and afferent input below the SCI. Eccentric motor control is ideal for monitoring this dysfunction since supraspinal input sets motor neuron activation below external forces and lengthening contractions occur. This exploratory study characterized eccentric motor control during overground locomotion after chronic, incomplete SCI (iSCI; n=16) compared to healthy controls with similar BMI and age (n=14). As these factors (i.e. age, mass, stature and gait speed) influence locomotion, controlling for them adds necessary rigor. Using kinematics, kinetics and 14-channel EMG, two distinct eccentric impairment patterns emerged - strut and crouch. When using the leg as a strut, the knee extends more than expected, the ground reaction force (GRF) shifts anteriorly compared to normal, promoting knee extension rather than flexion during the weight acceptance phase. In the crouch strategy, the knee flexes more than expected, the GRF shifts posteriorly, and knee flexion increases beyond normal, risking near collapse during weight acceptance. Principle component analysis (PCA) based on biomechanics and EMG metrics mapped the strut and crouch strategies onto the PCA space defined by healthy control strategies for the hip and knee. Based on factor loadings and within-strategy variability, the strut strategy was farther from normal, while crouch was more intermediate. Loading factors define the primary contributors to each principal component. Specifically, decreased rectus femoris eccentric activity distinguished strut from crouch strategy for the hip and knee after iSCI. The current study identified persistent eccentric neural dysfunction after recovery of some walking in chronic human SCI. Thus, regaining

locomotor function after SCI is not necessarily accompanied by restoration of eccentric motor control. Indeed, at least two patterns of dysregulation exist which will require different, more precise interventions.

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Poster

660. Spinal Cord Injury III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 660.06/H11

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Mission Connect, a project of the TIRR Foundation

Title: Defining boundaries of expected normal variability in outcome measures on the CatWalk gait analysis system

Authors: *M. ACEVES[1,3], V. A. DIETZ[2], J. N. DULIN[2,3], N. D. JEFFERY[1,3];
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Abstract: One of the most frustrating problems in spinal cord injury (SCI) research is the failure to translate experimental interventions from laboratory to clinic. While there are a multitude of reasons for this state of affairs, many of which have straightforward solutions, one rarely examined, but crucial, aspect is whether an intervention has sufficient magnitude of effect. This can be difficult to assess from group analysis alone. Effective therapeutic impact in the clinic is defined as a meaningful change from baseline in an individual, which implies the need to know how much natural variability there is in the outcome measurement. In this study we analyzed inherent variability in outcomes derived from the Catwalk gait analysis system so as to be able to apply similar individual-level analysis to putatively translatable laboratory interventions for SCI. Variability in outcome measure is a consequence of intraindividual, interindividual and analytical (*e.g.* measurement 'error') variation and must be determined in individuals at steady-state. In this study, uninjured male Sprague-Dawley rats (N=16) were acclimated to the CatWalk apparatus for 5 days prior to testing and then gait variables measured on each of 8 weeks, with 3 runs recorded at each weekly session. The magnitude of the various sources of variability were elucidated using hierarchical regression and then used to derive the reference change interval (RCI), which defines the boundaries within which an individual's outcome measures can spontaneously vary. As expected, there was considerable variability between different measures of hindlimb function, for example: stand, stride length, paw area, swing time, swing speed have RCIs of baseline +/- 85, 32, 65, 35 and 45% respectively.

Our results provide foundational data for individual-level analysis of laboratory interventions for SCI, which will complement group-level analysis and enhance understanding of effect size. The inherently high level of variability in some outcome measures implies poor sensitivity for detection of benefit because achieving results outside the RCI may not be physiologically plausible. Such analysis thereby also aids in experimental design.

Disclosures: **M. Aceves:** None. **V.A. Dietz:** None. **J.N. Dulin:** None. **N.D. Jeffery:** None.

Poster

660. Spinal Cord Injury III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 660.07/H12

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Dept. of Defense Grant W81XWH-17-1-0585
NIH Grant R01NS099872
UWIN and WRF funds for innovation in Neuroengineering

Title: Multisite activity-dependent spinal stimulation to promote motor recovery in chronic cervical spinal cord injury

Authors: *R. L. MURPHY[1], R. B. ROBINSON[1], A. J. WIDMAN[1], K. GILCHRIST[1], B. R. KONDILES[1], S. I. PERLMUTTER[1,2], S. LEE[1,3];
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Abstract: Cervical spinal cord injury (SCI) damages descending motor pathways that control movements of the hands and arms. A loss of motor function can be severely detrimental to the quality of life and independence of people with SCI. We use a rat model of moderate-severe cervical spinal contusion to develop activity- dependent, closed-loop, electrical stimulation treatments to improve motor recovery in chronic SCI. We previously showed that a single site of cervical spinal stimulation synchronized to volitional contractions of an impaired forelimb muscle produced robust functional improvements compared to controls in a food pellet reach-and-grasp task. We hypothesized that multiple sites of activity-dependent stimulation synchronized to the volitional activity of multiple impaired forelimb muscles (e.g., triceps, wrist extensors, and digit flexors) will produce greater functional benefits, by promoting plasticity in multiple circuits necessary for reaching and grasping. For this study, male and female rats were trained in 4 behavioral tasks: food pellet reach and grasp, pasta matrix, lever pull, and horizontal ladder walk with irregularly spaced rungs. These tasks assess different aspects of forelimb function. Once proficient at all tasks, rats received a moderate-severe, unilateral C4 spinal

contusion. After 4 weeks, the rats were implanted with an array of penetrating platinum-iridium microwires near the ventral motoneurons in spinal segments C5-C7 and wires in three muscles of the impaired forelimb for electromyographic (EMG) recording of muscle activity. Two weeks after implantation, animals were trained for 14 weeks in all 4 behavioral tasks. During this therapy period, stimulated animals received spinal stimulation in response to muscle activity of the impaired forelimb muscles. For 5 hours per day, including during the trained tasks, EMG from each muscle triggered sub-movement-threshold stimulation through a microwire that could elicit contractions of that muscle with higher stimulus currents. Non-stimulated control animals received only behavioral training during the therapy period. After the therapy ended, all animals were tested once each week to monitor long-term post therapy changes in functional outcomes. Multisite stimulation results in improved functional outcomes compared to unstimulated control animals. Recovery only became apparent after 5 weeks of therapy. Moreover, multisite stimulation appears to be effective in animals with more severe SCI than single site stimulation. These results suggest that multisite activity-dependent stimulation may prove to be a potent intervention to improve motor recovery in humans with SCI.

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Poster

660. Spinal Cord Injury III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 660.08/H13

Topic: C.11. Spinal Cord Injury and Plasticity

Support: US Department of Defense W81XWH-18-1-0695

Title: An innovative suppressor of cytokine signaling-3 (SOCS3) reduction peptide (SRP) to repair spinal cord injury

Authors: Y.-S. LEE, K. LI, A. KIM, ***C.-Y. LIN**;
Neurosci, Cleveland Clin., Cleveland, OH

Abstract: The pathophysiology of spinal cord injury (SCI) involves immediate physical damage and subsequent secondary injury including inflammation, which lead to functional deficiency below the injured level. Suppressor of cytokine signaling-3 (SOCS3) has attracted considerable attention for its prominent roles in affecting a broad range of cytokines/chemokines that mediate inflammation. Indeed, knocking down SOCS3 with Lentiviral delivery of short-hairpin ribonucleic acid (shRNA) can prevent neuronal loss after SCI, as shown in our studies, and it can promote axonal regeneration after optic nerve injury and corticospinal axon sprouting after SCI when genetically deleted. Given that both viral delivery of shRNA and genetic deletion have

limited clinical potential, we have developed an innovative peptide, SOCS3 reduction peptide (SRP), in order to prevent subsequent deleterious effects, including inflammation and functional impairments. Specifically, SRP can be easily delivered by subcutaneous injection and distributes to the spinal cord via its N-terminal blood-spinal cord barrier- and cell membrane-permeable domain, where it specifically binds to SOCS3 by its central SOCS3-binding domain and is then degraded in the lysosome as directed by its C-terminal lysosome-targeting domain. Our preliminary results demonstrate that injected SRP distributes to macrophages/microglia to be co-localized with lysosomes and SCI-upregulated SOCS3. SRP specifically and significantly reduces SOCS3, but does not affect suppressor of cytokine signaling-1 (SOCS1) levels, and it is associated with increased signal transduction and transcription-3 (STAT3) activity. Furthermore, SRP treatment post-SCI significantly decreased pro-inflammatory responses, as indicated by decreased expression of both inducible nitric oxide synthase (iNOS) and tumor necrosis factor-alpha (TNF-α). Importantly, we have exciting data showing that in a T8 contusion SCI model, SRP treatment significantly improves recovery of both locomotion and micturition two months after SCI.

Disclosures: **Y. Lee:** None. **K. Li:** None. **A. Kim:** None. **C. Lin:** None.

Poster

660. Spinal Cord Injury III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 660.09/H14

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH R01NS099076

Title: The susceptibility of cardiac disorders after spinal cord crush injury in rats

Authors: S. FERNANDES, J. WEINBERGER, I. W. IREDIA, V. TOM, *S. HOU;
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Abstract: High-level spinal cord injury (SCI) often interrupts supraspinal regulation of sympathetic activity in the heart. The loss of balance between autonomic components renders the exposure of cardiac disorders. However, few animal experiments have successfully been investigated to model the disease for potential therapeutic interventions. In the present study, we employed complete spinal cord crush injury, which is an ideal lesion for further cell transplantation, at the T2/3 or T9 level in rats; naïve rats served as a control. Using a radio-telemeter to record electrocardiogram (ECG) and blood pressure, we analyzed heart rate variability (HRV) and cardio-electric alterations 4 weeks after SCI. With 24-h recording, total HRV was reduced in rats with a T2/3 injury, but not T9/10. The T2/3 SCI cohort showed decreased low frequency (LF) but increased high frequency (HF) powers in frequency domains,

while standard deviation of R-R intervals (SDNN) and its derivations significantly declined in time domains, indicating reduced sympathetic and unopposed parasympathetic activity for the heart. During colorectal distention (CRD)-induced autonomic dysreflexia, more arrhythmia events were triggered in rats receiving T2/3 injury, such as bradycardia with sinus arrest, pause related aberrant conduction, ventricular ectopy, and possible atrial fibrillation. This suggests the vulnerability of cardiac electrical system under stress. Thus, the results illustrate that susceptibility of cardiac dysfunction is prevalent following SCI at high levels due to compromised autonomic homeostasis; rats with T2/3 spinal cord crush injury is a suitable model to study cardiac abnormalities.

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Poster

660. Spinal Cord Injury III

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Topic: C.11. Spinal Cord Injury and Plasticity

Support: National Institute of Neurological Disorders and Stroke R01 R01NS103481
Shriners Hospital for Pediatric Research SHC 84051
Shriners Hospital for Pediatric Research SHC 86000
Department of Defense SC140089

Title: Enhancing functional recovery from spinal cord injury in neonatal rats with the application of excitatory DREADDs

Authors: *J. MADRAK[1], R. SMIT[1], T. CAMPION[1], G. M. SMITH[2];
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Abstract: Spinal cord injury (SCI) can result in a cascade of problems and functional recovery from SCI is not always achievable. In many species, axonal regeneration has been observed as the primary mechanism of SCI repair in juveniles, while axonal sprouting from subcortical pathways has been observed to be critical for the repair of SCI lesions in older animals. We propose that there is a critical age between postnatal days 5 and 14, in which their neuronal rescue pathways transition from axonal regeneration to axonal sprouting for the repair of a spinal cord lesion. We aim to define and modulate specific sprouting mechanisms of subcortical pathways (i.e. propriospinal, reticulospinal and rubrospinal tracts) through the injection of excitatory Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) following cervical SCI in juvenile rats. Initially, experimental rats were injected with recombinant adeno-

associated (rAAV) and modified human muscarinic 3 (hM3) excitatory G-protein (Gq) coupled DREADD (D) receptors (hM3Dq). On postnatal day 14, unilateral C5 hemisections were induced in both rAAV-h3MDq injected rats and control rats. Post-injury, we introduced Cre-recomibinase (CRE) intracranially to transactivate the DREADDs. In the continuation of this study, hM3Dq receptors will be activated with constitutive delivery of clozapine-N-oxide (CNO) to excite the recovery pathways and potentially facilitate supplementary sprouting after injury. Behavioural assays will be used to assess the potential for excitatory DREADDs to promote functional rehabilitation following SCI. Tissue will be collected and analysed using immunohistochemical labels in an effort to map the reorganization of motor neurons terminating within C6-T1 regions and to ensure complete lesions. As this study concludes, we hope to address gaps in literature pertaining to axonal recovery mechanisms in early spinal cord injuries, including the mechanisms of recovery from SCI in juvenile rats, and whether or not constitutively activated excitatory DREADDs can precisely facilitate the sprouting of subcortical pathways to modulate functional rehabilitation after SCI.

Disclosures: **J. Madrak:** None. **R. Smit:** None. **T. Campion:** None. **G.M. Smith:** None.

Poster

660. Spinal Cord Injury III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 660.11/H16

Topic: C.11. Spinal Cord Injury and Plasticity

Support: TWU Research Enhancement Program
TWU Department of Biology

Title: Surface functionalized nanoparticles targeting corticospinal tract neurons through the high affinity cell surface receptor binding of brain-derived neurotrophic factor

Authors: *M. CAO[1], D. L. HYNDS[1], S. GHOSH[2];
[1]Texas Woman's Univ., Denton, TX; [2]Southeast Missouri State Univ., Cape Girardeau, MO

Abstract: Spinal cord injured (SCI) individuals endure life-long paralysis and other significant losses to the quality of life. However, the use of therapeutics to treat SCI is complicated by factors that limit the delivery of therapeutics and targeting to particular types of cells among the diverse cell types present in the central nervous system (CNS). Biocompatible nanocarriers that are capable of crossing the blood brain barrier can be used to target therapeutics to particular subsets of neurons. In our work, Ferromagnetic nanoparticles encapsulated in tunable polyethylene glycol (PEG) biopolymers were synthesized and surface functionalized with -COOH and -NH_2groups. They were fluorescently tagged to study the mechanism of cellular uptake and targeted drug delivery to neurons. In the present study, we analyzed the targeting of

nanospheres to cells expressing high affinity neurotrophic factor receptors (TrkA, TrkB, TrkC) using brain-derived neurotrophic factor (BDNF) modified nanospheres. Using BDNF to target specific neurons allows us to direct the nanospheres to the neurons and enhance axon growth from. Together, these results show the feasibility of using functionalized nanocarriers for targeted drug delivery to corticospinal tract (CST) neurons to encourage axon regeneration following nervous system damage.

Disclosures: M. Cao: None. **D.L. Hynds:** None. **S. ghosh:** None.

Poster

660. Spinal Cord Injury III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 660.12/H17

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH R01 NS091031

Title: Extent of corticospinal tract sprouting does not predict behavioral recovery following cervical spinal cord injury in the macaque monkey

Authors: *M. CROWLEY, J. GARNER, C. DARIAN-SMITH;
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Abstract: The corticospinal tract (CST) is the main descending pathway mediating voluntary hand movement in primates. Following cervical spinal cord injury (SCI), terminal sprouting of spared motor CST axons is known to occur, and has long been used as a biomarker of recovery. However, there is little evidence that links these sprouting patterns with the recovery of hand function (as measured behaviorally). Here we investigated behavioral function after injury to determine whether CST sprouting is a valid measure of recovery. Previous work in our lab (Darian-Smith et al., 2013; Darian-Smith et al., 2014) has shown that following a cervical dorsal root lesion (DRL), the primary somatosensory (S1) CST terminal projection retracts to 60% of its original domain, while the primary motor (M1) CST projection remains robust. In contrast, when a dorsal column lesion (DCL) is added to the DRL, both the S1 and M1 CST projections extend bilaterally and caudally, well beyond normal range. Considering the prevailing notion that CST sprouting tracks with behavioral recovery, we asked: *do these dramatic differences in terminal sprouting patterns reflect differences in the capacity for functional recovery after injury?*
We addressed this across the two types of primary afferent SCI by comparing the recovery of manual dexterity with CST terminal sprouting patterns. Monkeys were trained to retrieve a target object from a clamp using thumb and index finger opposition. They then received either a DRL (n=4) or a combined dorsal root/dorsal column lesion (DRL/DCL; n=4) that removed cutaneous

sensory input from the first three digits of one hand. Three performance parameters were measured before and after the lesions: 1) percentage of successful retrievals; 2) digit stratagem (the pattern of digit opposition); and 3) contact time (duration of digit contact with the object before retrieval). Current behavioral data from the monkeys receiving a DRL/DCL were directly compared with earlier published work of DRL-lesioned animals (Darian-Smith & Ciferri, 2005). Our findings show a similar capacity for recovery in both groups of monkeys, whereby an initially severe impairment of hand function is followed by significant recovery over many weeks. This indicates that while CST sprouting may play an important role in the recovery of hand function, its extent does not clearly track with behavioral recovery. These findings should be taken into consideration when interpreting any post-SCI data that uses axonal sprouting as a biomarker of functional recovery.

Disclosures: M. Crowley: None. **J. Garner:** None. **C. Darian-Smith:** None.

Poster

660. Spinal Cord Injury III

Location: Hall A

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Program #/Poster #: 660.13/H18

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH R01 NS091031

Title: Long term adaptation of dorsal horn circuitry after spinal cord injury in macaques

Authors: *K. M. FISHER, J. GARNER, C. J. DARIAN-SMITH;
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Abstract: The corticospinal tract (CST) is the major descending pathway controlling movement in primates and its expansion through evolution is linked to improved manual dexterity. It is becoming increasingly clear that the role of the CST is more nuanced than that of a simple motor output pathway and that subdivisions arising from outside motor cortex have an important role to play in sensorimotor function.
Our recent work demonstrates that the somatosensory (S1) CST has a discrete input territory within the dorsal horn which overlaps substantially with the incoming primary afferent population. Following a spinal cord injury that involves primary afferent input from the hand, this zone permanently loses much of its normal input, and becomes a region of immense change, where neuronal circuitry must reorganize for recovery to occur. Here, we asked what happens to the circuitry in this region of the dorsal horn during the chronic phase of recovery from spinal injury.
To do this, we mapped the terminal territory of both afferent and efferent inputs to the spinal cord, and then used various neuronal and molecular markers to probe specific connectivity using

confocal imaging. Three macaques received a combined injury of the dorsal roots and dorsal column (DRL/DCL), affecting sensation in digits 1-3 of the hand. One year post-injury, S1 cortex was mapped and anterograde tracers injected into the region corresponding to digits 1-3, contralateral to DRL/DCL. A week before perfusion Cholera toxin sub-unit b (CT-B) was injected into the finger pads of both hands to label primary afferents. Data from these animals was compared to previous control and DRL/DCL monkeys (4-5 month recovery period).
One year post injury, the afferent and efferent terminal territories were restored to their normal input domains. This indicates substantial pruning of the exuberant S1 CST sprouts present at 4-5 months post lesion (Darian-Smith et al., 2014; Fisher et al., 2018). The S1 CST once again projects to a discrete region of dorsal horn. Primary afferent neurons, though permanently reduced (to <5% of their original innervation), have sprouted considerably in order to repopulate an overlapping area. Since many other elements are known to have been restored at this time point (i.e. hand function, S1 CST terminal territory, peripheral receptor numbers – Crowley et al., 2019), compensatory changes are likely to occur at the circuitry level in this region of the dorsal horn. We will put these changes in the context of sensory gating which is known to take place in this area.

Disclosures: K.M. Fisher: None. **J. Garner:** None. **C.J. Darian-Smith:** None.

Poster

660. Spinal Cord Injury III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 660.14/H19

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Somatosensory deafferentation produces deficits in predictive control of bilateral upper limb coordination and asymmetries in postural stabilization

Authors: *J. SCHAFFER[1], S. JAYASINGHE[2], C. MAENZA[2], F. R. SARLEGNA[3], R. L. SAINBURG[4];
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Abstract: Large fiber sensory neuropathy (LFSN) results in loss of proprioception and discriminative touch sensations, and has been shown to produce deficits in intralimb coordination and in the ability to stabilize the limb, in the absence of visual feedback. We examined bimanual coordination in a LFSN patient (GL; age 70 years; right-hand dominant) and in age-matched control participants. The task required participants to move a single virtual bar with both hands to a rectangular target with horizontal orientation. The participants received visual feedback of the virtual bar, but not of the hand position along the bar-axis. Maintenance of midline positioning of the bar required negatively correlated displacements of the hands along

the axis of the bar. Whereas control participants tended to initiate movements with highly correlated hand displacements (~-0.6 Pearson r), GL initiated movement with poorly correlated hand motions (~-0.2 Pearson r). Because this coordination was measured early in movement, this reflected a deficit in predictive coordination between the hands, and asymmetries in hand kinematics. Deafferentation also produced an asymmetric deficit in stabilizing the hand at the end of motion. Specifically, the dominant arm showed substantial drift following motion, while the non-dominant arm oscillated near the end of motion. While this drift asymmetry occurred without visual feedback of the hand position, it was also substantial with visual feedback. These results indicate 1) predictive control of bilateral coordination is dependent on proprioceptive information, 2) asymmetries in motor control persist in the absence of proprioception, 3) stabilization of position at the end of motion is achieved through feedforward mechanisms for the non-dominant, but not for the dominant arm. This latter finding is consistent with the proposition that the non-dominant hemisphere may be specialized for control of positional impedance. While the findings with GL may reflect a unique adaptation to deafferentation, they suggest that end-position stability of the non-dominant arm can be specified through feedforward mechanisms that might exploit coactivation of muscles, in the absence of somatosensory feedback.

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Poster

660. Spinal Cord Injury III

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Program #/Poster #: 660.15/H20

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Large fiber sensory neuropathy produces asymmetrical deficits in limb movement and stabilization: in the absence of vision, the dominant arm drifts, while the non-dominant arm does not

Authors: *S. A. L. JAYASINGHE[1], J. E. SCHAFFER[2], C. MAENZA[1], F. R. SARLEGNA[3], R. A. SCHEIDT[4], R. L. SAINBURG[2];
[1]Neurol., The Pennsylvania State Univ., Hershey, PA; [2]Kinesiology, The Pennsylvania State Univ., University Park, PA; [3]CNRS and Aix-Marseille Univ., Marseille, France; [4]Biomed. Engin., Marquette Univ., Milwaukee, WI

Abstract: Large fiber sensory neuropathy (LFSN) results in loss of proprioception and discriminative touch sensations, leading to substantial movement deficits. Previous studies have revealed that such neuropathies produce profound deficits in intersegmental coordination and in limb stabilization following movement. The control processes that mediate coordination of

intersegmental dynamics and limb postural stability have been shown to depend on left and right hemisphere mechanisms, giving rise to lateralization of motor performance (Sainburg 2016). We now ask whether motor lateralization persists after LFSN. We tested an individual who has been living with LFSN for 40 years, following an acute post-viral onset at age 30. Her diagnosis confirmed profound somatosensory loss due to LFSN, bilaterally throughout all the joints of her arms and shoulder girdle. GL (female; age 70 years; right-hand dominant) performed a planar three-direction reaching task (with each hand) with and without visual feedback of movement. We analyzed both initial trajectory accuracy and final position stabilization accuracy, in terms of 1) initial movement direction, 2) final position accuracy (initial movement segment), and 3) final position stability (drift post initial movement segment). Our results indicated that regardless of visual feedback, left hand direction errors were greater than right hand errors. In contrast, final position accuracy of the left and right hands was similar with visual feedback, and while both showed greater errors without feedback, the right suffered from the loss of vision substantially more than the left hand. Following movement, only the right hand drifted substantially, when vision was removed. Thus, our findings indicate that motor lateralization is enhanced following long-term loss of proprioception. LFSN produced greater trajectory deficits in the left arm, and greater stability deficits in the right arm. Our results for the no-vision condition suggest that the lateralized control of initial trajectory accuracy, final position accuracy, and stability are mediated by feedforward process without the benefit of continuous proprioceptive feedback. Most remarkably, limb position drift, which was previously described as a characteristic feature of the LFSN (Sanes et al. 1984, Rothwell et al. 1982) did not occur in the non-dominant arm.

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Poster

660. Spinal Cord Injury III

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Topic: C.11. Spinal Cord Injury and Plasticity

Support: Department of Defense W81XWH1810530
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RPC 2016-0195

Title: Is transcranial magnetic stimulation a reliable tool for studying neurophysiological changes associated with functional recovery in individuals with incomplete tetraplegia?

Authors: *T. ARORA, K. A. POTTER-BAKER, K. O'LAUGHLIN, X. WANG, E. B. PLOW; Cleveland Clin. Fndn., Cleveland, OH

Abstract: Introduction:
Transcranial magnetic stimulation (TMS) is used to study neurophysiology in individuals with spinal cord injury (SCI). To ensure the changes in TMS are a true reflection of neurophysiological changes, it is important to test its reliability. Since, reliability may vary between the muscles above and below lesion that are more and less spared by injury, respectively, it is important to compare reliability of these muscles. Two types of measurement properties are suggested for studying reliability - agreement i.e. how similar are the test-retest measurements within unchanging individuals, and reliability (reliability$_{MP}$) i.e. how unchanging individuals are relative to others. The objective was to determine agreement and reliability$_{MP}$ of TMS metrics from upper extremity muscles of different impairment levels in individuals with incomplete cervical SCI.
Methods:
16 individuals [51$\pm$12 years (28-68 years) 3F] with chronic incomplete cervical SCI (C2-C6) resulting in tetraplegia (AIS B:4; AIS C:1; AIS D:11) participated in the study. We collected TMS metrics from one strong (MRC $\geq$ 3) and one weak (MRC < 3) upper extremity muscle in each participant during test and retest visits separated by at most 2 weeks. Evaluated TMS metrics included measures of corticomotor excitability, output, gain, and somatotopy. We calculated agreement properties [Standard Error of Measurement (SEM) and Smallest Detectable Change (SDC)], and reliability$_{MP}$ [Intraclass (ICC) and Concordance (CCC) correlation coefficients].
Results:
Data was obtained from 19 strong muscles (Biceps = 9; Deltoid = 3; EDC = 2; Triceps = 5) and 13 weak muscles (Biceps = 2; Deltoid = 2, EDC = 3; FDI = 1; Triceps = 5). Overall, measurement error was found to be high. Reliability$_{MP}$ values for strong muscles were greater than weak muscles. For strong muscles, active motor threshold, center of gravity in x-direction and active motor evoked potential amplitude had an excellent (ICC>0.90 and CCC>0.80) reliability$_{MP}$, whereas for weak muscles only active motor threshold had an excellent reliability$_{MP}$. Strong and weak muscles had moderate to good (ICC = 0.50-0.80 and CCC = 0.40-0.80) reliability$_{MP}$ for all other variables except for cortical map volume and recruitment curve slope, respectively, which had poor reliability (ICC < 0.50 and CCC < 0.40).
Conclusion:
High agreement values suggest a large change in TMS scores is required to be detected as a true change over and above the inherent measurement noise, therefore evaluative interpretations based on individual TMS change should be made with caution. High reliability$_{MP}$ suggests individuals with tetraplegia can be distinguished from one another using TMS.

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Poster

660. Spinal Cord Injury III

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Topic: C.11. Spinal Cord Injury and Plasticity

Support: The Grainger Foundation
Regenerative Medicine Minnesota
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Mayo Clinic Graduate School of Biomedical Sciences
Mayo Clinic Center for Regenerative Medicine
Mayo Clinic Rehabilitation Medicine Research Center
Mayo Clinic Transform the Practice

Title: Intentional modulation of spinal motor output during treadmill stepping enabled by epidural electrical stimulation in humans with severe spinal cord injury

Authors: *M. GILL[1], C. LOPEZ[1], M. LINDE[1], P. GRAHN[2], J. S. CALVERT[1], K. D. ZHAO[4], I. LAVROV[3], D. SAYENKO[5], K. H. LEE[1];
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Abstract: Dynamic task-specific training in the presence of epidural electrical stimulation (EES), termed multi-modal rehabilitation (MMR), has been shown to restore and enhance motor functions that were paralyzed for years in humans with spinal cord injuries (SCI). Evidence from animal models of SCI with EES and motor training suggests MMR enhanced synergistic functional reorganization of spinal neuronal connectivity resulting in the ability to generate independent stepping and standing in individuals with motor complete SCI. Dynamic task-specific training focuses on providing sensory input to spinal networks below the level of SCI via body weight support and tactile cues from trainers to optimize motor output. Kinematics, posture and joint alignment, as well as stepping speed are major contributing factors to spinal sensory input that impact motor output. Optimization of sensory input in order to improve motor output, termed locomotor training, is a therapeutic strategy to enhance muscle activity during standing or stepping after incomplete SCI. However, enhanced muscle activity does not translate to functional mobility nor neurological recovery for individuals with severe, motor and sensory complete SCI. Our team applied 12 months (approximately 2-3 sessions per week) of MMR in two humans with motor and sensory complete thoracic level SCI. Body weight support, sensory cues, and EES parameters were adjusted within, and across, sessions with the goal of facilitating independent standing and stepping performance. Here, we describe the evolution of intentional control over MMR-enabled motor activity in previously paralyzed muscles, recorded using skin

surface electromyography (EMG), during consistent body weight support, treadmill speed, trainer sensory cues, and EES parameters to assess supra-spinal influence on sensorimotor network activity in both subjects. These results, together with prior evidence from animal models of EES after SCI, indicate reorganization of human spinal network activity, and in turn, functionality, occurs over time in response to MMR.

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Poster

660. Spinal Cord Injury III

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Topic: C.11. Spinal Cord Injury and Plasticity

Support: Jack Jablonski Bel13ve in Miracles Foundation
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Mayo Clinic Center for Regenerative Medicine
Mayo Clinic Graduate School of Biomedical Sciences
Mayo Clinic Transform the Practice
Minnesota Government Office of Higher Education – SCI/TBI Grant
Regenerative Medicine Minnesota

Title: Comparison of transcutaneous and epidural electrical stimulation evoked motor responses during functional tasks in humans with spinal cord injury

Authors: *J. S. CALVERT[1], P. GRAHN[2], M. GILL[3], C. LOPEZ[3], I. LAVROV[4], M. LINDE[1], J. STROMMEN[1], L. BECK[1], D. VEITH[1], Y. P. GERASIMENKO[5], V. EDGERTON[6], D. SAYENKO[7], K. D. ZHAO[8], K. H. LEE[1];
[2]Dept. of Neurologic Surgery, [3]Physical Med. and Rehabil., [4]Neurosurg., [1]Mayo Clin., Rochester, MN; [5]Pavlov Inst. of Physiol, St Petersburg, Russian Federation; [6]Dept Integrative Biol. & Physiol., Univ. of California Los Angeles, Los Angeles, CA; [7]Houston Methodist Res. Inst., Houston, TX; [8]Mayo Clin. Dept. of Physiol. and Biomedica, Rochester, MN

Abstract: Introduction: Epidural Electrical Stimulation (EES) and Transcutaneous Spinal Stimulation (TSS) of the lumbosacral spinal cord have enabled a wide range of functions following spinal cord injury (SCI) in both animal and clinical experiments. Motor evoked responses have previously been used to investigate the effects of spinal stimulation on sensorimotor circuitry. However, the effect of descending voluntary control and ascending sensory input on motor evoked responses in humans has yet to be investigated in detail. Here, we report characteristics of human leg muscle evoked responses during EES- and TSS-enabled

standing and while supine. Methods: Two subjects diagnosed with functionally complete paraplegia due to SCI (American Spinal Injury Association Injury Scale A) were implanted with a 16-contact electrode array (Specify 5-6-5, Medtronic, Fridley, MN) placed over the dorsal epidural surface of the lumbosacral spinal cord (T11-L1 vertebral levels). Ten additional subjects with paraplegia due to SCI were tested with TSS of the lumbosacral cord at the lower thoracic and upper lumbar vertebral bodies. Skin surface electromyography (EMG) was collected from proximal and distal flexor and extensor muscles of the leg. ESS and TSS-evoked motor responses were analyzed during motor activities while supine and standing to characterize spinal network facilitation. Results: Evoked responses due to both EES and TSS resulted in similar characteristics such as amplitude, latency, and shape of response when the subjects were relaxed during supine activities. During voluntary efforts at low frequency stimulation, evoked responses were inhibited in both EES and TSS. Evoked responses during standing resulted in changes in shape, number of peaks, and amplitude compared to supine activities across both modalities. Conclusion: These results demonstrate that human spinal networks can modulate motor evoked responses through a combination of descending voluntary control and ascending sensory input, even years after injury.

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Poster

660. Spinal Cord Injury III

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Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 660.19/H24

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Startup funds from University of Kentucky College of Medicine

Title: Human apolipoprotein E isoforms influence neurite outgrowth and regeneration *in vitro* and serotonergic sprouting *in vivo*

Authors: *R. S. J. MAGGARD[1,2], C. M. CALULOT[1,2], E. E. HUFFMAN[1,2], D. R. STOLTZ[1,2], L. E. STRATTAN[1,2], L. E. MENDENHALL[1,2], K. J. RITTER[1,2], B. N. TURBA[1,2], A. L. SILVERSTEIN[1,2], J. D. HOFFMAN[3], G. NATION[4], A.-L. LIN[3], L. A. JOHNSON[4], W. J. ALILAIN[1,2];
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Abstract: Translating spinal cord injury (SCI) therapies which promote axonal regeneration from preclinical animal models into the human population is challenging. One potential obstacle is that human genetic predispositions may limit the efficacy of such experimental treatments. The clinically relevant ApoE4 (E4) allele, present in about 14% of the human population, corresponds to an increased incidence of Alzheimer's disease—however, its role in recovery from SCI is poorly understood despite suggestive data implicating its involvement. Indeed, two clinical studies found that SCI individuals with the E4 allele had less motor recovery than individuals without the allele despite longer time in rehabilitation. ApoE4 may mediate this diminished recovery by limiting regeneration and sprouting. Robust regeneration is energy intensive and requires efficient mitochondria, and studies have shown that ApoE4 impairs mitochondrial function. Given these mitochondrial deficits, we hypothesize that ApoE4 can impair regeneration and sprouting. To test this hypothesis, we investigated the impact of ApoE4 on sprouting and neurite outgrowth. In our experiments, we cultured dorsal root ganglia neurons from mice expressing human ApoE isoforms—ApoE2 (E2), ApoE3 (E3), or ApoE4—under the control of the endogenous mouse ApoE promoter. We then analyzed differences in 1) neurite complexity and 2) robustness of outgrowth between genotypes. In two of three independent experiments, E4 neurons had decreased neurite outgrowth and decreased neurite branching compared to E2 and E3 neurons. Data from the Spot Assay, an *in vitro* model of the glial scar and CNS regeneration, also suggest that chondroitin sulfate proteoglycans may inhibit regeneration in E4 neurons to an even greater extent than in E3 neurons. In addition, our preliminary *in vivo* data suggests that serotonergic sprouting after lateral C2 hemisection is impaired in E4 animals. Since outgrowth, sprouting, and regeneration all partially mediate recovery after CNS injury, impairments in these processes can adversely affect recovery. These foundational studies address not only the possible genetic influence of ApoE4 on recovery from CNS injury, but also a critical gap in knowledge—whether there is a genetic contribution underlying responses to treatment in SCI individuals.

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Poster

660. Spinal Cord Injury III

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Program #/Poster #: 660.20/H25

Topic: C.11. Spinal Cord Injury and Plasticity

Support: National Science Foundation Graduate Research Fellowship
UK College of Medicine Startup Funds

Title: Apolipoprotein E modulates respiratory motor plasticity following cervical spinal cord injury

Authors: *L. E. STRATTAN[1,2], K. J. RITTER[1,2], C. M. CALULOT[1,2], D. R. BRITSCH[1,2], A. L. SILVERSTEIN[1,2], E. E. HUFFMAN[1,2], W. J. ALILAIN[1,2];
[1]Spinal Cord and Brain Injury Res. Ctr., [2]Dept. of Neurosci., Univ. of Kentucky, Lexington, KY

Abstract: Each year, 17,700 Americans suffer a spinal cord injury, most of which occur at the cervical level. These injuries can interrupt neural pathways controlling breathing. One approach to promote breathing recovery is by enhancing plasticity in the spinal cord by strengthening synapses or activating pathways that were spared by the injury. Activating the latent crossed phrenic pathway can lead to motor plasticity known as long term facilitation (LTF), causing a recovery of breathing motor output. LTF can be induced through intermittent hypoxia (IH) or intermittent serotonin (5-HT) dosing. While a portion of the SCI population responds to IH with an increase in respiratory output, others remain non-responders. This inconsistency suggests that variability in the human population may influence how individuals respond to treatments that aim to enhance plasticity. Therefore, we propose that genetic diversity could be a key factor in determining an individual's propensity for plasticity. Apolipoprotein E (apoE) is a promising candidate gene that could be responsible for this variability. The E4 allele of apoE has previously been shown to reduce synaptic plasticity by decreasing expression of glutamate receptors when compared to the E2 or E3 alleles. This study investigates the impact of human apoE4 on respiratory motor plasticity following SCI. Chronically after C2 hemisection, animals were dosed with one isoform of the human apoE protein, E3 or E4, prior to induction of LTF. Concurrent diaphragmatic EMG recordings were analyzed for changes in breathing motor output indicative of LTF. Subsequent histological analysis of the region of the phrenic motor nucleus (C3-C6) demonstrated that LTF induction led to an increase in synaptic AMPA receptors in E3 animals, but this effect was attenuated in E4 animals. These results suggest that the human apoE allele may be inhibitory to respiratory motor plasticity following cervical spinal cord injury. Therefore, genetic diversity among the human SCI population is an important factor to be considered when developing therapeutics.

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Poster

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Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 660.21/H26

Topic: C.11. Spinal Cord Injury and Plasticity

Support: UK College of Medicine Start-up Funds

Title: Longitudinal analysis of gut microbiome composition after experimental cervical spinal cord injury

Authors: *J. S. NEWTON[1,2], E. E. HUFFMAN[1,2], D. R. STOLTZ[1,2], C. M. CALULOT[1,2], L. HAGER[1,2], R. S. MAGGARD[1,2], W. J. ALILAIN[1,2];
[1]Spinal Cord and Brain Injury Res. Ctr., [2]Neurosci., Univ. of Kentucky, Lexington, KY

Abstract: Following an experimental C2 spinal cord (SC) hemisection in rats, there is a gradual spontaneous recovery process that can take place over time. Additionally, interventions at later time points are more effective chronically after injury. What is not known is the mechanism mediating this observation. To begin to answer this question, we investigated the role of the gut microbiome after injury. Recent studies have emerged suggesting that the gut microbiome has critical implications on the proper functioning of the central nervous system (CNS). Indeed, gut dysbiosis, or a microbiome imbalance, can occur which can negatively impact the CNS. Neurotrauma, including spinal cord injury (SCI), can lead to acute gut dysbiosis leading to impaired recovery. It is our hypothesis that the composition of the gut microbiome is dynamic after injury with dysbiosis improving over time from an acute post-SCI state. In this study, we build upon these initial studies and investigate the impact of cervical SCI on the gut microbiome over time and up to chronic timepoints, as well as its impact on respiratory motor function and plasticity. In order to test our hypothesis, we performed a C2 hemisection on adult female rats and collected fecal samples from these animals, as well as from non-injured animals in order to assess microbiome composition at various timepoints post injury. Preliminary results suggest that following cervical SCI (up to 20 weeks post injury), robust differences in gut microbiome are apparent compared to non-injured animals. Future studies will classify bacterial identities and assess the impact of the post-injury gut microbiome on respiratory motor function and plasticity. As a majority of the SCI population are at the cervical level and at post-acute stages, this study is both important and translationally relevant.

Disclosures: J.S. Newton: None. **E.E. Huffman:** None. **D.R. Stoltz:** None. **C.M. Calulot:** None. **L. Hager:** None. **R.S. Maggard:** None. **W.J. Alilain:** None.

Poster

660. Spinal Cord Injury III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 660.22/H27

Topic: C.11. Spinal Cord Injury and Plasticity

Support: UK College of Medicine Startup Funds (WJA)
Kentucky Spinal Cord and Head Injury Research Trust Fellowship (EEH)

Title: Investigating the link between cervical spinal cord injury and lung injury/ respiratory distress syndrome

Authors: *E. E. HUFFMAN[1,2], J. S. NEWTON[1,2], D. R. STOLTZ[1,2], L. HAGER[1,2], W. J. ALILAIN[1,2];
[1]Spinal Cord and Brain Injury Res. Ctr., [2]Neurosci., Univ. of Kentucky, Lexington, KY

Abstract: The global incidence rate of traumatic spinal cord injury (SCI) is an estimated 768,473 persons per year, the majority of which occur at the cervical level. These high-cervical SCIs disrupt respiratory pathways and disable autonomous breathing, which introduce morbidity and mortality to SCI individuals. It has been shown that SCI individuals are at risk for developing acute respiratory distress syndrome (ARDS) and acute lung injury (ALI). ARDS/ALI are life-threatening diseases of the lung. They are primarily characterized by respiratory failure, widespread lung inflammation, intra-alveolar edema, and alveolar-capillary membrane damage. ARDS represents the most severe form of lung injury, while ALI is its less severe counterpart. However, in SCI individuals, the presence of either of these lung injuries predicts substantial mortality rates. While the correlative relationship between ARDS/ALI and SCI has been explored in retrospective clinical studies, the causal relationship is not well understood. Elucidating the relationship between SCI and ARDS/ALI may enable new ARDS/ALI treatment via techniques previously reserved for high-cervical SCI individuals. The present study attempts to explore the potentially causal relationship between SCI and ARDS/ALI in the rat model. We performed a C2 hemisection injury to the rat model and assessed ARDS/ALI at various timepoints. Our preliminary studies found an increased bacterial presence in the lung microbiome of SCI rats. This has been observed in human ARDS/ALI patients and is suggestive of an increased alveolar membrane permeability that is susceptible to bacterial translocation. Changes to the lung microbiome and alveolar-capillary membrane after SCI will be investigated in continuing studies. Additionally, we will verify the presence of ARDS/ALI by characterizing lung inflammation and evaluating interstitial edema. Collectively, this study and future directions will verify the mechanistic link between ARDS/ALI and SCI. This will be used to identify potential therapies to ameliorate respiratory distress and lung injury after SCI.

Disclosures: E.E. Huffman: None. **J.S. Newton:** None. **D.R. Stoltz:** None. **L. Hager:** None. **W.J. Alilain:** None.

Poster

661. Somatosensation: Non-Opioid Treatment of Pain

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 661.01/H28

Topic: D.03. Somatosensation – Pain

Support: USAMRMC Contract W81XWH-17-1-0672

Title: Antinociceptive properties of highly potent and selective state-independent inhibitors of Nav1.7

Authors: *J. T. BECKLEY[1], H. PAJOUHESH[2], G. LUU[2], S. KLAS[1], D. MONTELEONE[2], X. ZHOU[2], A. DELWIG[2], D. C. YEOMANS[3], J. C. HUNTER[2], J. V. MULCAHY[2];
[1]SiteOne Therapeut., Bozeman, MT; [2]SiteOne Therapeut., South San Francisco, CA; [3]Stanford Univ., Stanford, CA

Abstract: The voltage gated sodium channel (Nav) isoform Nav1.7 is highly expressed on dorsal root ganglia neurons that transmit nociceptive signals in response to noxious stimuli. Loss-of-function mutations of Nav1.7 result in congenital insensitivity to pain while gain-of-function mutations are associated with severe, episodic pain disorders. These findings implicate inhibition of Nav1.7 as a strategy for the discovery of novel non-opioid pain therapeutics. By leveraging natural guanidinium toxins as a molecular template, SiteOne Therapeutics has discovered a series of selective, small molecule Nav1.7 inhibitors. The objective of this study was to assess the potency and selectivity of these molecules and to evaluate the analgesic efficacy on a broad panel of animal pain models. Potency and selectivity were determined using whole-cell patch clamp electrophysiology with either stably or transiently transfected cell lines. Analgesic efficacy was assessed with acute pain models that evaluated nociceptive sensitivity to noxious thermal, mechanical, and chemical stimuli, and also with models that generated injury-evoked nociceptive hypersensitivity. Experimental procedures were approved by an Institutional Animal Care and Use Committee in accordance with the NIH Guide for the Care and Use of Laboratory Animals and conducted at an AAALAC-accredited facility. Efforts were taken to minimize pain and distress of animals. We have identified compounds with Kd values for human Nav1.7 that are less than 10 nM, with greater than 1000-fold selectivity over other Nav isoforms tested (Nav1.1-Nav1.8). These compounds were near equipotent on resting/closed and state-dependent protocols, indicating that they are state-independent inhibitors. In mice, compounds administered subcutaneously (SC) produced dose-dependent reductions in sensitivity to noxious thermal, mechanical and chemical stimuli. Naloxone did not reverse Nav1.7 inhibitor mediated antinociception in the thermal plantar test, indicating that analgesic efficacy was independent of mu opioid receptor activation. In a mouse model of incisional pain, SC administration of test compounds both reversed the thermal hypersensitivity in the injured paw and produced analgesia to the thermal stimulus in the non-injured paw. Our results support the hypothesis that targeting the extracellular vestibule of the channel is a viable strategy for selectively engaging Nav1.7 and suggest that state-independent Nav1.7 inhibitors may be efficacious pain therapeutics.

Disclosures: **J.T. Beckley:** A. Employment/Salary (full or part-time):; SiteOne Therapeutics. **H. Pajouhesh:** A. Employment/Salary (full or part-time):; SiteOne Therapeutics. **G. Luu:** A. Employment/Salary (full or part-time):; SiteOne Therapeutics. **S. Klas:** A. Employment/Salary (full or part-time):; SiteOne Therapeutics. **D. Monteleone:** A. Employment/Salary (full or part-time):; SiteOne Therapeutics. **X. Zhou:** A. Employment/Salary (full or part-time):; SiteOne Therapeutics. **A. Delwig:** A. Employment/Salary (full or part-time):; SiteOne Therapeutics. **D.C. Yeomans:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SiteOne Therapeutics. **J.C. Hunter:** A.

Employment/Salary (full or part-time):; SiteOne Therapeutics. **J.V. Mulcahy:** A. Employment/Salary (full or part-time):; SiteOne Therapeutics.

Poster

661. Somatosensation: Non-Opioid Treatment of Pain

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 661.02/H29

Topic: D.03. Somatosensation – Pain

Support: T32 Training Grant T32GM008306-28
Saint Louis University startup funds of Dr. Gina Yosten and Dr. Daniela Salvemini

Title: GPR160 as a novel target for the treatment of chronic neuropathic pain

Authors: *C. M. HARADA[1], Z. CHEN[1], L. A. GIANCOTTI[1], C. HADDOCK[1], T. M. DOYLE[1], G. KOLAR[2], W. K. SAMSON[1], G. L. C. YOSTEN[1], D. SALVEMINI[1];
[1]Pharmacol. and Physiol., [2]Pathology, St. Louis Univ. Sch. of Med., Saint Louis, MO

Abstract: Approximately 100 million American adults suffer from chronic pain that half consider to be uncontrolled. Increased medical costs and lost work amount to roughly $600 billion yearly in the United States alone. Over-the-counter drugs for mild to moderate pain often fail to control chronic pain; patients then turn to prescription drugs like antidepressants and opioids. However, antidepressants and opioids are not always effective and come with the risk of severe side effects. Opioids and other prescription pain killers accounted for 40% of accidental overdose deaths in 2015 and are at the heart of the current epidemic. Our research addresses the clear and urgent need for new non-narcotic treatments for chronic neuropathic pain by identifying a novel target: orphan G-protein coupled receptor GPR160 (**GPR160**). We screened a gene library of orphan G protein-coupled receptors to find a novel target for chronic pain treatment. We found GPR160 mRNA to be upregulated in a rodent chronic constriction injury (**CCI**) model of chronic pain. Previously, GPR160 was only known to be upregulated in certain cancers and in maturation and survival of prostate cancer cells. Our lab then established that attenuation of GPR160 gene and protein prevents and reverses mechanical allodynia in a rodent CCI model of pain. In addition, we have identified the endogenous ligand for GPR160. We found exogenous ligand induces mechanical sensitivity in rodents that is attenuated with GPR160 inhibition. Using this ligand we have discovered that GPR160 activation causes pain in a discrete pathway previously unknown to be related to GPR160 (manuscript in review). Interference in this pathway through the use of select small molecule inhibitors reverses established chronic pain. Moving forward, we are investigating GPR160 signaling in other rodent models of chronic pain. Our data suggests that GPR160 signaling is involved in multiple models of chronic pain, forming a novel and common mechanism. Our work establishes the basis

for further investigation into the development of pharmacological agents targeting GPR160 to treat chronic neuropathic pain.

Disclosures: C.M. Harada: None. **Z. Chen:** None. **L.A. Giancotti:** None. **T.M. Doyle:** None. **W.K. Samson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent submitted by Saint Louis University that covers the intellectual property described in this abstract (WO2017011738). **G.L.C. Yosten:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent submitted by Saint Louis University that covers the intellectual property described in this abstract (WO2017011738). **D. Salvemini:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent submitted by Saint Louis University that covers the intellectual property described in this abstract (WO2017011738).

Poster

661. Somatosensation: Non-Opioid Treatment of Pain

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 661.03/H30

Topic: D.03. Somatosensation – Pain

Support: Fonds de recherche du Québec en nature et technologies (FRQNT) Grant
Canadian Institutes of Health Research (CIHR) Grant

Title: Pepducins derived from the intracellular loops of the neurotensin type 1 receptor relieve pain

Authors: *R. L. BROUILLETTE[1], É. BESSERER-OFFROY[2], C. MONA[3], M. CHARTIER[1], S. LAVENUS[1], J. CÔTÉ[1], M. SOUSBIE[1], K. BELLEVILLE[1], J.-M. LONGPRÉ[1], É. MARSAULT[1], M. GRANDBOIS[1], P. SARRET[1];
[1]Univ. de Sherbrooke, Sherbrooke, QC, Canada; [2]McGill Univ., Montreal, QC, Canada; [3]Univ. of California, Los Angeles (UCLA), Los Angeles, CA

Abstract: In recent years, innovative approaches have been developed to better exploit the therapeutic potential of G protein-coupled receptors (GPCRs), a receptor family which has known remarkable success in drug discovery and development. These approaches include the design of cell-penetrating lipopeptides termed “pepducins” that are composed of a peptide sequence mimicking one of the intracellular loops of a GPCR of interest, conjugated to an N-terminal palmitic acid. The lipid moiety effectively anchors the pepducin to the cell membrane and facilitates its translocation into the cell, where it functionally interacts with its cognate GPCR at the receptor-effector interface. By doing so, pepducins may behave as allosteric

agonists or allosteric modulators of their target receptor. We recently designed a series of pepducins derived from the intracellular domains of the human neurotensin type 1 receptor (hNTS1), a GPCR which mediates many of the physiological effects of the neurotensin (NT) tridecapeptide, including analgesia, hypotension and hypothermia. Here, we report the cellular and physiological actions of this pepducin series. In CHO-K1 cells stably expressing hNTS1, we used BRET-based biosensors to monitor the pepducins' ability to engage G protein-dependent and G protein-independent signaling pathways. We found that our pepducin series preferentially promoted GαoA and Gα13 activation over β-arrestin recruitment, and inhibited NT-mediated β-arrestin recruitment, thus acting both as biased allosteric agonists and negative allosteric modulators of NTS1. Additionally, administration of the ICL1-derived pepducin, PP001, enhanced hNTS1 homomerization in a BRET titration experiment. *In vivo*, we found that i.t. administration (275 nmol/kg) of PP001 significantly reduced the rat nociceptive behaviors in acute (tail-flick), tonic (formalin), and neuropathic (chronic constriction injury) pain models. In contrast, ICL2-, ICL3- and C-terminal tail-derived pepducins did not reduce the pain response. Following i.t. injection, we further found by confocal microscopy that a TAMRA-labeled pepducin could reach the sensory neurons of the dorsal root ganglia. Finally, in order to elucidate which residues are critical for these actions, we synthesized an Ala-scan of PP001, monitored its effects on a CHO-hNTS1 cell monolayer by Electric Cell-substrate Impedance Sensing, and identified a critical ARKK motif. Altogether, our results indicate that our pepducin series modulates NTS1 receptor function and may thus serve to inform the design of novel NT-based analgesics.

Disclosures: R.L. Brouillette: None. **É. Besserer-Offroy:** None. **C. Mona:** None. **M. Chartier:** None. **S. Lavenus:** None. **J. Côté:** None. **M. Sousbie:** None. **K. Belleville:** None. **J. Longpré:** None. **É. Marsault:** None. **M. Grandbois:** None. **P. Sarret:** None.

Poster

661. Somatosensation: Non-Opioid Treatment of Pain

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 661.04/H31

Topic: D.03. Somatosensation – Pain

Support: Startup funds of Dr. Daniela Salvemini
Startup funds of Dr. Gina Yosten
T32 Training Grant GM008306-01

Title: GPR183 as a novel target for the treatment of neuropathic pain

Authors: *K. I. BRADEN, L. A. GIANCOTTI, Z. CHEN, D. SALVEMINI;
Dept. of Pharmacol. and Physiol., St. Louis Univ., Saint Louis, MO

Abstract: Neuropathic pain is a huge unmet medical need. It is estimated that approximately 7-13% of the general population suffers from neuropathic pain. The current treatment options are associated with unacceptable side effects coupled with minimal efficacy, therefore new targets are necessary. Our receptomic and unbiased transcriptomic approaches have identified the G-protein coupled receptor, **GPR183**, as a major GPCR whose transcript is significantly increased in the dorsal horn of the spinal cord ipsilateral to nerve injury in a model of traumatic nerve-injury induced neuropathic pain caused by constriction of the sciatic nerve in rats (CCI). The role of GPR183 signaling in nociceptive processing is not known. GPR183, also known as Epstein-Barr induced gene 2 (EBI2), was recently de-orphanized and its ligand identified as the oxysterol, 7α,25-dihydroxycholesterol (**7α,25-OHC**). GPR183 is expressed in the central nervous system (CNS) on astrocytes and microglia in humans and rodents.
Our findings reveal for the first time that acute intrathecal injection of 7α,25-OHC (23-240nM) in rodents caused a dose-dependent development of mechano-allodynia, that was blocked by pretreatment with an intrathecal injection of the GPR183 antagonist, NIBR189 (23μM), suggesting that GPR183 activation is pronociceptive. Moreover, systemic administration of NIBR189 (10mg/kg) at the time of peak mechano-allodynia after CCI surgery (D7) reversed allodynia in a time-dependent manner. These findings provide the first insight into the role of GPR183 signaling in neuropathic pain, warranting further investigation towards validating this receptor as a potential therapeutic target for the treatment of pain.

Disclosures: K.I. Braden: None. **L.A. Giancotti:** None. **Z. Chen:** None. **D. Salvemini:** None.

Poster

661. Somatosensation: Non-Opioid Treatment of Pain

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 661.05/H32

Topic: D.03. Somatosensation – Pain

Support: NIH Grant DK114546

Title: Frequency-dependent modulation of action potential transmission in afferent axons by DRG stimulation

Authors: *L. CHEN, T. GUO, S. SIRI, B. FENG;
Biomed. Engin., Univ. of Connecticut, Storrs, CT

Abstract: Background: Neuromodulation of dorsal root ganglion (DRG) has emerged as an effective therapy to relieve chronic pain. Compared to spinal cord stimulation that evokes paresthesia to mask the area of pain, effective DRG stimulation causes significantly less area of paresthesia and can even relieve pain in some patients with no appreciable paresthesia. We hypothesize that DRG stimulation can alleviate pain in the absence of paresthesia by blocking

action potential transmission in afferent axons. In this study, we implement ex vivo single-unit recordings from split dorsal root to assess the neuromodulatory effect of DRG stimulation on action potential transmission in mouse afferent axons at different frequencies. Methods: The L6 spinal nerve, DRG and dorsal root were harvested in continuity from male C57BL/6 mice (8-12 weeks, 25-35 g) and transferred to a tissue chamber flowed with oxygenated Krebs solution at 30°C. The L6 dorsal root was gently pulled into an adjacent recording chamber filled with mineral oil and carefully split into fine filaments (~ 10 μm) to record single-unit action potentials evoked by electrical stimulation of the L6 spinal nerve (0.5 Hz, 0.2 msec pulse width, cathodic 0.2-2 mA) via a suction electrode. A needle electrode (FHC, platinum-iridium, tip size ~Φ10 μm) contacting the dura mater of L6 DRG was used to deliver neuromodulatory stimuli (bipolar stimulation, cathodic first, constant current, 0.1 msec pulse width) to assess the effect of DRG stimulation on action potential transmission in afferent axons at a wide range of frequencies (10, 50, 100, 500, 1000 Hz). Data were digitized at 24 kHz, stored using a Tucker-Davis Technologies system (RZ5D, PZ5-32) and processed offline with customized programs (Mathworks R2018a). Results: The optimal frequency to achieve transmission block with the least stimulation duration is within 50 to 500 Hz for all tested afferents. Our preliminary data indicate the optimal frequency of 50 Hz to block unmyelinated C-fibers and 100-500 Hz to block thinly myelinated Aδ-fibers. Interestingly, DRG stimulations with frequency below or above the optimal range require longer duration to achieve transmission block, and the highest frequency tested (1000 Hz) can fail to block action potential transmission in some afferents. Conclusion: This study reveals the frequency-dependent blocking of action potential transmission in mouse L6 afferent axons by DRG stimulation. Outcomes of this study strongly suggest the therapeutic potential of DRG stimulation at optimal frequency range to attenuate nociceptive pain by blocking the neural transmission of sensitized afferents.

Disclosures: L. Chen: None. **T. Guo:** None. **S. Siri:** None. **B. Feng:** None.

Poster

661. Somatosensation: Non-Opioid Treatment of Pain

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 661.06/DP05/H33

ControlExtraData.DynamicPosterDisplay:
Dynamic Poster
Topic: D.03. Somatosensation – Pain

Title: The effect of music on the pain of adults in the intensive care unit: A systematic review of randomized controlled trials

Authors: *M. RICHARD-LALONDE[1], C. GÉLINAS[1,2], M. BOITOR[1], E. GOSSELIN[1], N. FEELEY[1,2], S. COSSETTE[3], L. L. CHLAN[4];

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Abstract: Introduction. Pain is prevalent in the adult intensive care unit (ICU), where clinical guidelines recommend using multimodal analgesic approaches. Music has been shown to reduce pain in other clinical settings. However, the effectiveness of music interventions on pain reduction in the adult ICU remains unknown. The objective was to determine the immediate [MRL1] effects of single-session music interventions on pain in the adult ICU, compared with standard care or noise reduction. Secondary objectives were to conduct subgroup analyses based on music intervention duration, music choice, timing, and provider. **Methods**. The protocol for this review was registered on PROSPERO (CRD42018106889). Medical (e.g. Medline, Cochrane) and music (e.g. Music Index, ViFaMusik) databases were searched for randomized controlled trials (RCTs) on music use in the adult ICU setting with the search terms [“music*” and (“critical care” or “intensive care”)]. Outcomes of pain were included for patients able to self-report (0-10 or 0-100 rating scales) and for patients unable to self-report (0-8 Critical-Care Pain Observation Tool or 3-12 Behavioral Pain Scale). Each study was reviewed by two independent reviewers for screening and data extraction. **Results**. Eighteen RCTs were found. Sample sizes ranged from 17 to 156 and included 1173 participants. The mean age of participants was 60 years old with 60% males and 40% females. Most RCTs included patients able to self-report (83%, n=978/1173). Studies with high risk of bias for randomization, allocation concealment and incomplete data were then excluded, leaving 10 studies to be included in the meta-analysis with a total of 706 participants, with a mean age of 55.9 years, 48.7% male and 51.3% female, all able to self-report. Music was found to be significantly effective in pain intensity reduction, with a standardized mean difference (SMD) of -0.78 [95% confidence interval (CI) -1.48, 0.09] when compared to standard care and a SMD of -0.51 [-1.12, 0.09] when compared to noise reduction. Duration was found to impact effectiveness of the music with interventions of a minimal duration of 20 min leading to a larger decrease in self-reported pain intensity. Subgroup analyses revealed that, compared to standard care 20-30 min of music significantly reduced self-reported pain intensity (SMD -1.07 [-1.63, -0.52]); and compared to noise reduction, 20-30 mins of music significantly reduced self-reported pain intensity (SMD -0.80 [95% CI -1.06, -0.55]). **Conclusion**. In the adult ICU, music interventions of a minimal duration of 20 minutes are effective to reduce pain.

Disclosures: M. Richard-Lalonde: None. **C. Gélinas:** None. **M. Boitor:** None. **E. Gosselin:** None. **N. Feeley:** None. **S. Cossette:** None. **L.L. Chlan:** A. Employment/Salary (full or part-time):; Grant funding from the National Institutes of Health.

Poster

661. Somatosensation: Non-Opioid Treatment of Pain

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 661.07/H34

Topic: D.03. Somatosensation – Pain

Support: Texas Tech University HSC Start-up funds

Title: Development of selective kappa opioid receptor antagonists for the treatment of chronic neuropathic pain

Authors: *M. HOSSAIN[1], G. JI[2,3], T. J. ABBRUSCATO[1], V. NEUGEBAUER[2,3,4], N. A. GERMAN[1,3];
[1]Pharmaceut. Sci., Texas Tech. Univ. Hlth. Sci. Ctr., Amarillo, TX; [2]Dept. of Neurosci., [3]Ctr. of Excellence for Translational Neurosci. and Therapeut. (CTNT), [4]Garrison Inst. on Aging, Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX

Abstract: Kappa opioid receptor (KOR) plays a vital role in neurological conditions including physiological functions and pathological disorders. KOR agonists modulate analgesia, diuresis, dysphoria, and show antipruritic activity. In addition, KOR antagonists can alleviate many CNS-related conditions, such as chronic pain, cocaine addiction, depression, psychosis, and schizophrenia. There is a need for the development of selective KOR antagonists. We identified a novel highly selective KOR antagonist with a *Ki* of 277 nM. This compound has shown excellent ability to cross the BBB *in vitro* (Papp 15.15) and *in vivo*. This compound is pharmacologically active in the well-established spinal nerve ligation (SNL) model of neuropathic pain in rats. In this experiment, a 40 - 50% reduction in pain-related behaviors was observed, using different outcome measures such as mechanical and thermal sensory thresholds (von Frey filaments and the tail-flick tests), audible and ultrasonic vocalizations. Here we report results from our ongoing work focused on the optimization of potency and drug-like profile of this hit molecule using a variety of medicinal chemistry approaches. Activity data of the proposed library of compounds are combined with the known crystal structure of the human KOR and used to build a comparative molecular field analysis (CoMFA) to enable in silico drug design. A variety of *in vitro* biological assays provide target validation and elucidate toxicity profiles of selected compounds. Overall, we report the development of a new class of highly selective kappa-opioid receptor antagonists with therapeutic potential for the treatment of neuropathic pain.

Disclosures: M. Hossain: None. **G. Ji:** None. **T.J. Abbruscato:** None. **V. Neugebauer:** None. **N.A. German:** None.

Poster

661. Somatosensation: Non-Opioid Treatment of Pain

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 661.08/H35

Topic: D.03. Somatosensation – Pain

Support: New York State Spinal Cord Injury Research Board (SCIRB)
Merit Review Funding from the Department of Veterans Affairs
Craig H. Neilsen Foundation

Title: Spinal electromagnetic stimulation results in immediate pain reduction and induces long-lasting functional improvements in patients with chronic low back pain (LBP). A pilot study

Authors: *H. PETROSYAN[1,2], M. FAHMY[2], A. TESFA[2], L. LIANG[2,1], V. ARVANIAN[2,1]; [1]Neurobio. and Behavior, Stony Brook Univ., Stony Brook, NY; [2]Northport VAMC, Northport, NY

Abstract: Chronic LBP is one of the main causes of disability affecting general population. About 80 percent of adults experience low back pain at some point in their lifetime. Opioids is the most common prescription drug in US adults with chronic LBP. Many alternative treatments currently used in clinics, including medication, acupuncture, physical therapy, electrical nerve stimulation and even surgery. However, there is no effective treatment available. In this study we have examined the effects of non-invasive electromagnetic stimulation (EMS) applied at lumbosacral level on pain reduction in patients suffering from chronic LBP. EMS is a non-invasive painless method of stimulating central and peripheral nervous systems. EMS is based on the principle of electromagnetic induction of an electric field through intact tissue to underlying structures. Repetitive EMS applied at cranial level (TMS) was found to alter excitability at cortico-motor circuitry and currently is an FDA approved treatment for drug resistant depression. We recently found that low frequency (0.2 Hz) EMS over the spinal cord induced neuromodulation of H-reflex responses, i.e. decrease in threshold intensity and facilitation of H-responses in chronic spinal cord injured rats. Importantly, in healthy human participants EMS applied at 0.2 Hz on L4-S1 spinal levels induced similar neuromodulation of H-reflex responses, i.e. leftward shift in threshold intensity and facilitation of H-responses. In animal models, in contrast with low frequency EMS, administration of high frequency (20Hz) EMS induced significant reduction of H-reflex amplitude and rightward shift of threshold intensities. In this study we have examined how, high frequency 20Hz spinal EMS is affecting humans suffering from chronic low back pain. The patients received up to 10 sessions of spinal EMS administered every other day. During each session participants received total 4000 pulses containing of 5 seconds of stimulation administered at 20Hz with 25 seconds break between. Pain was evaluated before and after each session using Visual Analog Scale (VAS) as well as Oswestry Disability

Index (ODI) was used to assess effects of treatment on functional changes. Our results revealed that spinal EMS resulted in immediate significant pain reduction at each session. Importantly, as the study progressed, prolonged administration of EMS resulted in overall sustained pain relief. These results demonstrate that SEMS can serve as an effective, non-invasive treatment approach for chronic low back pain. Further animal studies are required to examine mechanisms underlying these effects and are currently being conducted in our lab

Disclosures: H. Petrosyan: None. **M. Fahmy:** None. **A. Tesfa:** None. **L. Liang:** None. **V. Arvanian:** None.

Poster

661. Somatosensation: Non-Opioid Treatment of Pain

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 661.09/H36

Topic: D.03. Somatosensation – Pain

Support: Canadian Institutes of Health Research – Foundation Grant #35364

Title: Development of a NTS2-selective macrocyclic neurotensin (8-13) analog showing a good analgesic benefit/adverse effect profile

Authors: *M. CHARTIER, M. DESGAGNÉ, L. HAROUNE, M.-A. DANSEREAU, J.-M. LONGPRÉ, E. MARSAULT, P. SARRET;
Inst. De Pharmacologie - Univ. De Sherbrooke, Sherbrooke, QC, Canada

Abstract: Neurotensin (NT), which acts as a neuromodulator in the central nervous system produces potent opioid-independent analgesia. These NT's antinociceptive effects are exerted through activation of two NT receptor subtypes (NTS1 and NTS2), that belong to the class A GPCR family. NT is also responsible for other physiological effects, such as hypotension and hypothermia which are exclusively related to NTS1 activation. NTS2 is therefore a target of interest for developing new chemical entities showing good analgesic activity with minimal adverse effects. In addition, as a peptide, NT exhibits low oral bioavailability and poor resistance to proteolytic degradation which further limit its therapeutic use. Herein, Tyr^{11} was replaced by a Trp of NT(8-13), and a side-chain to side-chain macrocyclization was used to constrain the peptide conformation and improve its biological and metabolic properties. This study was thus aimed to characterize the antinociceptive activities of this macrocyclic NTS2-selective analog and to investigate its potential adverse effects. This macrocyclic NT analog exhibits 7.5 nM binding affinity for NTS2, with approximately 110 times lower affinity for NTS1 (871 nM), as well as an improved plasma stability profile (&gt24h) compared to NT (≈ 2 min). Analgesic efficacy was determined in rat pain models following intrathecal administration of escalating doses of the macrocyclic analog (ranging from 3 to 60 µg/kg). This constrained peptide

displayed dose-dependent and long-lasting analgesic effects in acute (ED50 = 17.69 µg/kg) and tonic pain (ED50 = 8.75 µg/kg), as assessed by the thermal tail-flick test and the formalin persistent pain model, respectively. The maximal possible effect in acute pain reached 100% with the highest dose tested. This NTS2-preferring analog also exhibited a potent mechanical antiallodynic effect at 60 µg/kg on days 7 and 14 in the CFA-induced chronic inflammatory pain model. Potential NT's adverse effects were also monitored by measuring changes in body temperature (60 µg/kg, i.t.), mean arterial blood pressure (0.01 and 0.1 mg/kg, i.v.) as well as smooth muscle contraction of isolated rat ileum (10^{-11} to 10^{-5}M). Our results revealed that this compound did not cause hypothermia or ileum relaxation but induced slight and short-lasting hypotension. Altogether, this NTS2-selective compound was found to be effective in reversing the nociceptive behaviors in three distinct rodent pain models without having serious adverse effects. These results thus highlight the strong therapeutic potential of NTS2-selective analogs for the management of chronic pain.

Disclosures: **M. Chartier:** None. **M. Desgagné:** None. **L. Haroune:** None. **M. Dansereau:** None. **J. Longpré:** None. **E. Marsault:** None. **P. Sarret:** None.

Poster

661. Somatosensation: Non-Opioid Treatment of Pain

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 661.10/H37

Topic: D.03. Somatosensation – Pain

Title: Efficacy of tramadol is lost in the late phase of the MIA-induced OA joint pain model in rat

Authors: H. RASHID, *J. DOUVILLE, R. SAMADFAM;
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Abstract: The atypical centrally acting analgesic tramadol is used for a variety of chronic pain conditions including chronic osteoarthritic (OA) joint and musculoskeletal pain. Tramadol is known to act through its weak opioid and monoaminergic mechanisms, and fewer side effects are reported than with traditional opioids. In the present study, we examined if efficacy of tramadol is maintained in the mono sodium iodoacetate (MIA)-induced OA joint pain model in rat when used over a longer duration, specifically in the NSAID-refractory late phase of the model. Joint pain was induced in rats by a single intra-articular injection of MIA (3 mg) into the right knee joint. Weight bearing deficit of the MIA-injected limb was then measured as an indication of joint pain using the Automated Dynamic Weight Bearing (ADWB) system. Tramadol was administered orally at 60 mg/kg in two different dosing protocols. In the first protocol, rats received tramadol twice daily continuously from Day 14 to Day 28 post model induction which is considered as the late phase of the MIA model. In the second protocol,

tramadol was administered only before each ADWB test (3 dosing over 2 days). Weight bearing assessments post tramadol dosing were performed on Days 15, 18, 21 and 28. ADWB data were analyzed off-line using the BioSeb software. A single intra-articular injection of MIA caused a significant reduction in weight bearing by the ipsilateral limb indicating presence of joint pain. The window of weight bearing deficit in the MIA rats was maintained during the assessment period of Day 14 to 28. In the first protocol when tramadol was continuously dosed from Day 14 to 28, moderate and significant relief of joint pain was observed on Day 15 only. Analgesic effects then gradually decreased over time and no significant effects were observed on Days 18, 21 and 28. In the second protocol, we wanted to examine whether loss of efficacy of tramadol was due to an apparent tolerance associated with the continuous dosing regimen, therefore effects of tramadol were assessed following dosing only before each ADWB test occasion. In this second protocol, tramadol produced moderate and significant effects on Day 15, and some minor but statistically significant effect was also observed on Day 18 while no effects were seen on Days 21 and 28. Overall, both dosing regimen of tramadol were not able to significantly change the MIA late phase pain response. This might be mainly due to the model's inherent characteristics of gradual joint deterioration and nature of pain in this late phase. These results also suggest that a minor role of tolerance by tramadol may also contribute to the efficacy loss.

Disclosures: H. Rashid: None. **J. Douville:** None. **R. Samadfam:** None.

Poster

661. Somatosensation: Non-Opioid Treatment of Pain

Location: Hall A

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Program #/Poster #: 661.11/H38

Topic: D.03. Somatosensation – Pain

Support: NIH R01MH084894
NIH R01MH111940

Title: Role of 5-HT_{2A} receptor in potentiation of oxycodone antinociception

Authors: S. SIERRA[1], X. CUNO LAVILLA[1], D. STEVENS[2], K. CONTRERAS[2], M. DAMAJ[2], W. DEWEY[2], J. GONZALEZ-MAESO[1];
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Abstract: Although opioid analgesics can rapidly relieve pain, their chronic use presents serious side effects including opioid overdose and addiction. Serotonin receptors, including the 5-HT_{2A}R, have been involved in a number of processes related to nociception. However, the antinociceptive effects induced by 5-HT_{2A}R receptor ligands and the neural circuits related to 5-HT_{2A}R-dependent pain management remain largely unexplored. Here we characterized the

neuroanatomical localization of 5-HT_{2A}R in the tail-flick reflex (TFR) circuit, and tested the effects of the 5-HT_{2A}R antagonist volinanserin (or M100,907) on antinociceptive, exploratory and rewarding behavioral phenotypes induced by the μ-opioid receptor agonist oxycodone. To do so, we first performed immunostaining in mouse dorsal root ganglion (DRG) and lumbar spinal cord. Hot water immersion test was carried out in adult C57BL/6 male mice. Animals were pretreated (i.p.) with volinanserin (0.03, 0.06 or 0.125 mg/kg), or vehicle, after which animals received cumulative doses (p.o.) of the μ-opioid receptor agonist oxycodone (0.25 to 32.0 mg) or the CB_1R/CB_2R agonist CP55,490, or vehicle. For locomotor activity and conditioned place preference (CPP) tests, mice were pretreated with volinanserin after which animals received a single dose of oxycodone. Our immunostaining experiments show that 5-HT_{2A}R is present in the DRG and ventral horn neurons of the spinal cord. Behavior assays suggest that volinanserin increases the antinociceptive effects of oxycodone, but not of CP55,490 in male mice. Additionally, volinanserin significantly decreases the hyperlocomotor activity induced by oxycodone whereas in the CPP test this 5-HT_{2A}R antagonist does not potentiate rewarding effects of oxycodone. Overall, these results suggest that 5-HT_{2A}R antagonism represents a novel and highly selective opioid-sparing pharmacological tool to reduce nociception in mice.

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Poster

661. Somatosensation: Non-Opioid Treatment of Pain

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Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 661.12/H39

Topic: D.03. Somatosensation – Pain

Support: NIH Grant DA041467
NIH Grant NS095057

Title: Sex differences in THC-induced recovery of activity in rats with hindpaw inflammation

Authors: A. WILSON-POE, ***A. A. BARADAR**, J. STICKNEY, M. M. MORGAN; Washington State Univ. Vancouver, Vancouver, WA

Abstract: The current opioid abuse crisis highlights the need for alternative pain medications. Cannabis has been proposed as a less addictive pain treatment, but cannabis is composed of many psychoactive substances and the effects on different pain conditions are not clear. Tetrahydrocannabinol (THC), the primary psychotropic substance in cannabis, has been shown to inhibit inflammatory pain in laboratory animals, but the high doses used in previous studies (e.g., 3.2 mg/kg) impair motor function thereby confounding assessment of nociception. The objective of the present study was to determine the ability of low doses of THC to restore

activity depressed by persistent inflammatory pain. Male and female Long-Evans rats were housed individually in a cage with a running wheel. Baseline activity was assessed on the seventh day in this cage. Hindpaw inflammation was induced immediately before the dark phase on Day 8 by injecting Complete Freund's Adjuvant (CFA) into the right hindpaw. Rats were injected with vehicle or THC (0.32, 0.56, or 1.0 mg/kg, s.c.) 48 hours after CFA injection. Administration of CFA into the hindpaw caused an almost complete depression of wheel running in both male and female rats. THC administration 48 hours later caused a transient recovery of wheel running that differed in female and male rats. In female rats, all three doses of THC caused a recovery in wheel running that exceeded baseline running and lasted approximately 1 hour. The lowest THC dose (0.32 mg/kg) caused the greatest recovery in wheel running. THC had almost no effect in male rats, although administration of the highest THC dose (1 mg/kg) caused a slight increase in wheel running (40% of baseline running levels). These data confirm in Long-Evans rats our previous data showing CFA-induced depression of wheel running in Sprague Dawley rats (Kandasamy et al., 2016). These data also confirm previous reports of greater antinociceptive effects of THC in female compared to male rats (Craft et al., 2012), but at much lower doses. THC-induced recovery of wheel running reveals that low doses of THC can produce antinociception in the absence of disruptive side effects.

Disclosures: A. Wilson-Poe: None. **A.A. Baradar:** None. **J. Stickney:** None. **M.M. Morgan:** None.

Poster

661. Somatosensation: Non-Opioid Treatment of Pain

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 661.13/H40

Topic: D.03. Somatosensation – Pain

Support: Italian Foundation for Multiple Sclerosis 2014/R/6
Fondazione CR Firenze under IG 2017 - ID. 20451 project

Title: Dexpramipexole blocks $Na_v1.8$ sodium channels and affords analgesia in multiple nociceptive and neuropathic pain models

Authors: *M. URRU[1], M. MUZZI[1], E. COPPI[2], G. RANIERI[1], D. BUONVICINO[1], E. CAMAIONI[3], A. PUGLIESE[2], B. S. TANAKA[4], M. ESTACION[4], S. G. WAXMAN[4], S. D. DIB-HAJJ[4], A. CHIARUGI[1];
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Abstract: Pain control is a vast, unmet medical need with a high societal cost impact. Current treatments (opioids, NSAIDs, antidepressants or anticonvulsants) are frequently inadequate or associated with adverse side effects. Voltage-gated sodium channels (Na_v) are crucial mediators of nociceptive transmission. Among these channels, the $Na_v1.8$ isoform is predominantly expressed in dorsal root ganglion neurons (DRG), a critical hub of nociceptive transmission. Dexpramipexole (DEX) is the R-isomer of the antiparkinson drug pramipexole. DEX recently failed a large phase III study in ALS patients, however, shows a favorable safety profile. Prior work from our group shows that DEX reduces I_A K^+ currents in rat hippocampal neurons. Here, we investigated the effect of DEX on sodium currents (I_{Na}) in rodent DRG neurons, as well as on pain-related behavior in different experimental models.
Patch clamp experiments demonstrated that DEX inhibits I_{Na} currents in a reversible manner with a IC_{50} of 294.4 nM. Inhibition appears selective for the Nav1.8 isoform, being absent in Nav1.8-null DRG neurons. Accordingly, DEX affords analgesia in nociceptive (formalin, writhing, inflammatory) and neuropathic (oxaliplatin, nerve ligation, diabetes) when administered at clinically-consistent doses (3 or 10 mg/kg) by means of i.p., oral or topical routes.
In light of the good safety profile of DEX in humans, our data point to a realistic translational potential of DEX for the treatment of different pain disorders.

Disclosures: M. Urru: None. **M. Muzzi:** None. **E. Coppi:** None. **G. Ranieri:** None. **D. Buonvicino:** None. **E. Camaioni:** None. **A. Pugliese:** None. **B.S. Tanaka:** None. **M. Estacion:** None. **S.G. Waxman:** None. **S.D. Dib-Hajj:** None. **A. Chiarugi:** None.

Poster

661. Somatosensation: Non-Opioid Treatment of Pain

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 661.14/H41

Topic: D.03. Somatosensation – Pain

Title: Potent analgesic activity of the novel M1/M4-selective muscarinic agonist NSX-0527

Authors: *J. OCKULY, J. BECK, S. HANSON, M. HENDRICKSON;
NeuroSolis, Inc., Madison, WI

Abstract: Despite many years of reluctance, the “opioid epidemic” has lately risen to the level of a national emergency in the public’s awareness. Medical treatments for both acute and chronic pain have relied heavily on morphine and morphine derivatives for centuries, along with the tacit acknowledgement that these compounds have an extremely heavy potential for addiction and subsequent abuse. The neurological expiation of opiate addiction can be summarized briefly as a disinhibition of dopaminergic pathways within structures of the basal ganglia associated with reward-seeking behavior and emotion. Novel analgesic drugs that bypass the dopaminergic

system are in higher demand than ever before. Muscarinic agonists are a class of compounds demonstrating clear analgesic activity, likely acting via stimulation of GABAergic interneurones within the brain and spinal cord, but previous attempts to develop drug candidates (e.g. xanomeline) have been abandoned due to poor tolerability. The novel M1/M4-selective orthosteric muscarinic agonist NSX-0527 and close-in analogue NSX-0559 were evaluated to determine their feasibility as analgesic drug candidates. Both compounds show good bioavailability (~75%) and brain penetration (~60%) along with excellent metabolic stability. In the tail-flick assay, they were more potent than morphine and xanomeline at inhibiting a spinally-mediated reflex response to a painful stimulus. Additionally, NSX-0559 was shown to have no activity at dopaminergic receptors - in fact, its efficacy is exclusively limited to muscarinic receptors, making potential side-effects predictable and manageable. In summary, NSX-0527 and NSX-0559 represent potential first-in-class antinociceptive treatments that are efficacious, well tolerated, and critically lack the capacity for addiction and abuse.

Disclosures: **J. Ockuly:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NeuroSolis, Inc. **J. Beck:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NeuroSolis, Inc. **S. Hanson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NeuroSolis, Inc. **M. Hendrickson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NeuroSolis, Inc..

Poster

661. Somatosensation: Non-Opioid Treatment of Pain

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 661.15/H42

Topic: D.03. Somatosensation – Pain

Support: NIH/NIDCR R01DE025393

Title: Non-viral delivery of OPRM1 gene and F2RL1 RNAi for oral cancer pain

Authors: ***K. INOUE**[1], N. H. TU[1], J. DOLAN[2], K. IMAMURA[4], S. YAMANO[3], B. L. SCHMIDT[1];
[1]Bluestone Ctr. for Clin. Res., [3]Dept. of Prosthodontics, [2]New York University, Col. of Dent., New York, NY; [4]Dept. of Periodontology, Tokyo Dent. Col., Tokyo, Japan

Abstract: Oral cancer patients often suffer from severe function-induced pain during eating, drinking and speaking. Quality of life is severely degraded in these patients. The intensity and prevalence of pain is generally higher in patients with oral cancer than in patients with other

types of cancer. We seek to eliminate oral cancer pain by reversing epigenetic changes with gene therapy. Our work will set the stage for a new class of drugs that selectively disrupt nociceptive signaling with limited side effects. Viral vector-based treatment of cancer pain has been evaluated in preclinical studies but is plagued by problems with immune response, limited DNA carrying capacity, and high cost. Synthetic, non-viral vectors might preclude these obstacles. To improve non-viral gene transfer efficiency, we developed a novel non-viral hybrid vector - a cell-permeable peptide combined with a cationic lipids.
OPRM1 gene encodes the μ-opioid receptor and is methylated and transcriptionally silenced in human oral squamous cell carcinoma. F2RL1 gene encodes protease-activated receptor 2 (PAR2). PAR2 belongs to the G-protein-coupled receptor family and is expressed in many cancer types. PAR2 is associated with tumor progression, production of pro-tumor cytokines and pain. The aim of this study was to attenuate oral cancer pain with OPRM1 gene and F2RL1 RNAi delivered with a non-viral vector.
We evaluated the efficacy of non-viral gene therapy (F2RL1 and RNAi) in an oral cancer mouse model generated with the carcinogen 4-NQO. We employed a dolognawmeter assay as well as hind paw withdrawal and thermal hyperalgesia assays to determine whether the gene therapy, (OPRM1 gene expression and F2RL1 gene suppression) produced anti-nociceptive effects. Our *in vitro* work revealed that F2RL1 was knocked down in HSC-3 cells and that mouse TG cells decreased F2RL1 gene expression. Cell proliferation of HSC-3 cells was also inhibited. Our *in vivo* work revealed that the mice with tongue tumors treated with F2RL1 RNAi exhibited decreased gnaw time in the dolognawmeter compared to random RNAi (indicating less nociception after treatment). In addition, mice treated with F2RL1 RNAi with and without OPRM1 gene exhibited higher mechanical and thermal thresholds.
We infer from our findings that non-viral delivery of the OPRM1 gene and F2RL1 RNAi targeted to the cancer microenvironment produce an analgesic effect. Accordingly, we assert that non-viral gene delivery holds potential for cancer pain treatment.

Disclosures: K. Inoue: None. **N.H. Tu:** None. **J. Dolan:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Author John C. Dolan fabricates dolognawmeter assays for profit as the single-member limited liability company Gnatheon Scientific.. **K. Imamura:** None. **S. Yamano:** None. **B.L. Schmidt:** None.

Poster

661. Somatosensation: Non-Opioid Treatment of Pain

Location: Hall A

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Program #/Poster #: 661.16/H43

Topic: D.03. Somatosensation – Pain

Support: NIH Grant 5R01DA035931-02

Title: Prevention of opioid-self administration by agmatine-based analogues

Authors: *C. PETERSON[1], K. PFLEPSEN[1], K. KITTO[1], G. L. WILCOX[2], C. A. FAIRBANKS[3];
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Abstract: B**ackground:** Chronic pain is a broadly experienced, debilitating condition that is a heightened health concern due to the concurrent pain and opioid epidemics. The currently available options for the treatment and management of chronic pain, opioids, are associated with risk of conversion to addiction and diversion from patients for whom use is intended. To this end, we have studied inhibition of the glutamatergic system, shown to play a central role in opioid addiction, to inhibit the development of opioid-seeking behavior in a rodent model of drug-seeking behavior. A decarboxylated form of L-arginine, agmatine, is able to prevent the development of fentanyl-seeking behavior in a model of mouse self-administration likely through its role as an N-methyl-D-aspartate antagonist. However, agmatine has shown limited penetration through the blood brain barrier (BBB) and a short systemic half-life, necessitating the need for central delivery. We have designed a strategically-substituted agmatine compound with the goal of improving its penetration through the BBB and increasing its half-life following systemic delivery in order to make it a more viable potential therapeutic for the treatment of opioid use disorders (OUD). **Methods: Prevention of Opioid Self-Administration** Mice (F, 21-30g) were given access to operant chambers and allowed to press either for oral oxycodone reward or an inactive control. Daily, the mice were given either a pre-treatment of a strategically-substituted agmatine (SSA) compound or vehicle control, i.p.. Daily lever-pressing was recorded as an indication of drug-seeking behavior. Additionally, this same cohort was allowed to lever press for food pellet reward following conclusion of oxycodone reinforcement. Area under the curve (AUC) was compared between SSA pre-treated and vehicle pre-treated groups.
Results: Pre-treatment with the strategically-substituted agmatine compound significantly decreased oxycodone seeking behavior, but had no impact on food-maintained responding. Additionally, the strategically-substituted agmatine compound showed no impact on motor coordination or cardiovascular function.
Conclusion: These data indicate that a strategically-substituted agmatine compound is capable of significantly reducing opioid-seeking behavior with a wide therapeutic window, avoiding the motor impairment and cardiovascular impairment typical of drugs of this class. Our future work includes optimization of dosing regimen as well as modeling the prevention of opioid relapse.

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Poster

661. Somatosensation: Non-Opioid Treatment of Pain

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 661.17/H44

Topic: D.03. Somatosensation – Pain

Title: Virtual embodiment treats chronic pain and improves function

Authors: A. F. ALVAREZ, J. PETROS, L. NGUYEN, *M. S. TRUJILLO;
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Abstract: Chronic pain is a major healthcare burden and is associated with depression, anxiety, functional impairment, and a significant burden on quality of life and productivity. Persistent pain is difficult to treat, and opioids are commonly prescribed despite the potential for misuse, abuse, and accidental overdose. There is an apparent need for non-addictive, non-invasive, non-pharmacological treatments for chronic pain. Rapid advancements in virtual reality (VR) technology has led to innovative therapeutic approaches for treating ailments such as anxiety, phobias, and post-traumatic stress disorder. VR has also been demonstrated to provide powerful analgesic effects and may be an effective tool for treating chronic pain. At Karuna Labs, we have developed a novel VR platform that combines virtual embodiment therapy (VET™) with graded motor imagery techniques to treat chronic pain. In virtual embodiment, the user experience can be manipulated and adjusted to modify how users interact with a virtual environment. Mirroring of movement where a contralateral limb is shown moving in VR space and augmentation where movement is overstated or understated are used to re-normalize maladaptive associations between movement and pain. A feasibility study on 24 chronic pain patients demonstrated that VET™ significantly reduced the intensity of perceived pain (as measured by paired t-test ($P < 0.05$) on subjective pain questionnaires) and patients who rated their pain as most severe saw the greatest improvement. Furthermore, this study demonstrated that VET™ has significant positive effects on alleviating pain as measured by a modified visual analog scale (paired t-test before and after each session ($P < 0.001$)). The current study expanded preliminary results to assess the ability of VET™ to treat generalized shoulder pain. We measured functional progress using a novel kinematic analysis tool that extracted features from movement within VET™ and tracked progress over the course of 8 sessions of VET™. This study demonstrated the potential of Karuna VET™ to serve as a digital function rehabilitation program that compliments current standards of care in treating chronic pain and improving function.

Disclosures: **A.F. Alvarez:** A. Employment/Salary (full or part-time):; Karuna Labs. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Karuna Labs. **J. Petros:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding

diversified mutual funds); Karuna Labs. **L. Nguyen:** A. Employment/Salary (full or part-time):; Karuna Labs. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Karuna Labs. **M.S. Trujillo:** A. Employment/Salary (full or part-time):; Karuna Labs. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Karuna Labs.

Poster

661. Somatosensation: Non-Opioid Treatment of Pain

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 661.18/H45

Topic: D.03. Somatosensation – Pain

Support: NIH NIDCR R21 DE028096

Title: Therapeutic scFv antibody for the treatment of neuropathic pain and anxiety

Authors: *A. KUNAMNENI[1], M. MONTERA[2], K. GOTT[2], M. KUO[1], N. SURI[1], R. DURVASULA[1], K. WESTLUND[2];
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Abstract: Development of effective non-opioid therapeutics tailored to specific chronic pain syndromes is sorely needed. Our recent microchip gene expression profile identified upregulated cholecystokinin B (CCK-B) receptor in trigeminal ganglia (TG) as one suitable target among many others. Thus, the CCK-B receptor is an ideal candidate to impact both nociceptive and limbic components of *chronic* pain. More importantly, its inhibition can reverse opiate tolerance. Based on the literature and the gene expression changes over time, the CCK-B receptor is implicated as one of the persisting functional targets suitable for development of therapeutics to inhibit *chronic* pain- and anxiety-related behaviors. Here we describe the isolation and characterization of a panel of CCK-B receptor specific single-chain fragment variable (scFv) antibodies using ribosome display technology. Furthermore, we demonstrate *in vivo* efficacy of our antibodies in a relevant model of established neuropathic pain. The CCK-B receptor scFv antibody administered 3 weeks after trigeminal nerve constriction model induction effectively reduced CCKB receptor RNA, as well as pain, anxiety, and depression related behaviors. This is the first example, to date, of scFv antibodies that can block the CCK-B receptor directly with high potency and specificity. This highlights the exciting potential therapeutic opportunity of a brain penetrant antibody for blocking this G protein coupled type of receptor.

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Poster

661. Somatosensation: Non-Opioid Treatment of Pain

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 661.19/H46

Topic: D.03. Somatosensation – Pain

Title: Antiallodynic effects of abobotulinumtoxinA (Dysport) in a rat model of MRMT-1-induced bone cancer pain

Authors: V. MAFFRE[1], C. FAVRE-GUILMARD[2], ***M. KALINICHEV**[2], Y. DARBAKY[1], L. DIOP[1];
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Abstract: A significant proportion of patients with advanced breast, prostate or lung cancer develop skeletal metastasis and suffer from bone cancer pain. The MRMT-1 mammary carcinoma model of bone cancer in rats mimics aspects of the clinical pathogenesis and symptoms, including chronic pain and can be used for evaluation of the efficacy of novel analgesic medication (Medhurst et al. 2002). There is growing clinical and preclinical evidence that in addition to well-characterized muscle-relaxant properties, AbobotulinumtoxinA (AboBoNT-A; Dysport) can reduce different types of pain. The objective of this study was to assess the antiallodynic effect of intra-plantar administrations of AboBoNT-A in the model of MRMT-1-induced bone cancer pain in rats. **Methods:** Adult, male, Sprague-Dawley rats were anesthetized before receiving inoculation of 3.10^4 MRMT-1 mammary carcinoma cells into the medullary cavity of the tibial bone or receiving a sham-operation. On day 11 after cancer cell inoculation, animals received an acute, intraplantar administration of AboBoNT-A (10, 20, 40 U/kg) or vehicle (saline; n=10/group). The tactile sensitivity of both hind paws was measured on day 11 before AboBoNT-A treatment (Baseline) and on days 14, 18 and 21 post inoculation corresponding to days 3, 7 and 10 post-Dysport injection using electronic Von Frey test. **Results:** MRMT-1 cancer cells induced, from 11 days to 21 days after inoculation into the medullary cavity of the tibia, a reduced and stable paw withdrawal threshold in the vehicle-treated group. A single intraplantar administration of AboBoNT-A (5, 10, 20 and 40 U/kg) produces, in a dose and time-related manner, an antiallodynic effect on MRMT-1-induced mechanical hypersensitivity. Maximum effect was observed with the dose of 40 U/kg (32% to 40%, $p<0.001$) while the lowest doses of 5 and 10 U/kg did not induce any significant effect. Control paw withdrawal thresholds and body weights were not impacted by AboBoNT-A injection. **Conclusions:** AboBoNT-A reduces mechanical allodynia induced by MRMT-1 cells in a bone cancer pain model in rats. These results suggest a possible effective and long-lasting reduction in chronic pain associated with metastatic bone cancer in humans.

Disclosures: **V. Maffre:** A. Employment/Salary (full or part-time):; ANS Biotech. **C. Favre-Guilmard:** A. Employment/Salary (full or part-time):; Ipsen Innovation. **M. Kalinichev:** A. Employment/Salary (full or part-time):; Ipsen Innovation. **Y. Darbaky:** A. Employment/Salary (full or part-time):; ANS Biotech. **L. Diop:** A. Employment/Salary (full or part-time):; ANS Biotech.

Poster

661. Somatosensation: Non-Opioid Treatment of Pain

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 661.20/I1

Topic: D.03. Somatosensation – Pain

Support: NIH Grant DA035931

Title: Influence of strategically substituted agmatines on opioid-induced neuroplasticity

Authors: *B. M. CLEMENTS[1], C. D. PETERSON[2], K. F. KITTO[2], G. L. WILCOX[3], C. A. FAIRBANKS[4];
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Abstract: In the face of the dual crises of chronic pain and opioid addiction, therapies remain to be developed to effectively treat opioid-induced neuroplasticity. Decades of work has supported the use of N-methyl-D-aspartate (NMDA) receptor and nitric oxide synthase (NOS) inhibitors to treat opioid tolerance and aspects of the addictive state, but adverse effects have limited clinical development. Recent work has shown that agmatine acts to reduce these maladaptive neuroplasticities without negative sides effects by acting specifically on NMDA receptors containing GluN2B subunits. Systemic agmatine, though, has been limited due to low blood-brain barrier permeability, necessitating high doses, and a short plasma half-life. To combat these issues, we have generated strategically substituted agmatines (SSAs) to increase distribution to the CNS and increase exposure to the drug. Previous work with these SSAs have shown benefit over agmatine as a treatment for chronic pain with no cardiovascular or motor deficits. Our objective is to confirm the influence of the SSAs on opioid-induced neuroplasticity, as seen with agmatine, by assessing opioid tolerance and comparing that response to the pharmacokinetics. Chronic Morphine Induced Analgesic Tolerance (52.5°C warm water tail flick assay): Mice were treated every 12 hours for 3 days with SSA1 (10 nmol, i.t.)/morphine sulfate (10 nmol, i.t.), SSA1/vehicle, morphine sulfate/vehicle, or vehicle/vehicle. Before the treatment. Mice were tested for thermal tail-flick latency prior to the start of treatment. Increasing doses of morphine were given centrally 24 hours after the final dose to assess tolerance. Dose response analysis showed morphine tolerance in morphine/vehicle group, but tolerance was not present in

SSA1/morphine group. Mice were then treated under the same research paradigm receiving systemic SSA1 (10 mg/kg, i.v.) against central morphine. Dose response analysis following induction of analgesic tolerance in systemic SSA1 animals shows similar behavior to central SSA1. Pharmacokinetics of SSA1 and the Conversion to Agmatine: Mice were injected with SSA1 (100 mg/kg, i.v.) or agmatine (100 mg/kg, i.v.) over a 4-hour time course. Serum and spinal cords were collected and tested for agmatine content using HPLC-UV/Vis. The change in agmatine following injection shows that SSA-1 drives higher plasma presence of agmatine, longer elimination half-life, and increased agmatine exposure in the CNS.
These data suggest that SSA-1 acts to reduce opioid-induced neuroplasticity, specifically as a function of opioid tolerance, potentially due to increased agmatine exposure in the CNS following SSA1 treatment.

Disclosures: B.M. Clements: None. **C.D. Peterson:** None. **K.F. Kitto:** None. **G.L. Wilcox:** None. **C.A. Fairbanks:** None.

Poster

661. Somatosensation: Non-Opioid Treatment of Pain

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 661.21/I2

Topic: D.03. Somatosensation – Pain

Support: NIH T32 GM075770
NIH UG3 NS108978

Title: Non-opioid analgesics to treat chronic pain through the cannabinoid-binding site in glycine receptors

Authors: *J. CAPOROSO[1], M. WELLS[1], L. JIANG[1], M. MOSES[2], K. KOPER[2], Q. CHEN[1], P. TANG[1,3,4], Y. XU[1,4,5,6];
[1]Anesthesiol., [2]Neurosci., [3]Computat. and Systems Biol., [4]Parmacology and Chem. Biol., [5]Structural Biol., [6]Physics and Astronomy, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Marijuana's analgesic action has been linked to allosteric positive modulation of glycine receptors (GlyRs) by Δ9-tetrahydrocannabinol (THC), a major psychoactive component in cannabis. GlyRs are the predominant inhibitory ligand-gated ion channels that mediate the nociceptive signals in the central nervous system, and the glycinergic mechanism of analgesia is independent of other undesirable psychoactive effects of THC. Therefore, the discovery and development of compounds that selectively bind GlyRs will likely produce analgesia without negative psychoactive effects. Top-ranked compounds from computational screening that were predicted to bind to the THC site in α3GlyR were previously validated using *in vitro* electrophysiology. The compound with the highest potency and selectivity (MJPY1) was used as

a lead scaffold to generate analogs for *in vivo* characterization of the analgesic effects against neuropathic pain in rodents using the Hargreaves, von Frey, and Thermal Place Preference tests. Peripheral neuropathy was induced in Sprague-Dawley rats by a chronic constriction injury to the sciatic nerve and analgesia was assessed after a 10-day healing period to minimize inflammatory surgical pain and maximize neuropathic pain. Intraperitoneal administration of MJPY analogs produced analgesia against neuropathic pain as early as 30 minutes post injection and lasted for at least 2 hours against both thermal and mechanical stimuli. In conclusion, we have discovered a novel class of analgesics for neuropathic pain that act at the THC-binding site in α3GlyR. More extensive testing is currently underway to fully characterize the structure-activity relationship and to optimize their pharmaceutical properties and analgesic effects. The analgesic action of these novel compounds may have a significant impact on chronic pain management and help curb the use of popular analgesics that have dangerous addictive and abuse potential.

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Poster

661. Somatosensation: Non-Opioid Treatment of Pain

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 661.22/I3

Topic: D.03. Somatosensation – Pain

Support: NIH NIDCR R21 DE028096

Title: Generation and characterization of highly potent and efficacious scFv antibodies against P2X4 receptor for the treatment of pain

Authors: *N. SURI[1], M. MONTERA[2], R. DURVASULA[1], K. WESTLUND[2], A. KUNAMNENI[1];
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Abstract: The P2X purinoceptor 4 (P2X4) plays a crucial role in signaling leading to chronic inflammatory and neuropathic pains, thus, the P2X4 receptor provides a new potential therapeutic target for their treatment. We have generated a panel of mouse single-chain fragment variable-antibodies (scFvs) recognizing extracellular peptide of P2X4 using cell-free ribosome display, to reduce pain signaling by neurons. A mouse scFv library was generated, and ribosome display was applied for anti-P2X4 scFv recombinant antibody selection. After three rounds of bio-panning, we isolated a panel of recombinant antibodies followed by ELISA, cross reactivity analysis, western blotting and immunofluorescence staining, anti-P2X4 scFv clones with high

specificity and affinity were successfully selected. The efficacy of this therapeutic will be further evaluated using established capsaicin-induced or formalin-induced mouse inflammatory pain models.

Disclosures: **N. Suri:** None. **M. Montera:** None. **R. Durvasula:** None. **K. Westlund:** None. **A. Kunamneni:** None.

Poster

661. Somatosensation: Non-Opioid Treatment of Pain

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 661.23/I4

Topic: D.03. Somatosensation – Pain

Support: NIH Grant R01-NS093990

Title: Sphingosine-1-phosphate type 1 receptors in the central nervous system contribute to the antinociceptive effects of FTY720 (fingolimod) in a mouse model of nerve injury-induced neuropathy

Authors: *D. E. SELLEY[1], G. DONVITO[1], V. D. MCLANE[1], S. SPIEGEL[2], K. F. HAUSER[1], A. H. LICHTMAN[1], L. J. SIM-SELLEY[1];
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Abstract: Modulation of the sphingosine-1-phosphate (S1P) system regulates nociception in models of acute and chronic pain. FTY720 (fingolimod) produces antinociception in multiple neuropathic pain models. FTY720 is phosphorylated *in vivo* to an agonist/functional antagonist (FTY720-phosphate) of multiple S1P receptor types, including the $S1P_1$ receptor (S1PR1). The present study assessed the role S1PR1 in the CNS in the antinociceptive effect of FTY720 in male mice with chronic constriction injury (CCI) of the sciatic nerve. S1PR1 was conditionally knocked out (cKO) in neurons, astrocytes and oligodendrocytes in the CNS using the nestin promoter to express cre recombinase in S1PR1-floxed mice (NC-S1PR1 cKO). S1PR1 activity was assessed in control (S1PR1-floxed) and NC-S1PR1 cKO mice using [^{35}S]GTPγS binding stimulated by S1P or the S1PR1 selective agonist SEW2871 in the spinal cord and multiple brain regions. Results showed ≥ 85% reduction in maximal [^{35}S]GTPγS stimulation by S1P and near-complete reduction in stimulation by SEW2871 in the spinal cord and all gray matter regions examined in the brain, suggesting that: 1) S1PR1 was deleted in NC-S1PR1 cKO mice and 2) the vast majority of S1P-stimulated [^{35}S]GTPγS binding was mediated by S1PR1 in the CNS of control mice. Control and NC-S1PR1 cKO mice then received CCI or sham surgery. After one week, mice were administered daily injections (i.p.) of vehicle or FTY720 (0.1 mg/kg) for 14 days. Mechanical hypersensitivity was assessed with Von Frey filaments 1 h after injections on

days 1, 7 and 14. NC-mediated cKO of S1PR1 did not affect baseline sensitivity in mice with sham surgery nor did it affect CCI-induced mechanical hypersensitivity. Repeated daily administration of FTY720 produced time-dependent reversal of hypersensitivity in CCI mice, which was significant at day 1 and maximal by day 14. Interestingly, FTY720 also significantly reversed CCI-induced hypersensitivity in NC-S1PR1 cKO mice, but the magnitude of reversal was reduced (by ~65% on day 14) compared to control mice. These results indicate that S1PR1 expression in the CNS: 1) is not required for development of CCI-induced mechanical hypersensitivity and 2) plays a major but not exclusive role in FTY720-mediated reversal of CCI-induced hypersensitivity.

Disclosures: D.E. Selley: None. **G. Donvito:** None. **V.D. McLane:** None. **S. Spiegel:** None. **K.F. Hauser:** None. **A.H. Lichtman:** None. **L.J. Sim-Selley:** None.

Poster

662. Touch: Neocortex Networks and Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 662.01/I5

Topic: D.04. Somatosensation – Touch

Title: Wiring specificity for output generation in the neocortex

Authors: *J. M. GUEST, A. BAST, M. SEETHARAMA, M. OBERLAENDER;
Max Planck Group: In Silico Brain Sci., Ctr. of Advanced European Studies and Res., Bonn, Germany

Abstract: Underlying structural and functional determinants that contribute to output generation in the neocortex during sensory information processing mostly remains unknown. It is thought that the primary source of output generation and thus the terminal point of sensory information processing in the neocortex are the pyramidal tract neurons (PTs). We have recently discovered that PTs have morphological and functional properties that reflect their respective sub-cortical target areas, indicating PTs receive inputs from different neuronal populations and or receive synaptic inputs at different dendritic compartments in a manner that reflects the subcortical targets. To test this hypothesis, we use a multidisciplinary approach that combines *in vivo* electrophysiological recordings with virus mediated optogenetic input mapping, anatomical reconstructions and biophysical modeling. Our results indicate a preference for thalamic input near to the location of the apical dendrite primary bifurcation of PTs and that the location of where the primary bifurcation occurs may be related to the PTs sub-cortical target. These results will then be used to constrain a biophysical model of a single PT within a realistic anatomical cortical reference frame to systematically characterize synaptic input integration that can give rise to long-range target related output patterns.

Disclosures: **J.M. Guest:** None. **A. Bast:** None. **M. Seetharama:** None. **M. Oberlaender:** None.

Poster

662. Touch: Neocortex Networks and Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 662.02/I6

Topic: D.04. Somatosensation – Touch

Support: ERC Grant No 633428
DFG (SFB 1089)
DFG (SPP 1041)

Title: Simple rules for complex wiring of neocortical networks

Authors: *D. UDVARY[1], V. J. DERCKSEN[2], P. HARTH[2], H.-C. HEGE[2], C. P. J. DE KOCK[3], B. SAKMANN[4], M. OBERLAENDER[1];
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Abstract: Principles that shape the complicated synaptic wiring patterns of the neocortex remain unknown. This knowledge is, however, essential for understanding how higher functions, such as sensory perception, are implemented within the mammalian brain. Here, we describe synapse formation mechanisms mathematically, and show how to link the theories' predictions with empirical connectivity measurements. We use the approach to elucidate the degree to which proximity between neuronal structures determines connectivity - a controversial topic for decades. We find that proximity-based wiring patterns are consistent with the available empirical data at subcellular, cellular and network levels. Proximity-based wiring will hence conceal connections that reflect activity-dependent synapse formation processes. Our approach disentangles these different mechanistic origins of wiring, a necessity for identifying structural correlates of sensory experience, learning or memory.

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Poster

662. Touch: Neocortex Networks and Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 662.03/I7

Topic: D.04. Somatosensation – Touch

Support: DFG (SPP2041)
DFG (SFB1089)
ERC (No 633428)

Title: Depth-specific relationships between the molecular identity, intrinsic physiology and morphology of inhibitory interneurons in the rat neocortex

Authors: *F. YANEZ[1], D. UDVARY[1], J. M. GUEST[1], B. SAKMANN[2], D. FELDMEYER[3], M. OBERLAENDER[1];
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Abstract: Inhibitory interneurons (INs) are commonly grouped into cell types based on their molecular identity, intrinsic physiology and/or axon morphology. Here, we systematically assess the relationships between these three classification criteria as a function of cortical depth in the vibrissal-related part of rat primary somatosensory cortex (i.e., barrel cortex). First, we determine the number and distribution of parvalbumin-, somatostatin- and calretinin-expressing INs throughout the entire barrel cortex. The data provides quantitative estimates at 50 micron resolution of the relative abundance of each of these molecularly defined IN classes across the cortical depth. Second, we objectively classify more than 300 *in vitro* recorded INs into physiological cell types based on their spiking patterns in response to somatic current injections (e.g., fast-spiking vs. non fast-spiking). The neurons are recorded across the entire cortical depth of the barrel cortex, and labeled with biocytin, which allows reconstructing their dendrite and axon morphology, as well as determining their respective somatic depth locations. Third, based on the axonal reconstructions, we objectively classify the neurons into morphological cell types (e.g., basket vs. Martinotti cells). For a subset of the recorded/reconstructed neurons, we additionally determine their respective molecular identity. We compare the relative abundances across the cortical depth of molecularly defined IN classes, with those determined by physiological and/or morphological properties. Our results provide quantitative insight into the relationships between the three main criteria that are currently used to classify INs, and reveal the degree to which somatic depth location in combination with molecular identity is predictive of an IN's physiological and/or morphological cell type, and vice versa.

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Poster

662. Touch: Neocortex Networks and Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 662.04/I8

Topic: D.04. Somatosensation – Touch

Support: ERC

Title: Cell type-specific structure and *in vivo* function of excitatory neurons in rat vibrissal motor cortex

Authors: *R. T. NARAYANAN, M. SEETHARAMA, J. M GUEST, A. JAVADOVA, M. OBERLAENDER;
Caesar, In Silico Brain Sci., Bonn, Germany

Abstract: Functional studies show that whisker stimulation evokes responses in both vibrissal somatosensory cortex (vS1) and vibrissal motor cortex (vM1). Conversely, multiple studies indicate stimulation of vS1 and vM1 both evokes whisker movements. Whereas the structure of vS1 has been described, very little is known about vM1. Here, we describe the location and extension of rat vM1 area by injecting trans-synaptic rabies virus onto the intrinsic muscles of the rat whiskers. We found that both vS1 and vM1 are located equal synaptic distance from the whisker muscle. Using cell-attached recording and biocytin labeling *in vivo*, we recorded electrophysiological properties and subsequently reconstructed dendrite-axon morphologies of neurons of vM1. The classification of neurons revealed that vM1 is composed of similar canonical cell types as vS1. However, the morphological properties of cell types are specific to the cortical area that they are located in. We conclude there are substantial similarities between these two cortices, indicating that both follow similar organizational principles.

Disclosures: **R. T. Narayanan:** None. **M. Seetharama:** None. **J. M Guest:** None. **A. Javadova:** None. **M. Oberlaender:** None.

Poster

662. Touch: Neocortex Networks and Models

Location: Hall A

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Program #/Poster #: 662.05/I9

Topic: D.04. Somatosensation – Touch

Support: PAPIIT-DGAPA IN201518
CONACyT Fronteras de la Ciencia No. 846

Title: Electrophysiological characterization of sensorimotor cortex neurons projecting to mesencephalic nuclei

Authors: *V. LOPEZ-VIRGEN, R. OLIVARES-MORENO, G. ROJAS-PILONI;
Inst. de Neurobiologia, UNAM, Queretaro, Mexico

Abstract: Layer 5 pyramidal tract neurons (PTN) arecanonical elements of the cerebral cortex. PTN are the main excitatory output to subcortical structures like striatum, superior culliculus, pons, red nucleus and spinal cord, among others. Nevertheless, little is known about the electrophysiological characteristics expressing the diversity of theseprojection neurons. The aim of the present work is to distinguish the electrophysiological characteristics *in vivo* of the thick-tufted layer 5 pyramidal neurons of the sensorimotor cortex projecting to tectum, red nucleus (RN) and pons.Twenty wild-type C57BL/6 mice adults were anesthetized with isofluorane in oxygen (2-3%).A small craniotomy were made to insert a stimulation electrode in RN, pons or tectum. Foryuxtacellular recordings *in vivo* in layer 5 a cranial window was made in sensorimotor cortex (2.46 mm to -0.80 mm, and 0.5 to 0.7 relative to bregma).In order to identify the different projection neurons, the antidromic responses and collision test was analyzed. The animals were perfused and 100-µm coronal sections were obtained, mounted and marked with NIssl staining to confirm the stimulation electrode location. We found that the differentprojection PTN differs in theirspiking patterns, frequency, and sensory responses according the subcortical projection.Thesedifferences in electrophysiological parameters suggest that the PTN projectingsubcortically functionally segregated.

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Poster

662. Touch: Neocortex Networks and Models

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Program #/Poster #: 662.06/I10

Topic: D.04. Somatosensation – Touch

Support: DFG (SFB-1089)

Title: Relationship between morphology, *in-vivo* electrophysiology, molecular identity and thalamocortical input of cortical inhibitory neurons

Authors: *F. MESSORE, J. M. GUEST, R. T. NARAYANAN, A. BAST, M. OBERLAENDER;
In Silico Brain Sci., Ctr. of Advanced European Studies and Res., Bonn, Germany

Abstract: Inhibitory interneurons in the neocortex, show a vast diversity in their morphological and electrophysiological properties. However, how such diversity on the single cellular level extends to both the sensory-evoked and the ongoing activity of these cells is still to be known in the deep layers, given their difficult accessibility and limits of current imaging techniques. Here we reconstruct the complete axon and dendrite morphology of cell attached in-vivo recorded inhibitory neurons in layer 5 of the rat barrel cortex, we also characterize the inhibitory neurons in term of their molecular identity, the degree of their primary thalamocortical inputs and spiking activity. Our data will provide a quantitative assessment of the relationship between the thalamocortical input, dendrite/axon morphologies and molecular identity with the in-vivo activity of these neurons. This research will aid to generate a more comprehensive cellular characterization and provide necessary information for future understanding of the microcircuits architecture of the neocortex.

Disclosures: F. Messore: None. **J.M. Guest:** None. **R. T. Narayanan:** None. **A. Bast:** None. **M. Oberlaender:** None.

Poster

662. Touch: Neocortex Networks and Models

Location: Hall A

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Program #/Poster #: 662.07/I11

Topic: D.04. Somatosensation – Touch

Support: ERC (No 633428)
BMBF/FKZ 01GQ1002 and 01IS18052

Title: Synaptic properties can dominate cortical output computations

Authors: *A. BAST[1], R. EGGER[2], M. OBERLAENDER[1];
[1]In Silico Brain Sci., Ctr. of Advanced European Studies and Res., Bonn, Germany; [2]Neurosci. Inst., NYU Sch. of Med., New York, NY

Abstract: Cortical output mainly originates from pyramidal tract neurons (PTs). The determinants of spike generation in PTs are complex, as they receive input from local and far away neuron populations, have extensive dendritic trees and express a plethora of active conductances. The interplay between these components as well as their importance for the overall computation that PTs perform remains poorly understood. Here, we characterize excitatory and inhibitory spatiotemporal synaptic input patterns, for which this computation is

mainly determined by synaptic properties and can be described analytically. We show, that such input patterns are present during the onset of sensory stimuli in vivo, allowing to predict the responses of PTs with high temporal accuracy. This explicit analytical description of a cortical computation can be a starting point to investigate which information is encoded in the so far enigmatic responses of PTs.

Disclosures: **A. Bast:** None. **M. Oberlaender:** None. **R. Egger:** None.

Poster

662. Touch: Neocortex Networks and Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 662.08/I12

Topic: D.04. Somatosensation – Touch

Title: Reconstruction of whisker-related neuronal networks throughout the rat brain

Authors: *A. MAHARJAN, J. M. GUEST, M. M. SEETHARAMA, M. OBERLAENDER;
In Silico Brain Sci., Ctr. of Advanced European Studies and Res., Bonn, Germany

Abstract: Rodents actively move their facial whiskers to explore their environment. The whisker system is thus a common model system to investigate principles of sensory information processing, mechanisms that underlie motor control, and for studying interactions between sensory and motor pathways. Recent studies have provided detailed insight into the central pattern generator pathways that drive rhythmic whisker movements (whisking) at the level of the brain stem. Furthermore, accumulating evidence suggests that disjoint cortical feedback pathways from both primary motor and somatosensory areas to a variety of brain stem structures may play a crucial role in whisker motor control. Here, we provide a quantitative account of the structural organization of these brain-wide whisker-related pathways in the rat. We inject replication competent rabies virus into a single intrinsic whisker muscle. The virus labels synaptically connected neurons via retrograde trans-synaptic spread. At first order spread, the virus labels motoneurons that innervate the infected muscle. Subsequently, at second order, the virus labels neurons that are presynaptic to these motoneurons. We quantify the distribution of rabies-labeled neurons throughout the rat brain for several experiments that reflect second, third and fourth order transsynaptic spread. We show that the injections provide consistent results across experiments, and which are in line with those reported previously using conventional neuroanatomical tracers. We find that sensory- and motor-related brain areas, both in the neocortex and brainstem, can contribute equally to whisker muscle control (i.e., in terms of the number of neurons). Moreover, we find that motor-related areas are typically labeled in both hemispheres of the brain at the same order of transsynaptic spread, whereas sensory-related areas appear to be more unilaterally connected to the muscle. Our data will aid future studies to better interpret functional measurements during whisker-based behaviors.

Disclosures: **A. Maharjan:** None. **J.M. Guest:** None. **M.M. Seetharama:** None. **M. Oberlaender:** None.

Poster

662. Touch: Neocortex Networks and Models

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Program #/Poster #: 662.09/I13

Topic: D.04. Somatosensation – Touch

Support: NIH R01-NS091439

Title: An approach towards visualizing airflow around animal faces and whiskers

Authors: ***T. L. JANSSEN**[1], J. M. THOMAS[2], M. J. HARTMANN[1], V. GOPAL[2]; [1]Northwestern Univ., Evanston, IL; [2]Elmhurst Col., Elmhurst, IL

Abstract: We describe an apparatus to track airflow around animal faces, with a particular focus on the nose, snout, and whiskers. Using neutrally buoyant bubbles as tracer particles, we are able to visualize the airflow around a 3D printed, biologically accurate model of a rat head. The system allows us to characterize how the rat's facial features affect the flow profile for various orientations of the head (both yaw and pitch). The present work describes the velocity field around the rat head in 2D planes for a flow that is steady in the mean. Unlike traditional particle image velocimetry (PIV) methods, our method does not require high-speed video, but rather makes use of low frame-rate videos. A custom tracking algorithm detects bubble tracks in each frame and uses these tracks to extract flow parameters. An extension of this work is being used to understand sensing for various flow regimes involving upwind bluffs. We anticipate that quantification of the effects of head orientation on flow around the rodent head will lead to a better understanding of how rodents orient their whiskers to optimize sensing in various flow profiles. We discuss how an extension of these results may aid in quantifying flow profiles for other animals.

Disclosures: **T.L. Janssen:** None. **J.M. Thomas:** None. **M.J. Hartmann:** None. **V. Gopal:** None.

Poster

662. Touch: Neocortex Networks and Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 662.10/I14

Topic: D.04. Somatosensation – Touch

Support: NSF Grant BCS-1734981
NSF GRFP to HME DGE-1324585

Title: A robotic pinniped: Using biomimetic robotic whiskers to sense fluid flow

Authors: *H. M. EMNETT[1], K. J. KLECZKA[1,2], T. L. JANSSEN[1], M. J. Z. HARTMANN[1,2]; [1]Mechanical Engin., [2]Biomed. Engin., Northwestern Univ., Evanston, IL

Abstract: Many pinnipeds use their whiskers as a primary sensing modality when hunting. The whiskers bend and vibrate in response to the different flow patterns left by the pinnipeds' prey. In the present work, we describe the design of a biomimetic, robotic pinniped that can be used to sense flow underwater. The components of the system are plastic whiskers, artificial sensing "follicles," and a morphologically-accurate 3D printed head. Because no sensing occurs along the length of a real pinniped whisker, the artificial whiskers can be made out of plastic, with an artificial robotic follicle serving as a sensor at each whisker base. The plastic was carefully chosen to have material properties similar to that of a real pinniped whisker and can be fabricated to have the same geometry as whiskers found on either a sea lion or a harbor seal. The artificial follicle, located at the base of each whisker, is built to measure the specific mechanical signals most important for sensing flow. The whiskers, with their sensing follicles, are mounted to a 3D printed model of either a seal or sea lion head. These heads are based on 3D scans of real animals and the locations of the whisker basepoints match those on the real animal. We then use this robotic pinniped to analyze how different flow patterns affect the signals at the base of the whiskers, and thus how an animal might use these varying signals during active hunting. In the future, we anticipate using this apparatus as a method to determine which information is the most salient during wake tracking.

Disclosures: H.M. Emnett: None. **K.J. Kleczka:** None. **T.L. Janssen:** None. **M.J.Z. Hartmann:** None.

Poster

662. Touch: Neocortex Networks and Models

Location: Hall A

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Program #/Poster #: 662.11/I15

Topic: D.04. Somatosensation – Touch

Support: Atención Problemas Nacionales 464
Productos Medix 3247
Fundación Miguel Alemán

Title: Animals can use optogenetic-induced brain modulations as a conditioned stimulus, regardless of the cell type, type of modulations (activation or inhibition), and brain region opto-stimulated

Authors: *J. LUIS-ISLAS[1], G. B. FLORAN[1], R. GUTIERREZ[2];
[1]Physiology, Biophysical and Neurosciences, CINVESTAV, Mexico city, Mexico; [2]Pharmacol., CINVESTAV - IPN, Mexico City, Mexico

Abstract: Brain manipulations (e.g., optogenetic) have been used to perturb brain activity to evaluate their necessity of a behavior. Nevertheless, these Brain perturbations can generate interoceptive cues that can be used to guide behavior. Most studies have a focus on the somatosensory cortex (S1). However, we reason that any brain region will be able to generate interoceptive cues. We hypothesize that pairing an arbitrary optogenetic stimulation, regardless of the brain region, with a relevant behavioral event, will induce plasticity on brain circuits associating to that event, such as now the opto-stimulation will be able to drive behavior. To test this idea, first, we used the Thy1-ChR2 mice to photoactivate either cortical pyramidal neurons from layer V (in the prefrontal cortex, PFC) or its fibers to the nucleus accumbens shell (NAcSh). Thy1-ChR2 mice were trained in a two sipper sucrose alternating task, where -in order to receive two drops of sucrose- they had to alternate between two opposite left and right sippers (Phase 1). Additional licks in the rewarded sipper will no longer release more sucrose until mice licked the opposite sipper. In half of the trials, when the subject heads halfway toward the opposite port, a 1 s train of photostimulation (20Hz) + a tone were delivered, mice use these cues to change its direction and return to the previously rewarded port to be rewarded again with sucrose. If they continued and licked the opposite sipper, mice were punished (with 2 airpuffs). After learning, the tone was removed, and phase 2 begins: the subjects had to predict punishment only using photostimulation. We found that transgenic mice can avoid punishment, by only using the photostimulation cue (tone off). The same task was also developed with VGAT-ChR2 mice (ChR2 in GABAergic neurons), with fiber in PFC or thalamic reticular nucleus (TRN) or with Ires-Cre mice (ChR2 or ArchT in GABAergic neurons of lateral hypothalamus) showing similar results. Thus, optogenetic stimulation can be a predictive signal of an outcome, regardless of its original function. Finally, we tested if subjects can learn different rules by discriminating between 2 photostimulation frequencies (i.e., 20 Hz had to lick in a right port, 10 Hz had to do at opposite). We found that subjects can perform above 85% of correct trials. In conclusion, we demonstrate that arbitrary optogenetic stimulation evokes brain modulation and animals can use it as an interoceptive cue (conditioned stimulus), regardless the region, type of modulation (activation or inhibition) or frequency. This work paves the way to investigate how artificial network's modulations can be perceived for animals and how they can report them

Disclosures: J. Luis-Islas: None. **G.B. Floran:** None. **R. Gutierrez:** None.

Poster

662. Touch: Neocortex Networks and Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 662.12/I16

Topic: D.04. Somatosensation – Touch

Title: A 3D model for precise registration of neuronal morphologies

Authors: *M. M. SEETHARAMA, R. NARAYANAN, J. M. GUEST, M. OBERLAENDER;
Caesar, Bonn, Germany

Abstract: Delineating the structural organization of any brain region of interest often involves reconstructing and analyzing neuronal morphologies from that region. Since only a handful of neurons can be reconstructed per animal, it becomes essential to have a standardized 3D model into which anatomical data from different animals can be precisely registered. Such a model will account for not only the inter animal variability but also the variability across experimental conditions.
Here, we present such a standardized 3D model for rat vibrissal motor cortex, along with the precision involved in registering morphologies into the standard model. Registered neuronal morphologies can be readily compared with one another and hence can be accurately assigned to their respective morphological cell types.

Disclosures: M.M. Seetharama: None. **R. Narayanan:** None. **J.M. Guest:** None. **M. Oberlaender:** None.

Poster

662. Touch: Neocortex Networks and Models

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Topic: D.04. Somatosensation – Touch

Support: NIH Grant DC010809

Title: Swimming alters dynamics of lateral line afference in larval zebrafish

Authors: *D. A. SKANDALIS, E. T. LUNSFORD, J. C. LIAO;
Whitney Lab. for Marine Biosci., Univ. of Florida, St Augustine, FL

Abstract: Corollary discharge to sensory organs suppresses afference when the organism's own actions might overwhelm the sensory system. In fish, the lateral line detects water perturbations that might emanate from important extrinsic sources (exafference), but could also result from swimming (reafferance). Reafference is thought to be minimized by hindbrain cholinergic efferent neurons which project to the lateral line and reduce the probability of afferent spikes, though the effect of endogenous levels of efferent activity during swimming on afferent spiking dynamics has not been directly assessed. If the corollary discharge to the lateral line operates similarly to that in other organisms, fish may maintain generally high levels of sensitivity except while swimming, potentially resulting in insensitivity to critical exafferent stimuli. We recorded extracellular spontaneous and mechanically evoked afferent spike rates during fictive swimming of larval zebrafish (*Danio rerio*, n=20) while alternating 1 s of posterior lateral line neuromast stimulation (frequencies 5, 20, or 40 Hz) with 2 s off. Afferents responded most strongly to the first stimulus, after which the probability of an afferent response significantly decreased. Following stimulation, afferents displayed a refractory period proportional in duration to the stimulation frequency. Spontaneous and evoked spike rates decreased during swim bouts as predicted, but were not completely suppressed. We also found that this response persisted after the end of the swim in a post-swim refractory period. Despite the decreased evoked spike probability while swimming, the vector strength increased, indicating greater fidelity of spike timing to the original stimulus. This opposite relationship of spike probability and vector strength suggests that although information volume may decrease during the swim, information content may increase. Taken together, these results show that the corollary discharge does not completely suppress afference during the swim to render the fish insensitive. Rather, the lateral line maintains sensitivity to a degree dependent on the timing of exafferent and reafferent stimuli during or after the swim bout. We propose that such time dependence may be a general feature of hair cell systems and their regulation, such as in the inner ear and vestibular systems.

Disclosures: D.A. Skandalis: None. **J.C. Liao:** None. **E.T. Lunsford:** None.

Poster

663. Chemosensory Processing III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 663.01/I18

Topic: D.05. Olfaction and Taste

Support: NIH Intramural Grant

Title: Inhibitory control of sparse odor-coding in an insect olfactory-circuit

Authors: *S. RAY, Z. N. ALDWORTH, M. A. STOPFER;
NICHD, NIH, Bethesda, MD

Abstract: In the olfactory systems of insects and mammals, olfactory receptor neurons respond to a broad range of odors with vigorous spiking, but higher order neurons respond to odors much more sparsely and selectively. This transformation of the neural code for odors is mediated by feedback inhibition. The locust has been a good model system to study this process. In this animal, a single Giant GABAergic Neuron (GGN) is known to receive excitatory input from all higher order olfactory neurons known as Kenyon Cells (KCs), and, in turn, to inhibit every KC. Thus, GGN's membrane potential reflects the spiking response of the entire KC population. To better understand the role of feedback inhibition in olfactory coding, we built a detailed computational model of the olfactory circuit of the locust including a biophysically detailed GGN, all 50,000 KCs, and their inputs from the 830 projection neurons (PNs) that stand between the receptor neurons and the KCs. Our GGN model showed that, despite the neuron's large size and nonspiking nature, it is capable of transmitting electrical signals from its input region to its distant output branches to inhibit all KCs. Simulations of our model further showed that feedback inhibition from GGN greatly sparsens the firing of the KC population, while allowing a given KC to respond to a larger range of inputs from PNs. Based on parameters from our own experiments and the existing literature, we simulated the network model with various connectivity schemes and PN activity patterns with the goal of reproducing both realistic sparse spiking in KCs and realistic odor-evoked sustained depolarization of GGN. We found this required two things: (1) the synapses connecting GGN to KC must be diverse in strength, resulting in a mixture of weak and strong inhibition; and (2) different subsets of PNs must become active at different times during odor stimulation. Our model also predicted that the spike rates of a small portion of KCs should be unusually high. We confirmed this prediction with patch clamp recordings of many KCs made in vivo. Finally, our in vivo recordings showed that some odors hyperpolarized GGN. An identified neuron, IG, is known to inhibit (and receive inhibition from) GGN, but simply adding this connectivity to our model could not realistically reproduce GGN's hyperpolarization. Our analysis suggests an additional unknown neural pathway must exist to drive IG's activity. Thus, our work reveals a complex, well-regulated network of excitation and inhibition, and a new olfactory pathway, to transform neural codes for odors in the brain.

Disclosures: S. Ray: None. **Z.N. Aldworth:** None. **M.A. Stopfer:** None.

Poster

663. Chemosensory Processing III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 663.02/I19

Topic: D.05. Olfaction and Taste

Support: ONR Grant N000141612426
NSF CAREER Award 1453022

Title: Odor valence encoding in the antennal lobe and its behavioral correlates

Authors: *R. CHANDAK[1], M. TRANER[3], B. RAMAN[2];
[1]Biomed. Engin., Washington Univ. In St. Louis, St Louis, MO; [2]Biomed. Engin., Washington Univ. In St. Louis, Saint Louis, MO; [3]Biomed. Engin., Washington Univ. in St. Louis, St Louis, MO

Abstract: The olfactory system receives a plethora of volatile stimuli inputs from an organism's surroundings. Predicting and understanding how neural activities encode the overall preference to olfactory stimuli, or valences, which guide primal behaviors such as fleeing away from a predator or towards food, are open challenges in systems neuroscience. In this study, we used the locust (*Schistocerca americana*) olfactory system to examine this issue. We began by examining innate preferences of locusts to an exhaustive panel of odorants comprising putative appetitive and aversive stimuli. By assaying the palp-opening responses of locusts using a simple binary metric - open or closed palp position, we ascertained whether or not individual locusts preferred an odorant. Combining information across a collection of locusts, we were able to calculate a preference index for each odorant in our panel. We also quantified this distribution for each sex separately to investigate any differences in valences arising due to gender differences. In addition, we studied the acquired behavior preferences of locusts using an appetitive conditioning assay. For this, we used odors with widely different preference indices to study whether a potential distinction exists between appetitive and aversive stimuli in their efficacy to induce associative learning. Our results indicate that starved locusts could be conditioned to associate an odor with a food reward only when the odorant was innately attractive. Aversive odors were not learnable. Surprisingly, reinforcing the offset responses of aversive odorants induced cross-learning for attractants in some cases. To understand the neural distinction between odorants with distinct overall valences, we are examining neural responses from excitatory projection neurons (PNs) in the locust antennal lobe that receive inputs directly from receptor neurons in the antenna. We will also study if local field potential oscillations observed in higher olfactory centers vary systematically with odor valence. In sum, we hope to understand how orthogonal behaviors (i.e., attraction and repulsion) are encoded in the antennal lobe and if neural responses can predict the valence and learnability of an odor.

Disclosures: R. Chandak: None. **M. Traner:** None. **B. Raman:** None.

Poster

663. Chemosensory Processing III

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Topic: D.05. Olfaction and Taste

Support: ONR Grant N000141612426 to B.R.

NSF Grant 1453022 to B.R.

Title: Concentration-dependent switch in neural ensembles in the locust antennal lobe

Authors: *S. NIZAMPATNAM, D. SAHA, B. RAMAN;
Washington Univ. In St. Louis, Saint Louis, MO

Abstract: Identifying the intensity of a stimulus is an essential task for most sensory systems. While it is important to encode the identity of a stimulus invariant with respect to intensity, we sought to examine whether and when this invariance breaks down in an invertebrate model of the olfactory system. Increasing concentration of stimulus has been shown to activate additional, low-sensitive sensory neurons. As a result, the overall combination of neurons activated is thought to vary subtly with increasing intensity. This simple mechanism would allow subtle variations in the ensemble responses with stimulus intensity while allowing the odor-evoked responses to still cluster predominantly based on stimulus identity (Stopfer et al., 2003). We extended these earlier studies by examining how responses in the second-order projection neurons and local neurons in the antennal lobe, which directly receives input from sensory neurons, vary over a wide range of stimulus intensity (over 4 log units of dilution). Consistent with other reports in fruit flies (Olsen et al., 2010), our results also indicate that the local neuron responses scale linearly with concentrations to possibly facilitate gain-control computation in the antennal lobe. However, the projection neurons responses were altered in a non-linear manner. Most projection neurons that were activated at lower intensities were suppressed at higher intensities. As a result, at very different concentrations, we expect the ensemble neural responses evoked by the same stimulus became more distinct than neural activity encoding different odorants. This is currently being systematically investigated. Whether such drastic switch in ensemble projection neuron responses with intensity is observed for most odorants, and whether such ensemble responses changes correlate with variations in the behavioral responses to the same stimulus is also being currently explored.

Disclosures: **S. Nizampatnam:** None. **D. Saha:** None. **B. Raman:** None.

Poster

663. Chemosensory Processing III

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Topic: D.05. Olfaction and Taste

Support: DFG, RTG 1960
DFG, CRC 1218 project B07

Title: Cell type specific mechanisms for spike frequency modulation in the insects olfactory system

Authors: J. E. RADERMACHER, J. M. KLUSSMANN, D. FUSCA, S. CORNELIUSSEN, *P. KLOPPENBURG;
Biocenter, CECAD, Univ. of Cologne, Cologne, Germany

Abstract: In the insect olfactory system peripheral input from olfactory receptor neurons is strongly processed in the antennal lobe, the functional equivalent of the vertebrate olfactory bulb. Signal processing in the antennal lobe is accomplished by a highly interconnected network of local interneurons and projection (output) neurons. These interactions structure olfactory representation and ultimately shape the tuning profile of the projection (output) neurons. Here we analyzed intrinsic electrophysiological properties of cholinergic uniglomerular projection neurons and GABAergic local interneurons in the antennal lobe of the cockroach *Periplaneta americana*. While both neuron types are essential for odor processing in the antennal lobe, they have very different physiological tasks requiring specific physiological and morphological neuronal phenotypes. Local interneurons form synaptic connections exclusively in the antennal lobe and provide interactions between the glomerular pathways. While uniglomerular projection neurons also contribute to olfactory information processing within the antennal lobe, a main task of projection neurons is the transfer of preprocessed odor information from the antennal lobe to higher order centers in the protocerebrum. This study assessed whether and how the different tasks in odor information processing are reflected in the physiological phenotypes of these neurons. To this end we measured active and passive cellular parameters based on responses to defined current- and voltage clamp protocols of neurons that were pharmacologically isolated from synaptic input. We found significant cell-type-specific differences, with GABAergic local interneurons showing strong postinhibitory rebound after hyperpolarization, while uPNs showed spike frequency acceleration during sustained depolarization. The postinhibitory rebound of type I LNs was mediated by low voltage activated Ca^{2+} currents, whereas the spike frequency acceleration of uPNs was mediated by a combined effect of an inactivating voltage dependent K^+ current (I_A) and activation of calcium-activated non-specific cation current I_{CAN}.

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Poster

663. Chemosensory Processing III

Location: Hall A

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Program #/Poster #: 663.05/DP06/I22

ControlExtraData.DynamicPosterDisplay:
Dynamic Poster

Topic: D.05. Olfaction and Taste

Title: Mapping the Aedes aegypti antennal lobes

Authors: *S. SHANKAR, C. J. MCMENIMAN;
Johns Hopkins Univ., Baltimore, MD

Abstract: The antennal lobes (ALs) are the primary olfactory centre of the brain of the yellow fever mosquito, *Aedes aegypti*. In mosquitoes, the ALs mediate processing of a diversity of volatile odorants that drive innate behaviors such as host seeking, egg laying and foraging. Anatomically, the ALs are composed of functional units of neuropil known as glomeruli. An individual glomerulus is the point at which the axonal projections of olfactory sensory neurons expressing a single type of chemoreceptor, or complement of chemoreceptors converge and synapse with the dendritic arbors of projection neurons and local interneurons. Previous studies on the *Ae. aegypti* ALs, have reported between 35 and 49-50 glomeruli arranged around a non-glomerular core of mechanosensory neuropil known as the Johnston's Organ Centre. Here, we re-investigated the AL neuroanatomy of this mosquito species using improved labelling and imaging techniques. We present 3D models based on manual image segmentation and reconstruction of the left and right ALs from 10 male and 10 female mosquito brains. We observe that the AL is entirely composed of 77-80 olfactory glomeruli, and based on depth and spatial position, along the anterior-posterior, ventral-dorsal and medial-lateral axes, we classify 13 glomerular spatial groups in the male and female ALs. In our model, 70 individual glomeruli were spatially invariant and could be identified in at least 80% of all AL reconstructions, while the remaining glomeruli were classified as spatially variant, possibly reflecting morphological distortions in neuroanatomy as a result of *in vitro* dissection, fixation and imaging. Although we did not identify any sexually dimorphic glomeruli in the *Ae. aegypti* ALs, we found overall that the volume of the female antennal lobe, was approximately 1.5 times larger that of the male mosquitoes. We also present detailed two-dimensional maps, of representative male and female ALs, in which individual glomeruli were assigned a name based on spatial group and depth. Furthermore, using the binary QF2-QUAS binary expression system, we trace the neuronal projections of three classes of chemosensory neurons, to find non-overlapping subsets of 62 *Orco*, 14 *Ir8a and* 1 *GR1* positive glomeruli in each AL. These studies describe a revised model of the *Aedes aegypti* ALs. The high-resolution anatomical map presented here will serve as a useful reference for future functional imaging studies that aim to identify glomeruli activated by human odors to decode the molecular and cellular basis of mosquito attraction to humans.

Disclosures: S. Shankar: None. **C.J. McMeniman:** None.

Poster

663. Chemosensory Processing III

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Program #/Poster #: 663.06/I23

Topic: D.05. Olfaction and Taste

Support: DARPA Grant HR00111990034

Title: Sensitivity, specificity, and plasticity in the honeybee antennal lobe

Authors: *S. HANEY[1], H. LEI[2], B. H. SMITH[2], M. BAZHENOV[1];
[1]UCSD, La Jolla, CA; [2]Arizona State Univ., Tempe, AZ

Abstract: Sensing the environment involves both detection and categorization of stimuli. Olfactory systems need high sensitivity to quickly detect new and potentially important odors, but also need to be capable of classifying odors into categories to judge an appropriate response. However, these goals can be in conflict. While increasing sensitivity can be achieved by producing a large spiking response, excessive activity can produce a low signal to noise ratio and even saturate decoding circuits leading to poor categorization. We have shown that the honey bee can modulate which end of this spectrum it operates on depending on experience and plasticity. Previously, we have found that repeated and unrewarded exposure to a single odor sensitizes bees to all other odors, an effect termed novelty detection. This change is evident through an increased spike count and behavioral modification in response to the novel odors. Our computational modeling revealed that the novelty detection effect can be mediated by plastic disinhibition of the local inhibitory networks in the bee antennal lobe (AL). In this new work, we show that with increased sensitivity to the novel odors comes decreased specificity about each new odor identity. Specifically, we found that novelty detection mechanism: 1) decreases the overall impact of the local inhibitory networks; 2) decreases oscillatory synchrony; 3) decreases discriminability between two novel odors but increases discriminability between novel and familiar odors. Our study predicts that the honey bee brain can modulate AL inhibitory circuits locally in accordance with the current importance of the stimuli. Thus, pervasive but unrewarded odors give little response but are well characterized whereas novel but potentially interesting odors elicit large responses but initially are poorly characterized. This allows for a plasticity-, experience-, and odor-dependent manner of valuing two fundamental conflicting sensory goals: sensitivity and specificity.

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Poster

663. Chemosensory Processing III

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Topic: D.05. Olfaction and Taste

Support: NIH/NICHD Intramural award to MS

Title: Electrophysiological examination of neurons in the palp olfactory pathway of locusts

Authors: *Z. N. ALDWORTH[1], M. A. STOPFER[2];
[1]NIH-NICHD, Bethesda, MD; [2]NICHD, NIH, Bethesda, MD

Abstract: Insects have proven to be a valuable model for studying the chemical senses, from sensory detection through behavior. An important question how neural circuits combine olfactory and gustatory cues. While the mushroom body is a candidate site for the combination of odor and taste information, the routes by which these modalities are combined remains unclear (Scott 2018). Most previous research has examined the olfactory pathway from the antenna to the primary calyces of the mushroom body, which play important roles in associative learning. However, another pathway that may allow olfactory and gustatory information to combine begins at the palps. The palps are composed of two pair of antenna-like organs near the mouthparts of insects which are used for feeding and food selection (Blaney & Chapman, 1970). In locusts, the tips of the palps are covered with several hundred contact chemosensilla, along with a small number of odor-detecting sensilla basiconica (Blaney, 1977). Each olfactory sensillum is innervated by 10-15 olfactory receptor neurons, which send their projections through the suboesophogeal ganglion to a region below the antennal lobe called the Lobus Glomerulatus (LG, Ignell et al, 2000). Olfactory information originating in the palp is kept segregated from antennal information through this first layer of processing (Dippel et al, 2016). From the LG, olfactory information ascends to the lateral horn and accessory calyx of the mushroom body, which are also the primary targets of gustatory information ascending along the tritocerebral tract (Frambach & Schürman, 2004). Convergence of gustatory and olfactory information in the accessory calyx potentially provides a location in the mushroom body potentially important for multimodal integration and associative learning.
To examine the suitability of the palp-accessory calyx pathway to serve as the substrate for combining olfactory and gustatory modalities, we make intracellular recordings from PNs receiving input in the LG and extracellular recordings from the palps and lateral horn. These recordings are made in combination with stimulation using both odorants and tastants, allowing us to test consecutive stages along the pathway for responsiveness to both stimulus modalities.

Disclosures: Z.N. Aldworth: None. **M.A. Stopfer:** None.

Poster

663. Chemosensory Processing III

Location: Hall A

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Program #/Poster #: 663.08/I25

Topic: D.05. Olfaction and Taste

Support: NSFC 31772683

Title: Chronic exposure to La_2O_3 nanoparticles impairs honeybee's olfactory learning ability by damaging nervous system

Authors: *Y. LIU[1,2], Y. ZHANG[1], L. YIN[1];
[1]Inst. of Apicultural Research, CAAS, Beijing, China; [2]Univ. of California, Irvine, Irvine, CA

Abstract: Nanoparticles (NPs) are increasingly used in industrial, agricultural and biological processes. However, little is known about the potential effects of nanoparticles on honey. In this study, we orally treated Apis *mellifera* L.with a set of concentrations of La_2O_3 (1, 10, 100, 1000 ppm) to test and determine their effect on survival, feeding rate and learning and memory behaviors, and further analyzed the neuronal apoptosis, synaptic units in the mushroom bodies and expression of selected memory or stress-related genes.
The results show that survival rates and feeding rates decreased in bees fed sugar syrup containing La_2O_3. Learning behavior was significant impaired by La_2O_3, while memory was not affected. La_2O_3 of 1ppm can induce nerve cell apoptosis in the brain of honeybees. We also found that the synaptic units density in the calyces of mushroom decreased after exposed to La_2O_3. Furthermore, memory-related genes expression were downregulated, stress-related genes expression were upregulated. Here, we provide evidence that nanoparticle La_2O_3 damages nervous system and thus impairs the olfactory learning ability.

Disclosures: Y. Liu: None. **Y. zhang:** None. **L. Yin:** None.

Poster

663. Chemosensory Processing III

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Topic: D.05. Olfaction and Taste

Support: NSF IDEAS

Title: Effects of odor exposure on peripheral and central olfactory processing in *Drosophila*

Authors: *Z. GUGEL[1], E. J. HONG[2];
[2]Div. of Biol. & Biol. Engin., [1]Caltech, Pasadena, CA

Abstract: Plasticity is widely studied across different sensory systems and behavioral paradigms. Previous work in *Drosophila* olfaction has uncovered potential changes in odor preference and behaviors such as walking after chronic odor exposure. The synaptic and circuit mechanisms underlying these changes are unknown. Specifically, it is unclear if odor exposure alters odorant detection and coding at the level of olfactory neurons (ORNs) and antennal lobe projection neurons (PNs). Here, we perform a detailed characterization of the synaptic and cellular effects following chronic odor exposure. We exposed flies for two days to odorants known to selectively activate a single ORN type. PN odor responses were measured using patch-clamp electrophysiology following rearing. We find that odor exposure increases DL5 PN spike rates to low odor concentrations compared to paraffin-oil exposed flies. Surprisingly, we see evidence that other PNs have a heightened sensitivity after indirect rearing, which may be a result of a broad increase in lateral excitation across the antennal lobe. When we chronically reared flies to target another glomerulus, VM7, we find an increase in odor-evoked depolarization but no change in PN spike rates in the directly reared glomerulus. This result suggests that the effects of rearing are odor-dependent. To determine whether PN responses are a result of a change in input, we measured ORN spike rates and find no difference in paraffin and odor-reared responses. Next, we measured ORN-PN synaptic strength using a novel optogenetic technique to selectively recruit unitary EPSCs (uEPSCs) in PNs. The size of the uEPSCs was not different across the conditions, suggesting that the effects of PN sensitivity cannot be explained by a change in synaptic strength. Lastly, current injection reveals that directly reared PNs show heightened spike rates, suggesting that direct rearing may alter PN excitability.

Disclosures: Z. Gugel: None. **E.J. Hong:** None.

Poster

663. Chemosensory Processing III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 663.10/I27

Topic: D.05. Olfaction and Taste

Support: NSF 1707221
NSF 1453022

Title: Characterization of odor-evoked response dynamics in three different neural populations in the fly olfactory system using light-sheet microscopy

Authors: H. RONG[1], L. ZHANG[2], C. J. GREER[3], S. PARK[5], R. DESHPANDE[1], F. BROOKS[5], T. E. HOLY[7], M. ANASTASIO[6], *B. RAMAN[4];
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Abstract: In insects, volatile chemical cues are received in the insect antenna where combinations of olfactory receptor neurons (ORNs) transduce these chemical signals into electrical signals and transmit them to downstream antennal lobe. In the fruit fly antennal lobe, the ORN signals are then relayed to at least two distinct populations of projection neurons: glutamatergic, uni-glomerular projection neurons (ePNs) and GABAergic, multiglomerular projection neurons (iPNs). How are the sensory input from ORNs transformed by these two distinct sub-populations of neurons within a single neural circuit? To understand this, using a custom-build light-sheet imaging setup, we monitored odor-evoked neural responses in transgenic flies expressing genetically encoded calcium indicators (GCaMP6f) in any one of these neural populations. We obtained 3D volumetric data with high spatial and temporal resolution. Neural activities in different neural compartments, such as dendritic processes (in the antennal lobe) and axonal projections (in the lateral horn) of ePNs and iPNs were monitored simultaneously. The three neural populations exhibited distinct tuning and temporal dynamics. We found the ePN projections to the lateral horn (LH) were functionally clustered, and that the response tuning between neighboring clusters appeared to be gradual (i.e. nearby lateral horn regions received functionally similar ePN inputs). On the other hand, the distribution of functional clusters in the calyx were not tightly clustered in space and seemed to be more dispersed. These results, while consistent with the recently published anatomical EM studies, reveal how sensory inputs from a single upstream neural network may be arranged topographically or non-topographically in distinct downstream targets. Further, we found that the information content varied as a function of time. Consistent with prior result in zebra fish, our preliminary results indicate that after odor onset, calcium signals in ePN and iPN axonal terminals were not odor specific but these coarse representations were refined over time to become more odor-specific. Interestingly, in many flies, after termination of odor stimulus, another bout of responses (i.e. OFF responses) were observed that activated ensembles of regions that were not activated during odor presentation. In sum, our data obtained with high temporal resolution, allowed us to examine how response dynamics may play an important in the fruit fly olfactory system.

Disclosures: H. Rong: None. **L. Zhang:** None. **C.J. Greer:** None. **S. Park:** None. **R. Deshpande:** None. **F. Brooks:** None. **T.E. Holy:** None. **M. Anastasio:** None. **B. Raman:** None.

Poster

663. Chemosensory Processing III

Location: Hall A

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Program #/Poster #: 663.11/I28

Topic: D.05. Olfaction and Taste

Support: BBSRC Grant BB/N007948/1
MRC studentship to JYHW

Title: Octopaminergic neurons have multiple targets in *Drosophila* larval mushroom body calyx and regulate behavioral odor discrimination

Authors: *L. M. MASUDA-NAKAGAWA, A. D. MCLACHLAN, J. H. WONG, B. A. WAN, M. MONTAGNESE, S. ZHANG;
Dept. of Genet., Univ. of Cambridge, Cambridge, United Kingdom

Abstract: Behavior depends on discrimination of selective sensory representations. These are modified dynamically by changes in behavioral state, facilitating context-dependent selection of behavior. These are mediated by brain signals carried by noradrenergic input in mammals, or octopamine (OA) in insects. To understand the circuit mechanisms of this signaling, we characterized the function of two OA neurons, in the input region to the memory center, the mushroom body calyx, in larval *Drosophila*. Here they target multiple neurons, including olfactory projection neurons (PNs), the inhibitory neuron APL, a pair of extrinsic output neurons, but relatively few mushroom body intrinsic neurons, Kenyon cells. The OA receptor Oamb, a *Drosophila* alpha-1-adrenergic receptor ortholog, localized to PN terminals, and optogenetic activation of OA neurons both potentiated PN activity, and compromised odor discrimination behavior. Our results suggest that OA neurons gate odor signals for sensory processing via extrinsic inputs at the input to the olfactory learning circuit.

Disclosures: L.M. Masuda-Nakagawa: None. **A.D. McLachlan:** None. **J.H. Wong:** None. **B.A. Wan:** None. **M. Montagnese:** None. **S. Zhang:** None.

Poster

663. Chemosensory Processing III

Location: Hall A

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Program #/Poster #: 663.12/I29

Topic: D.05. Olfaction and Taste

Support: PICT 2015-0364

Title: Beyond sensory representations: Primary olfactory cortex reflects non-olfactory task-related variables

Authors: N. FEDERMAN, S. A. ROMANO, M. AMIGO DURAN, ***A. MARIN-BURGIN**; IBioBA-Conicet-Max Planck partner Inst., Buenos Aires, Argentina

Abstract: Sensory representations are typically thought as neuronal activity patterns that encode physical attributes of the outside world. However, increasing evidence is showing that as animals learn the association between a sensory stimulus and its behavioral relevance, stimulus representation in sensory cortical areas can change. Moreover, internal state as well as animal movements related to a particular task have been shown to modulate cortical activity. To study the dynamics of sensory cortex representations as behavior evolves, we developed a spatial context-olfactory task in which mice learn that an odor is rewarded when presented in a specific spatial context. We measured the activity of piriform cortex (PC) neurons in head-fixed mice running in a virtual reality environment. We find neurons not only responding to odors, but also to visual contexts and to water reward, indicating that the PC encodes information about relevant aspects of the task. Moreover, by analyzing the population activity dynamics using Principal Components Analysis (PCA), we find different population trajectories evolving through time that can discriminate aspects of different trial types. We then further dissected the contribution of different sensory and non-sensory variables to the modulation of PC activity at the level of individual trials, using a statistical approach based on Generalized Linear Models (GLMs). Our results show that, after animals have learned the context-odor-reward association, animal position in the virtual environment is a spatial element of the task that has considerable weight on PC responses. Furthermore, we found that variables related to both sensory and non-sensory aspects of the task (e.g., odor, context, reward, licking, sniffing rate and running speed) differently modulate PC activity, suggesting that the PC may use information from other brain areas to adapt odor processing depending on experience and behavior.

Disclosures: N. Federman: None. **S.A. Romano:** None. **M. Amigo Duran:** None. **A. Marin-Burgin:** None.

Poster

663. Chemosensory Processing III

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Program #/Poster #: 663.13/I30

Topic: D.05. Olfaction and Taste

Support: CMRPG2H0211
107L7837

Title: Calretinin expressing interneurons are increased in olfaction and aggression related brain regions in forebrain specific-connective tissue growth factor knockout mice

Authors: *H.-C. CHANG[1], L.-J. LEE[1,2,3];
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Abstract: Connective tissue growth factor (CTGF) is essential in the development of the connective tissue. In the nervous system, CTGF is expressed in some distinct areas, such as the olfactory bulb and cortical subplate; however its function is still largely unknown. In order to elucidate the role of CTGF in the nervous system, *Emx1-Cre* driven forebrain-specific *Ctgf* knockout (Fb*Ctgf* KO) mice were generated. The expression of CTGF in the brain, including the olfactory bulb, is completely removed in the KO mice. Fb*Ctgf* KO mice showed exaggerated aggressive behaviors and greater c-fos expression in the medial amygdala (MeA). The aggressive behaviors in Fb*Ctgf* KO mice might be associated with increased calretinin (CR)-positive cells in the glomeruli of the olfactory bulb. In the present study, we examined the density of CR-positive cells in olfaction and aggression-related brain regions, including the anterior olfactory nucleus (AON), orbitofrontal cortex (OFC) and MeA. Compared with control mice, the numbers of CR-positive cells increased significantly in the AON and OFC of the Fb*Ctgf* KO mice; whereas in the MeA, the densities of CR-positive neurons were comparable between control and mutant mice. The density of CR-positive cells was also increased in the barrel cortex in Fb*Ctgf* KO mice, suggesting that the number of cortical CR-expressing neuron could be regulated by the presence of CTGF in the cortex. Increased CR-positive cells in the OFC might reduce the suppressive effect of OFC to the MeA thus enhance the aggressive performance in Fb*Ctgf* KO mice.

Disclosures: H. Chang: None. **L. Lee:** None.

Poster

663. Chemosensory Processing III

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Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

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Topic: D.05. Olfaction and Taste

Support: Grant No. 81661148053

Title: Cell-type-specific whole-brain monosynaptic afferent inputs to the anterior and posterior piriform cortex

Authors: *L. WANG[1,2], Z. ZHANG[2], J. CHEN[3], Q. LIU[2], F. XU[2,1,4];
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Abstract: The piriform cortex (PC) is a key sub-region of the olfactory cortex involved in olfactory processing and memory coding, it also implicated in various neurological and psychiatric disorders such as epilepsy, Alzheimer's disease and autism spectrum disorder. The PC is commonly divided into the anterior (APC) and posterior (PPC) parts, the APC and PPC differ markedly in their anatomical structures and physiological functions. However, the afferent connections of the two PC subdivisions, especially in a cell-type-specific manner remain poorly understood. Here, we mapped the whole-brain afferent inputs to the two main cell types (glutamatergic excitatory pyramidal neurons and GABAergic inhibitory interneurons) within the APC and PPC by adeno-associated virus and rabies virus-mediated cell-type-specific retrograde trans-synaptic tracing system. We found that excitatory and inhibitory neurons in both PC subdivisions receive similar afferent inputs dominantly from the olfactory areas, isocortex, hippocampal formation, cerebral nuclei and brain stem. Furthermore, we discovered that the input distributions are distinct between the two PC subdivisions. The APC preferentially innervated by some subregions of the olfactory areas and isocortex for both two types of neurons, supporting the function of the APC in encoding information about odor structures and odor associated contextual cues or values; whereas the inputs from hippocampal formation and amygdala were higher for the PPC, implying the function of the PPC in experience and emotion dependent information processing. Overall, our results expand our knowledge of the cell-type-specific afferent innervation of different PC subdivisions and provide a structural architecture for revealing the diverse function of the PC.

Disclosures: L. Wang: None. **Z. Zhang:** None. **J. Chen:** None. **Q. Liu:** None. **F. Xu:** None.

Poster

663. Chemosensory Processing III

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Topic: D.05. Olfaction and Taste

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DARPA Grant HR0011-18-2-0024
NIH R01 Grant DC014367
NIH R01 Grant DC014701

Title: Computational characterization of feedforward inhibitory neurons of anterior piriform cortex

Authors: *F. CAVARRETTA[1,2], T. A. CLELAND[2], C. LINSTER[1];
[1]Neurobio. and Behavior, [2]Psychology, Cornell Univ., Ithaca, NY

Abstract: The anterior piriform cortex (aPC) is an allocortex that integrates afferent inputs from the olfactory bulb (OB) with olfactory and non-olfactory information received from other brain regions. The axons of aPC pyramidal neurons extensively innervate the OB as well as other brain areas, providing feedback as well as feedforward processing.
In previous work, we modeled the biophysical properties of semilunar (SL) and superficial pyramidal (SP) cells, two classes of principal neurons in the aPC, along with their afferent and associative connections. Here we propose detailed models of two classes of aPC feedforward inhibitory neurons, horizontal (HZ) and neurogliaform (NG) cells, both of which are located in layer Ia, as well as bitufted (BT) cells, which are located in layer II. These interneurons have different intrinsic membrane and morphological properties and display distinct firing patterns. Based on the diverse data-dependent constraints imposed on these models, we propose that synaptic inhibition from HZ and NG cells is branch-specific on SP apical dendrites, as previously reported, but targets SL apical dendrites nonspecifically. Moreover, by assessing the outcomes of various HZ and NG connectivity profiles on balanced feedforward inhibition and the afferent fiber excitation of SLs and SP cells, we further suggest that HZ cells preferentially inhibit SL cells, whereas NG cells inhibit both SL and SP cells. Finally, again constrained by experimental data, we model the afferent fiber connectivity onto BT cells, and assess the hypothesis that the BT odor response is also driven by SLs. For each of these interneuron classes, we illustrate their specific dynamic effects on SL and SP responses, providing insight into the distinct functional roles of each interneuron class.

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Poster

663. Chemosensory Processing III

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Topic: D.05. Olfaction and Taste

Support: NIH Grant DC013802
NIH Grant DC016307

Title: Age-dependent increase of bouton-like structures in the mouse lateral olfactory tract

Authors: T. SATO[1], F. M. SEIBT[1], R. HOMMA[1], F. IMAMURA[2], ***S. NAGAYAMA**[1];
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Abstract: Olfactory information is transferred from the olfactory bulb to the olfactory cortex through the long axons of mitral and tufted cells whose axonal shafts are myelinated and bundled in the lateral olfactory tract (LOT). Here, we found previously unknown bouton-like structures along the mitral/tufted cells axons in the LOT. These structures were consistently observed regardless of the neurolabeling techniques, such as adeno-associated virus injection, electroporation labeling, or transgenic mouse lines. Protocadherin21(Pcdh21)-Brainbow mice generated by crossing Pcdh21-Cre (Cre expressing in mitral/tufted cells) mice with cre-inducible Brainbow mice allow us to observe a large population of axons as well as to identify each axonal structure. Using this transgenic mouse line, we evaluated the development of the bouton-like structure. Interestingly, these bouton-like structures were not detected in young (1-month old) mice but appeared in mice older than 3-month old. The number and size of the bouton-like structures increased in an age-dependent manner up to 6 months. After the 6 months, the amount of bouton-like structures did not increase although their size kept increasing. Surprisingly, these structures were not immunopositive to SV2, a marker for synaptic vesicle. In addition, these structures did not show calcium transient induced by the electrical stimulation of LOT in an acute slice preparation in which the LOT structure were almost intact. Therefore, these structures would not be canonical presynaptic sites, in which calcium is used for vesicle release. Moreover, our immunohistochemical analyses found that some of the bouton-like structures expressed the mitochondria marker, Tom20, and the autophagy marker, p62. These data suggest that the bouton-like structures in the LOT would rather be structures reflecting the change of internal metabolic conditions associated with aging.

Disclosures: F.M. Seibt: None. **F. Imamura:** None. **S. Nagayama:** None. **T. Sato:** None. **R. Homma:** None.

Poster

663. Chemosensory Processing III

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Program #/Poster #: 663.17/I34

Topic: D.05. Olfaction and Taste

Support: NIH Grant GR5270777

Title: Neural circuit mechanisms of information routing in the mouse olfactory cortex

Authors: *S. DASTE[1], S. REZAEI-MAZINANI[2], W. A. MENA OROSTICA[2], A. FLEISCHMANN[1];
[1]Neurosci. and the Robert J. and Nancy D. Carney Inst. for Brain Sci., Brown Univ., Providence, RI; [2]Ctr. for Interdisciplinary Res. in Biol. (CIRB) and CNRS UMR 7241 and INSERM U1050, Collège de France, Paris, France

Abstract: The Piriform Cortex (PCx), part of the mammalian olfactory system, encodes information about olfactory stimuli and odor memories. Piriform neurons project broadly to multiple target areas, including the Lateral Enthorinal Cortex (LEC), Cortical Amygdala (CoA), and the medial Prefrontal Cortex (mPFC). However, whether odor information is selectively transmitted to different target areas or broadly transmitted everywhere is poorly understood. Moreover, it is also unknown how information routing is shaped by learning and experience. Here we address these questions by recording neuronal activity in the PCx of awake behaving mice using GRIN lens technology and two-photon microscopy. We monitor the activity of a specific subset of PCx neurons by labelling neurons based on their projection targets using retrogradely transported AAVs. We chronically record the activity of up to 300 PCx neurons, and we can determine their odor-evoked population response properties under passive odor presentation and during appetitive learning. We will present preliminary data characterizing the response properties of piriform projecting neurons to LEC, CoA, mPFC and we will test our hypothesis that learning and experience reshape piriform response by recruiting relevant subsets based on context and valence. Together, our experiments will provide new insights into how olfactory information from piriform is broadcasted to targeted areas and how it is shaped by experience.

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Poster

663. Chemosensory Processing III

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Program #/Poster #: 663.18/I35

Topic: D.05. Olfaction and Taste

Support: Howard Hughes Medical Institute
Helen Hay Whitney Foundation

Title: The role of olfactory landmarks in place cell formation and navigation

Authors: *W. FISCHLER[1], N. R. JOSHI[3], L. J. KITCH[4], M. J. SCHNITZER[5], L. ABBOTT[2], R. AXEL[1];
[1]ZMBBI, [2]Neurosci., Columbia Univ., New York, NY; [3]Dept. of Cell Biol., Harvard Med. Sch., Boston, MA; [4]Stanford Univ., Stanford, CA; [5]Depts. Biol. & Applied Physics, Stanford Univ. Dept. of Biol., Stanford, CA

Abstract: A cognitive spatial map in the hippocampus combines internal information generated by an animal's movement in space (path integration) with sensory information from external landmarks. We have examined the convergence of external olfactory cues with internal self-

motion information to determine how mice represent, recognize, and employ olfactory landmarks to estimate their location relative to a reward site. We recorded the activity of GCaMP6f expressing neurons in the CA1 region of the hippocampus with a micro-endoscope while mice learned an odor guided virtual navigation task. Head-fixed mice were required to run on a featureless rotating ball in total darkness to reach a water reward located a virtual linear distance of 4 meters from the starting point. After 1-2 weeks of training without odor cues, 5.8% of the imaged neurons exhibited the properties of place cells. The number of place cells was maximal at the starting location and decreased exponentially with distance along the track. In the absence of odor cues the mice decreased their running speed and initiated anticipatory licking after traveling about 2m along the 4m track.
The mice then performed the task for 4 days with odor cues at 1m and 3m, and we observed a 6-fold increase in the number of place cells. In trials with either limonene or pinene 35% of recorded cells were classified as place cells. The animals suppressed licking and maintained high running speeds for ~3.5m of travel, licking ~0.5m before the goal location. The increase in place cell numbers occurred at all locations but was particularly pronounced at 1m and 3m, the locations of odor cues with the number of place cells decreasing exponentially as a function of distance from the cue. The place cell representations differed on limonene and pinene trials, demonstrating remapping.
Examining the emergence of place cells during training allowed us to observe the convergence of path integration with olfactory cues to establish spatial landmarks. Over the 4 days of training the number of place cells steadily increased. Place cells first emerged at the location of the 1m odor cue and as more place cells formed in the region between 1m and 3m, we observed the generation of an additional peak in place cell density at 3m. The emergence of place cells at the 3m odor cue coincided with the improvement in behavior. The topology of the hippocampal map, represented by population state trajectories, evolved to represent both the sensory and spatial structure of the environment. These results are consistent with a transformation of the internal representation of odor cues into distinct odor landmarks that serve to guide navigational behavior.

Disclosures: **W. Fischler:** None. **N.R. Joshi:** None. **L.J. Kitch:** None. **M.J. Schnitzer:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inscopix. **L. Abbott:** None. **R. Axel:** None.

Poster

663. Chemosensory Processing III

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Program #/Poster #: 663.19/I36

Topic: D.05. Olfaction and Taste

Support: 5U19MH114830-02

Title: Three-dimensional reconstruction of the layers of the main olfactory bulb and hippocampus proper in the allen mouse brain common coordinate framework

Authors: *Q. WANG, J. ROYALL, M. NAEEMI, K. HIROKAWA, L. NG, H. ZENG, J. A. HARRIS;
Allen Inst. for Brain Sci., Seattle, WA

Abstract: The main olfactory bulb and hippocampus proper in the mouse brain have multi-layered cellular architectures, and play crucial roles in olfaction, and in spatial navigation, learning and memory, respectively. In widely used 2D mouse brain atlases (Dong, 2018; Paxinos and Franklin, 2012), these layers were delineated based on cytoarchitecture and chemoarchitecture. However, in 3D atlases based on MRI images (Kjonigsen et al., 2014), transformation from 2D to 3D (Hjornevik et al., 2007), or our serial 2 photon tomography average template with multimodal references (Allen Mouse Brain Common Coordinate Framework, version 3, CCFv3), these layers were not three-dimensionally reconstructed. Since individual layers contain different cell types and efferent and afferent connections, it is important to reconstruct these layers in 3D for better understanding the functions of the two structures. The layers of the main olfactory bulb and hippocampus proper can be revealed with multimodal reference datasets, including cytoarchitecture, myeloarchitecture, genoarchitecture, chemoarchitecture and connectivity. To reconstruct these layers in CCFv3, we curated multimodal reference datasets from the Allen Institute portal (brain-map.org) in addition to the average template in which different layers of the main olfactory bulb and hippocampus proper have distinct brightness. By overlaying these references to the average template, we confirmed that the distinct bands of brightness in the average template correspond to specific layers of the two structures, and manually reconstructed these layers in 3D space, pixel by pixel, with 3D drawing software ITK-SNAP. In this study, we reconstructed 5 layers in the main olfactory bulb and CA3, and 4 layers in CA1 and CA2. In total, we added 14 3D reconstructed volumes into CCFv3, making 670 total structures in the final product. By adding new 3D volumes into CCFv3, we also demonstrate the flexibility of CCFv3 which can be improved periodically with additional data and updated knowledge. This improvement is critical for the detail and accuracy of neuroanatomical structures in CCFv3. Therefore, the newly updated CCFv3 will provide wider applications as a standard 3D digital mouse brain atlas for integrating, analyzing, visualizing, and modeling multimodal large-scale datasets generated from the Allen Institute for Brain Science and across the neuroscience community.

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Poster

663. Chemosensory Processing III

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Topic: D.05. Olfaction and Taste

Support: NIH Grant 4R00DC014516-03
National Science Foundation Graduate Research Fellowship

Title: A molecular atlas of cortical chemosensation

Authors: *J. R. HOWE, VI[1], C. L. CHAN[2], D. LEE[2], C. M. ROOT[2];
[1]Neurosci. Grad. Program, [2]Biol. Sci., UCSD, La Jolla, CA

Abstract: The paleocortex is an evolutionarily ancient, highly distinct region of the brain, with a unique three-layered structure and a wide range of functions centered on olfaction. One such region, the posterolateral cortical amygdala (plCoA), has recently been shown to assign innate emotional valence to certain odors, a dense connectivity to subcortical structures associated with the assigned valence, and a rostrocaudal valence topography. However, nearly nothing is currently known about the molecular features of any of the plCoA's constituent cells, preventing genetic access and drastically constraining the range of research that can be done in the region. Here, we performed droplet single-cell RNA sequencing on the paleocortical plCoA and the neocortical gustatory cortex (GC), a chemosensory region with a rostrocaudal taste topography, to create transcriptomic profiles of tens of thousands of individual cells, revealing dozens of classes of novel cell types and their relationships in these cortices. We have isolated cells based on their cortical layer, sex, and rostrocaudal coordinates, allowing identification of layer-specific, sex-specific, and topographic features among subpopulations of cells in the plCoA and GC. We also compare shared and distinct features between transcriptomes of cells in the plCoA and GC, illuminating the molecular relationship between these two regions in particular and the two cortical structures in general. In these experiments, we have identified molecular features of paleocortical structure, as well as created a resource that will greatly expedite genetic access to GC and plCoA subpopulations, accelerating future research into cortical chemosensation.

Disclosures: J.R. Howe: None. **C.L. Chan:** None. **D. Lee:** None. **C.M. Root:** None.

Poster

663. Chemosensory Processing III

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Program #/Poster #: 663.21/DP07/I38

ControlExtraData.DynamicPosterDisplay:
Dynamic Poster
Topic: D.05. Olfaction and Taste

Title: Towards characterizing brain-wide neural circuitry dynamics underlying chemosensory avoidance in larval zebrafish

Authors: *K. SY, D. CHAN, H. LAI, Z. LI, J. CHOI, V. MOK, H. KO;
The Chinese Univ. of Hong Kong, Hong Kong, China

Abstract: Chemicals provide important environmental cues to guide animal behavior. While bilateral olfactory input is required for several animal species for optimizing odor navigation, the underlying circuit mediating bilateral integration of chemosensory information remains poorly understood. We employ larval zebrafish to study the bilateral integration of chemical signals upon encountering cadaverine, a diamine molecule released by decaying flesh, that drives chemosensory guided behaviour. In a customized arena where fluidic streams are spatially defined by laminar flow, we observed that 5 - 7 dpf freely swimming zebrafish larvae actively avoid the cadaverine-containing stream by increasing turn angles of subsequent swim bouts. Such behaviour necessitates bilateral olfactory input, as unilateral ablation of olfactory placode largely compromised the avoidance. Further on, we have built an integrated microfluidics - light sheet imaging platform for precise chemical stimulation while performing simultaneous neural activity and behavioural imaging, to characterize the brain-wide circuitry mediating the sensorimotor transformation.

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Poster

663. Chemosensory Processing III

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Program #/Poster #: 663.22/I39

Topic: D.05. Olfaction and Taste

Support: Howard Hugues Medical Institute

Title: Unstable odor responses in piriform cortex

Authors: *C. E. SCHOONOVER[1], A. P. FINK[2], R. AXEL[3];
[2]Neurosci., [3]ZMBBI, [1]Columbia Univ., New York, NY

Abstract: The tuning properties of sensory neocortices are stably maintained over long periods in spite of continuous dendritic spine turnover. We have measured the stability of odor representations in piriform cortex (PCx), a three-layered paleocortical structure. In order to observe stimulus responses separated by long intervals, we developed an electrophysiological recording strategy that supports observation of a fixed population of single units for up to one month. In animals presented odorants at weekly intervals we find that representations are unstable; a linear classifier trained to classify responses to a panel of odorants recorded on day 1 performs nearly at chance one month later. However, we observe long term stability if odorants are presented at daily intervals. This stability depends on regular exposure: if daily odorant presentation is halted, representations become unstable once again. These results contrast with the stability of representations in sensory neocortices, even when stimulus presentation is infrequent. We hypothesize that this distinction reflects differences in circuit architecture between neocortex and paleocortex. Neocortex receives patterned thalamic input and exhibits local horizontal connectivity. This organization permits loss and restoration of similarly tuned synapses, ensuring the stability of sensory tuning. In contrast, PCx is characterized by unstructured innervation from olfactory bulb and distributed horizontal connections. Synaptic turnover in PCx is therefore likely to result in instability in stimulus representations, presenting a problem for the maintenance of learned behaviors elicited by odors. Our observations suggest that if PCx encodes odor identity, these representations must be transmitted to a more stable repository of odor information. Alternatively, PCx may not encode odor identity and instead may function in more transient processes of sensory recognition and learning.

Disclosures: C.E. Schoonover: None. **A.P. Fink:** None. **R. Axel:** None.

Poster

663. Chemosensory Processing III

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Topic: D.05. Olfaction and Taste

Support: NSF 1724218

Title: Normative modeling of sensory network dynamics for stimulus tracking

Authors: *S. MALLIK[1], D. SAHA[2], B. RAMAN[2], S. CHING[1];
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Abstract: We consider the question of how early sensory networks enable the detection and tracking of sensory stimuli in a combinatorial coding space. We do this through a normative, optimization-based framework wherein sensory networks provide input to a downstream latent decoder. Specifically, our model for sensory tracking uses the notion of a detection space where high dimensional stimuli are mapped via a dynamical, linear decoder onto lower dimensional, mutually orthogonal axes corresponding to different stimulus identities. The normative objective of the sensory network is to provide an activity to the decoder in a way that achieves high-fidelity trajectories (i.e., sensory decoding/tracking) in an efficient manner. It turns out that the optimal encoding strategy achieves this objective when sensory neurons respond to a stimulus onset by emitting a phasic transient followed by persistent tonic excitation. Upon withdrawal of a stimulus, the decoded latent state returns to its equilibrium following another short burst of phasic activity. Further, these optimal sensory responses are generated through a network with architecture and dynamics that are commensurate with known combinatorial coding systems, such as olfaction. Indeed, the synthesized network is highly compatible with that which is observed in the olfactory network of locusts. Interrogating the modeled network makes several predictions about tradeoffs in the speed and accuracy of sensory detection, as well as responses to stimulus mixtures.

Disclosures: S. Mallik: None. **D. Saha:** None. **B. Raman:** None. **S. Ching:** None.

Poster

663. Chemosensory Processing III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 663.24/I41

Topic: D.05. Olfaction and Taste

Support: NIH grant T32 AG020506
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Northwestern PDMD Advisory Council

Title: Mapping *in vivo* olfactory network connections in the human brain

Authors: *S. L. COOPER[1], D. SMITH[1], G. ZHOU[1], C. ZELANO[3], F. PESTILLI[4], T. B. PARRISH[2], T. KAHNT[1];
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Abstract: Olfaction is important for human cognition, but the anatomy of the human olfactory system is poorly understood. Diffusion magnetic resonance imaging (dMRI) is an attractive method for characterizing the fiber pathways that connect olfactory regions, but these areas are often obscured by blurring and imaging artifacts, due to their close proximity to the sinuses. Typical tensor models used to model white matter structure are also incapable of characterizing curving and crossing fibers within a single voxel. In this project, we addressed these shortcomings and designed a dMRI protocol for visualizing olfactory system structure. Subjects (n=5, 4 female) participated in olfactory threshold, odor discrimination, and odor identification tasks. We then collected dMRI and anatomical scans. Subjects wore 3D-milled head cases, matched to the scanner coil and to each subject's face and head, preventing motion during scanning and improving image quality. We collected dMRI scans with 1.5 mm isotropic resolution, b = 1000 s/mm^2, and 90 diffusion directions. We used a WIP (Siemens work in progress) multi-shot echo planar imaging sequence to reduce blurring and image artifacts. We also collected a 1.0 mm resolution whole brain T1-weighted anatomical scan, and a 0.5 mm resolution T2-weighted scan covering the ventral-anterior portion of the brain, including the orbitofrontal cortex and olfactory bulbs. Anatomical images were used to locate olfactory regions of interest, which were used as seeding regions for generating tractography models. We fit a constrained spherical deconvolution model from MRtrix2 to the dMRI data, capable of characterizing crossing and curving fibers within single voxels.Tractography data seeded from the olfactory bulb show the lateral olfactory tracts. Tracts were observed passing between piriform cortex seeds and orbitofrontal cortex, anterior cingulate cortex, fornix, mediodorsal thalamus, amygdala, hippocampus, entorhinal cortex, insula, and occipital cortex. Future analyses will determine microstructure properties for white matter voxels in the identified pathways, including fractional anisotropy, an indirect measure of white matter integrity, and relate them to measures of olfactory perception.

Disclosures: S.L. Cooper: None. **D. Smith:** None. **G. Zhou:** None. **C. Zelano:** None. **F. Pestilli:** None. **T.B. Parrish:** None. **T. Kahnt:** None.

Poster

663. Chemosensory Processing III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 663.25/I42

Topic: D.05. Olfaction and Taste

Support: T32 HL 007909
R21 DK 118505
R01 DC 015426

Title: Satiety alters sensitivity: Effects of food intake on olfactory processing in humans

Authors: *L. K. SHANAHAN[1], T. KAHNT[1,2];
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Abstract: Odors serve as important cues for guiding food search and intake. Some previous work has demonstrated that olfactory sensitivity is enhanced in the hunger state when compared to the sated state, which could facilitate food search when nutrients are needed most. However, there are conflicting reports in the literature, and the neural mechanisms underlying these changes are not well understood. Here, we designed a novel paradigm to measure sensitivity to food odors. Human subjects performed a binary choice task where they smelled odor mixtures containing food and non-food components (e.g., pizza and pine), and indicated the component they perceived as dominant in the mixture. To compare behavior across hungry and sated states, subjects completed this task before and after a food odor-matched meal (e.g., pizza). Preliminary behavioral findings suggest that subjects are less likely to identify the food component as dominant in the mixture in the sated state, specifically for the mixture containing the matched food odor. By using functional magnetic resonance imaging (fMRI), we can study the neural correlates underpinning this shift in choice behavior. More specifically, we can gain insight into whether state-dependent changes in odor perception are driven by bottom-up or top-down influences. Our work will promote a richer understanding of the relationship between food intake and odor perception, which may have implications for eating disorders and obesity.

Disclosures: L.K. Shanahan: None. **T. Kahnt:** None.

Poster

663. Chemosensory Processing III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 663.26/I43

Topic: D.05. Olfaction and Taste

Title: Resting state fMRI study of the olfactory region in autism

Authors: *M. L. LAWRENCE, T. IKUTA;
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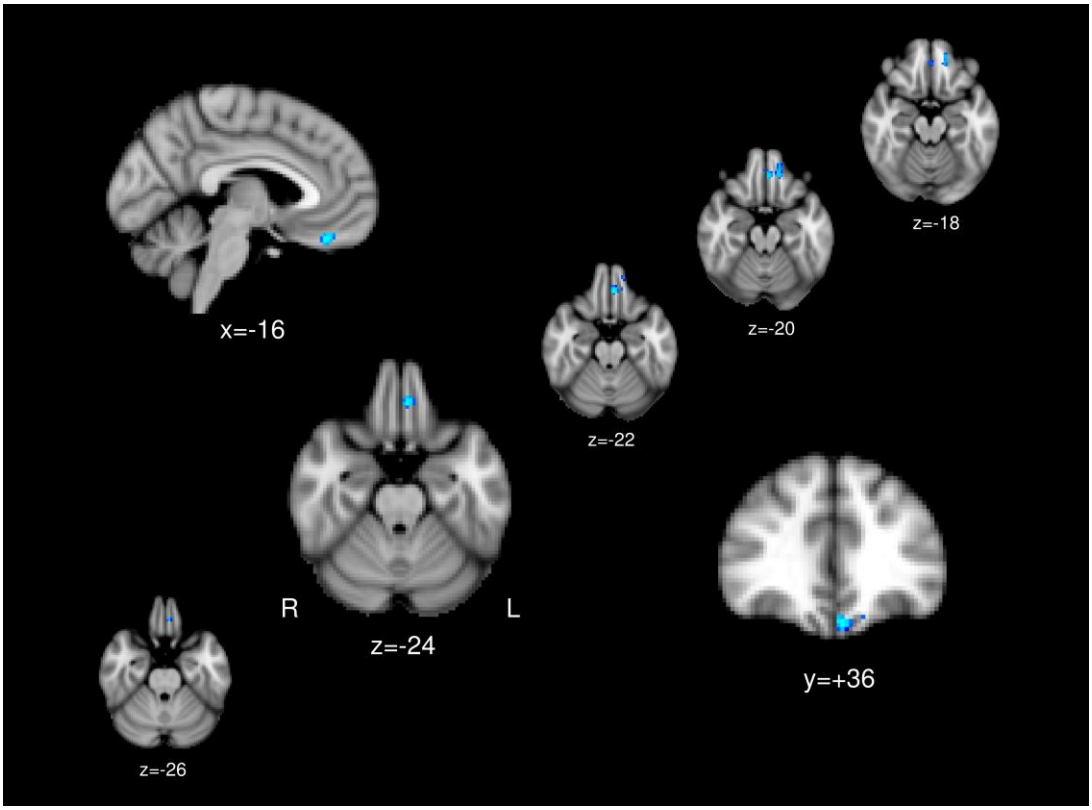
Abstract: Olfactory dysfunction has been found in many neurological and psychiatric disorders such as Schizophrenia, Alzheimer's disease, and Parkinson's disease. Autism Spectrum Disorder (ASD) has also been found to involve olfactory dysfunctions. However, the olfactory system in ASD has rarely been studied despite that the olfactory system may uniquely reveal underlying conditions. In this study, we aimed to examine the olfactory regions of the brain to elucidate the other parts of the brain that are differently connected to the olfactory regions in ASD. Using resting state fMRI data from Autism Brain Imaging Data Exchange (ABIDE), we analyzed the functional connectivity of the olfactory regions in 60 individuals with ASD and 60 without ASD.

Whole brain functional connectivity of the four olfactory regions (Olfactory Bulb, Olfactory Tract, Anterior Piriform Cortex, and Posterior Piriform cortex) was independently tested to test the group differences. While three other regions did not show a statistically significant difference between two groups in their connectivity to the rest of the brain, the APC showed lower connectivity to the ventromedial PFC (vmPFC) in the ASD group compared to the typically developing group. The vmPFC has been shown to be responsible for self-related processing and values in decision making. Consistent with previous findings, our results suggest that the olfactory processing and decision making is not well communicated. It is implicated that odor information is not well registered to the processes of decision making.



Disclosures: **M.L. Lawrence:** None. **T. Ikuta:** None.

Poster

663. Chemosensory Processing III

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 663.27/I44

Topic: D.05. Olfaction and Taste

Title: Primacy model and the evolution of the olfactory receptor repertoire

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[1]Cold Spring Harbor Laboratory, Watson Sch. of Biol. Sci., Cold Spring Harbor, NY; [2]Neurosci. Inst., New York Univ., New York, NY; [3]Cold Spring Harbor Lab., Cold Spring Harbor, NY

Abstract: Understanding sensory processing relies on establishing a consistent relationship between the stimulus space, its neural representation, and perceptual quality. In olfaction, the difficulty in establishing these links lies partly in the complexity of the underlying odor input space and perceptual responses. Based on the recently proposed primacy code for concentration invariant odor identity representation and a few simple assumptions, we have developed a theoretical framework for mapping the odor input space to the response properties of olfactory receptors. We analyze a geometrical structure containing odor representations in a multidimensional space of receptor affinities and describe its low dimensional implementation, the primacy hull. We suggest statistical tests that can be used to detect correlations in receptor-ligand activity or olfactory connectivity data consistent with a primacy hull. We further discuss implications for the structure of feedforward connectivity in the early olfactory network.

Disclosures: H. Giaffar: None. **D. Rinberg:** None. **A. Koulakov:** None.

Poster

663. Chemosensory Processing III

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Program #/Poster #: 663.28/J1

Topic: D.05. Olfaction and Taste

Support: NIH Grant DC014701

Title: A physicochemical model of odor sampling

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Abstract: To date, efforts to describe olfactory physicochemical sampling have been heuristic. The primary strategy has been to compose lists of many physicochemical properties, or molecular descriptors, of various odorous molecules and cross-reference these lists with perceptual or physiological datasets. While these approaches offer some predictive utility, they are not ultimately generative. For example, they cannot be used to explain the perceptual decomposition of odor mixtures, nor to study how the same physicochemical odor scene will be differently sampled by the noses of different animal species (potentially resulting in different profiles of similarity). We here present a general physicochemical sampling model based on established pharmacological laws in which arbitrary combinations of odorant ligands and receptors can be constructed and their individual and collective effects on the resulting odor

representation studied. Receptors occupy regions of a physicochemical quality space, or Q-space; this space maps the strength and efficacy of ligand-receptor interactions and enables recognition of the physical similarities among chemical species that are likely to be reflected in overlapping receptor interactions. Odors may comprise one or many ligands in characteristic concentration ratios; each ligand exhibits receptor-specific affinities and efficacies. Ligands interacting with common receptors compete with one another for dwell time; these competitive interactions appropriately simulate the degeneracy that fundamentally defines the capacities and limitations of odorant sampling. The outcome of these competing interactions is expressed as a pattern of receptor activation levels, thereafter mapped to glomerular presynaptic activation levels based on the convergence of sensory neuron axons. The metric of greatest interest is the perceptual discrimination sensitivity, a measure of how effectively the olfactory system at this level is able to recognize a small change in the physicochemical quality of a stimulus. This model captures the effects of changing the numbers and selectivities of receptors, the effects of increased numbers of ligands (eventually yielding "olfactory white"), the benefits of antagonist ligands, and the modest reduction in discrimination exhibited by transgenic mice in which olfactory sensory neuron targeting of glomeruli has been disrupted.

Disclosures: T.A. Cleland: None. **M.E. Gronowitz:** None. **A. Liu:** None.

Poster

664. Selective Attention

Location: Hall A

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Program #/Poster #: 664.01/J2

Topic: D.07. Vision

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JSPS KAKENHI Grant Number 19H01091
Magnetic Health Science Foundation
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Title: Influence of static magnetic field stimulation on the accuracy of tachystoscopically presented line bisection

Authors: *H. KIRIMOTO[1], T. MIMA[2], K. OGATA[3], H. NAKAZONO[4], D. TSURU[1], N. KUBO[1], X. CHIN[1], S. TOBIMATSU[5];
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Abstract: Introduction: Oliviero et al. (2011) reported that 10 min of transcranial static magnetic field stimulation (tSMS) using a strongly powered cylindrical neodymium, iron and boron (NdFeB) magnet can reduce the amplitude of motor evoked potentials (MEPs), Since then, tSMS is getting a lot of attention as a new non-invasive brain stimulation (NIBS) techniques next to conventional methods, such as rTMS and tDCS. Further, we showed that tSMS over S1 decreases the amplitude of the N20 component of somatosensory evoked potentials (SEPs) following median nerve stimulation (Kirimoto et al., 2014), tSMS over M1 reduces the N33 component of SEPs (Kirimoto et al., 2016), and modulate cortical nociceptive processing (Kirimoto et al., 2018), similar to other NIBS techniques.
Objective: This study aimed to investigate the possibility of non-invasive modulation of visual spatial cognition by the application of tSMS over the parietal association cortex or temporal lobe in healthy humans.
Methods: Subjects performed a visuo-spatial task requiring judgements about the symmetry of prebisected lines. Visual stimuli consisted of symmetrically or asymmetrically transected lines, tachystoscopically presented for 150 ms on a computer-monitor. Performance was examined before immediately after, and 10 min after tSMS of 20 min. We used a cylindrical NdFeB neodymium magnet (diameter, 50 mm; height, 30 mm) with a surface magnetic flux density of 534 mT, maximum energy density of 49 MGOe, and a nominal strength of 862 N for tSMS. An NdFeB magnet or a non-magnetic stainless cylinder (for sham stimulation) was settled on the scalp over the right parietal association cortex (P4) or temporal lobe (C6) of 16 subjects for periods of 20 min.
Results: 9 of 16 subjects misjudged prebisected lines by consistently underestimating the length of the right-side segment (that is by judging lines to be exactly prebisected when the bisection mark was actually located to the left of the true midpoint, or by judging segment longer when lines were exactly bisected). In these subjects who showed leftward bias, scores of tasks were significantly improved at tSMS over C6 as compared to tSMS over C4 and sham stimulation conditions. In the right-biased group, no intervention effects ware observed for stimulation under any condition.
Conclusions: The main result of the present study is that transient inhibition of right temporal lobe, induced by tSMS, improves the visual spatial cognition, as tested with a line's length judgement task.

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Poster

664. Selective Attention

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 664.02/J3

Topic: D.07. Vision

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Title: fMRI guided electrophysiology of spatial attention shifts in the macaque superior parietal lobule

Authors: *M. DE VITIS[1,2,3], P. F. BALAN[1,3], C. GALLETTI[2], P. FATTORI[2], R. VOGELS[1,3], W. VANDUFFEL[1,3,4,5];
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Abstract: We continuously shift our attention between items in the visual environment, and this represents a fundamental process for guiding goal-directed behavior. Visual spatial attention improves behavioral performance by allowing subjects to focus on the most relevant information in complex scenes and suppress irrelevant signals. Several human fMRI and TMS studies showed the involvement of superior parietal lobule (SPL) in covert shifts of attention. Despite hints from monkey electrophysiology (Galletti et al., 2010) and fMRI (Caspari et al., 2015), still little is known about the underlying neuronal mechanisms. Guided by monkey fMRI maps, we recorded single and multi-unit activity from shift-selective regions in medial SPL (parietal areas V6/V6A) using laminar probes.
Our covert selective spatial attention paradigm was highly similar to that of human (Molenberghs et al., 2007) and monkey (Caspari et al., 2015) fMRI experiments, and allowed us to dissociate attentional shift and stay, and motor events (used to probe the allocation of attention). Stimuli consisted of 2 pairs of yoked shapes, each containing a relevant and irrelevant stimulus (one located in the center of the receptive field (RF), and the other diametrically opposed). The display always contained one of the two pairs. A replacement of the first stimulus pair by the second could induce a spatial attention shift when the relevant stimulus position changed to the opposite visual hemifield (shift event). Alternatively, when the relevant stimulus of the new pair appeared at the same position as the relevant stimulus of the preceding pair this corresponded to a stay event. The allocation of attention was probed behaviorally by dimming events (50% of the trials) of the relevant/irrelevant stimuli, separated in time from the shift/stay events.
We recorded activity from 192 multi-unit sites in areas V6/V6Av of one rhesus monkey. We found that the average population activity of all recorded neurons was higher for shift than stay events (Wilcoxon test, $p<0.05$, FDR corrected) when the direction of the shifts pointed towards the RF. Conversely, when shifts pointed to the opposite direction, the activity for stay events was higher in early and late stages of the attention period (Wilcoxon test, $p<0.05$, FDR corrected). Shift-selective population activity peaked around 40-60 ms after event onset, when 66.7% of cells showed significant shift-selective activity (contrast shift vs. stay, Wilcoxon test, $p=10^{-5}$).

Consistent with the human and monkey fMRI data, these results show a strong correlate of shifting covert spatial attention at neuronal level within parietal areas V6/V6A in the absence of overt behavior.

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Poster

664. Selective Attention

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Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 664.03/J4

Topic: D.07. Vision

Support: DFG SFB 779/TP-A1

Title: Isolating subcomponents of the N2pc: item-, feature-, and space-based selection

Authors: *M. V. BARTSCH[1], H. STRUMPF[2], C. TEICHMANN[2], M. A. SCHOENFELD[2,1,3], J.-M. HOPF[2,1];
[1]Leibniz Inst. for Neurobio., Magdeburg, Germany; [2]Univ. of Magdeburg, Magdeburg, Germany; [3]Kliniken Schmieder Heidelberg, Heidelberg, Germany

Abstract: The N2pc is a well-known component of the event-related brain response, widely used to investigate the allocation of attention during visual search. Visual search, however, involves a number of attentional selection processes, including feature-based attention (feature guidance), shifts of spatial attention, and target discrimination. The separate contribution of those subprocesses to the N2pc is often not acknowledged, and currently not well understood. Here, we report data from two ERP experiments aiming at clarifying the specific contribution of feature-, space- and item selection to the N2pc response. To this end, we recorded event-related potentials (ERPs) in human observers when performing two experiments employing different versions of a cued visual search task. Experiment 1 (23 subjects) was setup to isolate spatial shift of attention by comparing tasks where subjects either searched for a color-defined target across the whole visual field (VF) versus within a pre-defined VF. Experiment 2 (22 subjects) assessed the contribution of feature-based attention by comparing the selection of a color-defined target in a pre-defined VF with the selection of the same target at a pre-defined spatial location independent of its color. We find that, while all experimental conditions elicit robust N2pc effects, variations of amplitude and time course of the ERP response revealed a sequence of attentional subprocesses. Specifically, feature-attention was found to be reflected by early portions of the N2pc, while later portions index processes of target discrimination. Intermediate portions following feature-attention reflect shifts of attention. Taken together, the results

emphasize that the N2pc should be conceived of as a multi-component process that can be decomposed in feature, space and item selection processes.

Disclosures: M.V. Bartsch: None. **H. Strumpf:** None. **C. Teichmann:** None. **M.A. Schoenfeld:** None. **J. Hopf:** None.

Poster

664. Selective Attention

Location: Hall A

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Program #/Poster #: 664.04/J5

Topic: D.07. Vision

Support: NIH R01EY005911

Title: Isolating attentional modulation in superior colliculus associated with behavioral sensitivity, decision criterion and motor preparation

Authors: *S. GHOSH, J. H. R. MAUNSELL;
Dept. of Neurobio., Univ. of Chicago, Chicago, IL

Abstract: Like those in visual cerebral cortex, neurons in the superior colliculus (SC) of monkeys are strongly modulated by attention. It has been a point of contention whether attention-related enhancement of neuronal activity in the SC is associated with selective increase in behavioral *d'* in neurons' receptive field or is instead associated with animals' response bias, which can be closely linked with motor planning. We trained rhesus monkeys in a novel visual orientation-change detection task that precisely dissociates perceptual sensitivity (*d'*), decision criterion and motor planning by presenting choice targets spatially orthogonal to the attended locations. Monkeys' attentional performance (*d'*) and decision criterion at the neuron's receptive-field location were independently controlled, and sequentially switched between high and low levels within short blocks of trials by adjusting relative reward probabilities associated with stimuli in the left and right visual hemifields. Multiple SC neurons were recorded simultaneously while the animal did the task. Results from two animals showed that SC neurons increased their rate of firing when behavioral selectivity (*d'*) increased at their receptive-field location. This attentional modulation was stronger for visuomotor neurons compared to purely visual neurons, and was negligible in motor neurons. Unlike selective *d'*, change in decision criterion had no effect on spiking of these same SC neurons. These results confirmed that SC neurons contribute selectively to specific attentional states, and increased attentional performance can enhance spiking of SC neurons independent of decision criterion or motor planning towards the receptive field.This behavioral task has special significance for isolating distinct behavioral components associated with attention states in brain areas that respond to motor actions.

Disclosures: S. Ghosh: None. **J.H.R. Maunsell:** None.

Poster

664. Selective Attention

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 664.05/J6

Topic: D.07. Vision

Title: Properties of saccade vergence eye movements in athletes

Authors: *Y. YOSHIMURA[1], T. KIZUKA[2], K. MATSUDA[3], S. ONO[2];
[2]Hlth. and Sport Sci., [1]Univ. of Tsukuba, Ibaraki, Japan; [3]Human Informatics Res. Inst., AIST, Ibaraki, Japan

Abstract: It is well known that saccades are one of the eye movements to capture moving objects accurately with eyes. Saccades are rapid eye movements that shift the line of sight between successive points of fixation. For saccades in the two dimensions (2D) that are smaller than about 20 degrees, there is a linear relationship between peak velocity and amplitude. Saccades above 20 degrees, peak velocity shows a progressive increment with asymptotic values of about 500 degrees per second. The relationship between peak velocity and amplitude over a very wide range of saccades is called “main sequence”. Most of the previous studies dealing with saccades have reported saccades in the 2D. Although there are several studies have reported about saccades in the depth, it is still uncertain about the main sequence of saccade-vergence eye movements. Eye movements in the depth are called vergence eye movements. Vergence eye movements are disconjugate eye movements opposed to saccades in the 2D which are conjugate eye movements. Therefore, the purpose of this study was to clarify the properties of the main sequence of saccade-vergence eye movements in athletes. The subjects were college students belonging to college sports teams. The subjects were seated in front of stationary visual targets, which were 14 mm diameter balls positioned at different vergence angles (i.e. 2, 5, 10, 20 degrees). The subjects gazed at each target in order from nearest to farthest and vice versa. Ten repeated trials were conducted at each distance. Eye position was detected by the eye tracking system based on corneal reflections. The results showed that peak eye velocity of saccades in the depth task was slower than 2 dimensional saccades. Regarding the vergence eye movements, peak eye velocity of the convergence eye movement was larger than divergence. Furthermore, each subject showed different properties of the main sequence of saccade-vergence eye movements. These results could be associated with the different ability of depth perception in space.

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Poster

664. Selective Attention

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Program #/Poster #: 664.06/J7

Topic: D.07. Vision

Support: Princeton Neuroscience Institute Innovation Fund

Title: Visual awareness modulates visuospatial attention

Authors: *A. I. WILTERSON, N. KIM, C. KEMPER, M. S. A. GRAZIANO;
Princeton Univ., Princeton, NJ

Abstract: The discovery that attention to a stimulus and awareness of a stimulus are separable is arguably one of the most crucial experimental findings in the study of awareness. However, though separable, the two processes may still influence each other, and the nature of that interaction remains unresolved. The goal of the present five experiments was to examine how awareness influences attention. We measured two aspects of attention at three levels of awareness. Human subjects performed a visual attention task in which a cue affected subjects' attention, as measured by their reactions to a subsequent target. The task measured both exogenous attention drawn to the location of the cue, and endogenous attention directed to a location predicted by the cue. Awareness was tested at three levels. First, subjects were aware of all relevant aspects of the task. Second, subjects were visually aware of all stimuli, but unaware of the predictive contingencies between the cue and target. Third, subjects were unaware of the contingencies and also visually unaware of the cue. The results showed that all aspects of attention measured here were possible under all awareness conditions. Removing awareness of the cue-target contingencies had little effect on the present measures of attention. Removing awareness of the cue also left exogenous and even endogenous aspects of attention present, but endogenous attention was slower to develop. The results suggest that awareness and attention interact, but that awareness plays a modulatory rather than a necessary role.

Disclosures: A.I. Wilterson: None. **N. Kim:** None. **C. Kemper:** None. **M.S.A. Graziano:** None.

Poster

664. Selective Attention

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Topic: D.07. Vision

Support: Office of Naval Research (ONR) Multidisciplinary University Initiative (MURI), N00014141067

Title: Multifaceted visual search reveals separate cortical subsystems for different aspects of the task

Authors: *S. SLIVKOFF[1], L. WEHBE[2,1], J. GALLANT[1];
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Abstract: Introduction: Previous studies show that the attention state of the brain affects its representation of visual features (Cukur et al. 2013, Harel et al. 2014, Baldauf et al. 2014). However, these studies only probed a limited stimulus set or a limited number of attention states. This makes it difficult to determine whether their results generalize to new conditions or if they are only relevant to the conditions examined. These previous studies were also unable to fully establish how their results might be affected by behavioral factors such as task difficulty and target detection.
Methods: We use functional magnetic resonance imaging (fMRI) to investigate the interaction between visual search and the representation of various task-relevant features in human cerebral cortex. For this we created a naturalistic visual search experiment with 14 distinct search conditions, controlling for potentially confounding factors such as target detection. This complex experimental design was optimized using mixed integer linear programming. We used voxelwise encoding models to characterize how cortical activity (as measured by the blood oxygen level-dependent signal) is affected by various experimental factors including the search target, stimulus content, target detection. We used separate datasets for training and testing in order to control for over-fitting, estimate prediction accuracy, and test generalization.
Results: We find that stimulus content, search target, target detection, and trial difficulty each elicit distinct spatial distributions of cortical activity. Each of these experimental factors predicts brain activity in different subregions within occipital, intraparietal, and prefrontal cortices. We also observe large differences in magnitude and spatial distribution of cortical activity associated with different search targets. In particular we find large differences in the spatial distribution of regions engaged by high-level semantic targets and low-level color targets. These effects are found in each individual subject, not merely at the group level.
Conclusion: We used a large number of distinct search conditions in order to characterize how attention interacts with a variety of experimental factors including search target, stimulus

content, target detection, and task difficulty. By characterizing all of these factors simultaneously within a cross-validated model, we were able to disentangle the effects of each factor and reveal that each predicts activity in a distinct set of cortical areas.

Disclosures: S. Slivkoff: None. **L. Wehbe:** None. **J. Gallant:** None.

Poster

664. Selective Attention

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Topic: D.07. Vision

Support: Wellcome Trust 093104
MRC MR/P013031/1
NIH EY014924

Title: Top-down retinotopic coordination of cortical state across V1, V4 and FEF of the Macaque

Authors: *J. VAN KEMPEN[1], M. BOYD[1], M. A. GIESELMANN[1], N. A. STEINMETZ[2], T. MOORE[3], T. A. ENGEL[4], A. THIELE[1];
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Abstract: Spontaneous activity fluctuations are ubiquitous in cortex. The strength and coordination of these fluctuations between neuronal populations are affected by cortical state, and they reflect changes to neural excitability which influence sensory processing and behaviour. Recent evidence (Engel et al., 2016) revealed that fluctuations in cortical state, previously presumed to occur synchronously across the entire cortex, are modulated locally by spatial top-down attention in V4. Global cortical states can thus be coordinated by cognitive demands and operate on a local scale. Such local, attention-related state changes also occur within primary visual cortex (V1), and they co-occur between V1 and V4 (Program No. 145.12, SFN 2018). Here we investigate whether the coordination of cortical state is mediated in a top-down, bottom-up, or globally coordinated manner.
We recorded simultaneously from V1 and V4 using 16-contact laminar electrodes in 3 Macaque monkeys performing a selective attention task. In a different data set, we recorded simultaneously from 16-contact laminar electrodes in V4 and single or 16-contact electrodes in FEF. We used a Hidden Markov Model (HMM) to characterize On-Off dynamics in multi-unit activity, and investigated the effects of these dynamics on activity within and across areas.
As reported previously, cortical states are correlated between V1 and V4. State transitions in

either area are preceded and followed by activity changes in the other area. Although coordination of state changes is not deterministic, on average, state transitions in V4 precede state transitions in V1, suggesting that V4 activity-changes drive cortical state changes in V1. Similarly, we found that FEF firing rate changes precede cortical state transitions in V4. Together these results suggest that On-Off transitions traverse along the cortical hierarchy in a top-down manner.
Fitting a 4-state HMM to V1 and V4, in which either or both areas could be in an Off or On state, revealed that, when both areas were in an Off state, it was more likely for V4 than V1 to transition to an On state. Moreover, when both areas were in an On state, it was more likely for V4 than V1 to transition to an Off state. Critically, behavioural performance increased from when both areas were Off, through V1 On - V4 Off, through V1 Off - V4 On, to V1 and V4 On. Thus, cortical state is coordinated across retinotopic locations in a feedback manner, whereby FEF activity changes precede state transitions in V4, and V4 state transitions precede V1 state transitions.

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Poster

664. Selective Attention

Location: Hall A

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Program #/Poster #: 664.09/J10

Topic: D.07. Vision

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Title: Linking noise correlations to spatiotemporal population dynamics and network structure

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Abstract: Co-fluctuations of neural activity are generally characterized as correlations between pairs of neurons, termed noise correlations. Noise correlations depend on anatomical dimensions, such as cortical layer and lateral distance, and they are also dynamically influenced by behavioral states, in particular, during spatial attention. Specifically, recordings from laterally separated neurons in superficial layers find a robust reduction of noise correlations during attention [1]. On the other hand, recordings from neurons in different layers of the same column find that changes of noise correlations differ across layers and overall are small compared to lateral noise-correlation changes [2]. Evidently, these varying patterns of noise correlations echo

the wide-scale population activity, but the dynamics of population-wide fluctuations and their relationship to the underlying circuitry remain unknown.
Here we present a theory which relates noise correlations to spatiotemporal dynamics of population activity and the network structure. The theory integrates vast data on noise correlations with our recent discovery that population activity in single columns spontaneously transitions between synchronous phases of vigorous (On) and faint (Off) spiking [3]. We develop a rate network model of cortical columns, which replicates cortical On-Off dynamics. Each unit in the network represents one layer—superficial or deep—of a single column. Units are connected laterally to their neighbors within the same layer, which correlates On-Off dynamics across columns. To test the theory, we analyze linear microelectrode array recordings of spiking activity from all layers of the primate area V4 during an attention task.
First, at the scale of single columns, the theory accurately predicts the broad distribution of attention-related changes of noise-correlations in our laminar recordings, indicating that they largely arise from the On-Off dynamics. Second, the network model mechanistically explains differences in attention-related changes of noise-correlations at different lateral distances. Finally, the theory accounts for differential modulation of noise correlations during spatial attention in superficial and deep layers. Our work provides a unifying framework that links network mechanisms shaping noise correlations to dynamics of population activity and underlying cortical circuit structure.
[1] Cohen & Maunsell, Nat Neurosci, 2009 [2] Nandy et al, Neuron, 2017 [3] Engel et al, Science, 2016

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Poster

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Title: Effects of local and global attention states on mouse superior colliculus activity during a visuospatial selection task

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Abstract: Visuospatial attention allows one to ignore vast amounts of irrelevant stimuli by enhancing the information in an important space of the visual field. Its neural correlates and its behavioral output have been studied in detail in cortex, but complementary substrates including the superior colliculus (SC) are less well studied, particularly in mice. We utilize a mouse spatial selection task in which the probability that a subtle stimulus change, whose detection is required to receive a water reward, is much higher (80%) in one side of the visual field than in the unlikely (20%) side (McBride, Lee & Callaway 2019). Under these circumstances, these "80/20" mice learn to ignore one location and selectively attend to the other. In contrast, "50/50" mice train with equal probability in either location and therefore perform equally in response to changes in either location. The task consists of 3 epochs: 1) a bilateral visual stimulus that corresponds to trial onset, 2) a variable delay period, and 3) a unilateral change in stimulus contrast that corresponds to the response window. Using this paradigm, we have previously made bilateral electrophysiological recordings in the primary visual cortex (V1) using 64 channel silicone laminar probes. Results demonstrate performance-related selective changes in local field potentials, noise correlations, and spiking activity in 80/20 mice, and global changes in 50/50 mice. This task therefore allows measurements of the neural correlates of spatial selection and can potentially be used to investigate underlying mechanisms as well as substrates that control spatial selection. Here, we use the same behavioral paradigm to investigate task-related activity during selective and global brain states while recording from SC. We find that SC activity in response to the visual stimulus at trial onset is much greater in the superficial layers of the likely hemisphere, even though that stimulus is identical in both visual fields. This suggests that SC on the "likely" side is primed to respond more strongly. In contrast, we find that following the stimulus change there is more activity on correct than incorrect trials. This effect is bilateral even though the stimulus change is unilateral. This activity is consistent with transfer of bilateral cortical activity (observed in our prior studies) being transferred to the SC and then being used to generate the motor response. Planned experiments that will allow SC to be optogenetically inactivated during specific epochs of this task are expected to allow the roles of the SC in attentional control, visual stimulus detection and motor responses to be separated.

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Poster

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Title: Humans can attend to complex latent image dimensions

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[4]Dept. for Psychology, [5]Ctr. for Vision Res., [6]Vision: Sci. to Application, York Univ., Toronto, ON, Canada

Abstract: The visual system needs to compress the massive amount of information in the natural world into a more tractable form. One method to accomplish this is to represent regularities within the high dimensional data by a small number of latent variables. This method of removing redundancies in the input has successfully explained a number of physiological properties of biological sensory systems. In a similar fashion, a type of artificial neural network called Generative Adversarial Nets (GAN) are trained to reproduce realistic looking images from a lower-dimensional input, and so provide a possible candidate for a low dimensional latent representation of natural images. If the brain uses latent variables similar to those learned by a GAN to efficiently represent natural images, then people should be able to attend to changes along such dimensions. In this experiment, subjects watched movies that consisted of sequences of images created by moving along regular paths through a GAN's latent space. We hypothesized that people are sensitive to changes in the GAN's latent space, and can attend to specific latent dimensions. We found that human observers were not only able to detect changes in the complex high-dimensional feature dynamics of these movies, but they are able to selectively attend to high-probability changes at the cost of detecting fewer low-probability ones. This is despite being unable to verbalize their strategy in simple terms of typical feature descriptors such as color, motion, or shape. This supports the idea that the GAN's latent dimensions are--to some extent--matched to the latent dimensions used by the human visual system.

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Topic: D.07. Vision

Support: NIH Grant EY025026

Title: Attention modulation of visual responses in cortical area V4 is cell-class and layer specific

Authors: X. WANG, A. S. NANDY, *M. P. JADI;
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Abstract: Perception is mediated by the concerted activity of a variety of neuronal cell classes that are embedded in the layered architecture of the sensory cortex. Attention is a critical component of perception, improving our ability to detect and discriminate task-relevant signals. To uncover the neural mechanisms of attention, it is therefore critical to understand how the activity of different cell classes is modulated by the deployment of attention. Here we analyzed cortical layer-specific neuronal responses from area V4 as monkeys performed an attention-demanding orientation change detection task. We used unsupervised machine learning techniques to identify cell classes based on either electrophysiological or functional properties. We found evidence of cell-class and layer-specific patterns of attention modulation in area V4. Visual responses show qualitatively different modulation patterns for the same cell class in different layers. Sensitivity to visual stimuli is also qualitatively different across cell classes and layers. This heterogeneity of attention-mediated information processing implies different functional modules that provide a neurobiological foundation for the normalization model of attention. Our findings also suggest that the normalization mechanism of attention is not homogenous across cortical layers.

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Poster

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Topic: D.07. Vision

Support: German Research Foundation (FOR 1847)

Title: Rapid learning of a fixation-based visual selective attention task and its effects on V1 firing rates

Authors: *J. R. DOWDALL, M. L. SCHOLVINCK, Y. ZHANG, A. PETER, J. VEZOLI, P. FRIES;
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Abstract: Behaviorally relevant information receives preferential processing through mechanisms of selective attention. In the lab, visual selective attention is typically studied with tasks requiring subjects to maintain fixation and deploy attention to a peripheral stimulus. Under natural conditions, primates typically direct their gaze to the attended stimulus. Therefore, we hypothesized that attention is intrinsically biased to the fixated stimulus. We trained several macaques (Macaca mulatta) in two versions of a change detection task, utilizing two simultaneously presented stimuli that extended from the fovea into the periphery. The stimuli were either photos of natural objects (e.g., fruits, leaves) or artificial shapes. At the fovea, the

two stimuli overlapped such that their depth ordering determined which stimulus was fixated. Stimulus changes were small local hue changes, appearing at random times and random positions within the peripheral portion of the stimuli. Four macaques learned task 1: They maintained fixation until a change occurred on either one of the two stimuli (equally probable), and were rewarded for saccading to the change. Subsequently, these macaques, and two macaques naïve to task 1, were trained in task 2. In task 2, they maintained fixation until two simultaneous changes appeared (one on each object), but were only rewarded for saccading to the change on the fixated object. All but one of the macaques (i.e., 5/6) learned task 2 within 14 training days (criterion: >80% correct; training of the remaining macaque ended for other reasons). This included two animals that had no prior experience with an attentional cue nor with distractor suppression. We recorded multi-unit activity (MUA) from area V1 in two macaques during stable performance in task 1, as well as the learning period and stable performance in task 2. In task 1, the MUA response was transiently enhanced around 200 ms post-stimulus onset for the fixated compared to the un-fixated stimulus. In task 2, this transient enhancement was followed by sustained enhancement. These results suggest that attention is initially biased toward the fixated stimulus - even when both stimuli are equally behaviorally relevant. Thus, if both stimuli are behaviorally relevant (task 1), this effect is transient. If only one stimulus is behaviorally relevant (task 2), the effect is sustained. This bias toward the fixated stimulus may explain the rapid cue learning. In summary, this fixation-based attention task offers a more ecologically appropriate attention task that macaques learn quickly, which reduces training time and provides a means to investigate the interplay between attention and learning.

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Poster

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Program #/Poster #: 664.14/J15

Topic: D.07. Vision

Support: NIH R01-EY025648 (JG)

Title: Dynamic neural reconstructions of attended object features using EEG

Authors: *J. CHEN, M. D. STARKS, J. D. GOLOMB;
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Abstract: We live in a dynamic world and our environment contains far more stimuli than our brain can process at one time. Visual attention allows us to select relevant information and ignore irrelevant information. It is critical to understand how visual attention helps us process selective

feature information. Recently, fMRI has been widely used to reconstruct object features by applying inverted encoding models (e.g. Sprague & Serences, 2015). However, investigating the dynamics of cognitive processes, like neural mechanisms of attentional selection, requires more temporally sensitive methods. Here, we presented a series of studies using human electroencephalography (EEG) and steady-state visual evoked potential (SSVEP) to dynamically track attended object features. In one task, two gratings were shown on the screen, and subjects were asked to covertly attend to one of them and detect subtle orientation changes. The two gratings flickered at the same frequency but had different orientations. We were able to successfully reconstruct the attended orientation through time. Importantly, we reconstructed the attended orientation without including any location information in the model, using the EEG signal from all posterior electrodes. As trials increased in time, there appeared to be a better reconstruction of the attended grating's orientation. We also observed weaker reconstructions of the unattended grating's orientation. Moreover, the quality of the attended item's reconstruction appeared to be anti-correlated with the quality of the unattended item's reconstruction, perhaps indicative of an oscillation in attention with a limited attentional resource pool. Interestingly, topographic activity maps revealed no obvious lateralization between hemispheres as a function of whether the left or right item was attended. This lack of lateralization may indicate that activity in this context may be reflective of feature-content and not feature-location. These results illustrate the potential of using EEG to provide noninvasive neural measurements of attended feature representations. This could be particularly useful when studying the temporal dynamics of cognitive processes such as attention switching.

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Poster

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Title: The effect of visual attention on the responses of dorsal lateral prefrontal cortex neurons in virtual environments

Authors: *B. W. CORRIGAN[1], R. A. GULLI[2], M. ROUSSY[1], R. LUNA[1], A. J. SACHS[3], J. C. MARTINEZ-TRUJILLO[4];
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Abstract: While there has been significant research on the effects of covert attention on the responses of neurons in the lateral prefrontal cortex of macaques, there has been less exploration of the effects of overt attention. This is particularly important during natural behavior, when animals tend to foveate the objects of interest. To address this issue we implanted two male macaca mulatta with two 96-channel Utah arrays (Blackrock microsystems, Utah) on the dorsal and ventral aspects of the left principal sulcus, just anterior to the arcuate, in areas 8a and 9/46. We had them navigate a virtual maze and perform an associative memory task. In a given block, there would be two objects presented at a certain position on the maze, the target object was indicated by the maze wall texture (e.g., wood walls means the target is the orange object and steel walls means it is the purple object). Each object location (left or right of the corridor) could vary from trial to trial. Because we wanted to look at the effect of feature-based attention during overt attention, we looked at the first fixations on an object after appearance when it was the target and when it was not. We recorded from 139 neurons in monkey T and 381 in monkey B. We examined the responses of neurons during overt attention: when the object is being foveated. We conducted a two way ANOVA on foveations to a specific object, with factors of position (left or right of the subject) and whether it was the target or the distracter. Monkey T had a significant main effect for position in 31% of neurons, a main effect of target in 17% and an interaction in 17%. Monkey B had a significant main effect for position in 35% of neurons, a main effect of target in 39% and an interaction in 21%.
These results show that the responses of lateral prefrontal cortex neurons are modulated by the behaviorally relevance of the object that is overtly attended. They also show that this effect is shaped by the position of the object in the environment. Further analyses aim at disentangling the role of these and other factors on the responses of single LPFC neurons and the entire population.

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Poster

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Topic: D.07. Vision

Support: NSERC

Title: Multivariate analysis of electrophysiological signals reveals task-dependent attentional modulation of shape and surface features

Authors: *N. LEE, L. GUO, A. NESTOR, M. NIEMEIER;
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Abstract: It has been shown that attention to features such as motion, colour or contours acts upon early stages of processing to aid perception throughout the visual field. Further, this feature-based attention appears to work along parallel, additive channels if more than one feature is attended. We have continued to find additive effects of attention in a difficult object perception task that necessitated perceptual integration and decisional processes, suggesting that attention may be applied to whole objects and therefore, later stages of perception. To elucidate the time course of attention to object features, we recorded EEG from 64 scalp electrodes from human participants while they viewed and interacted with real objects. Objects were one of two shapes and surface features, respectively. Between two experiments we tested two categories of surface features: in Experiment 1, we investigated newly formed colour-weight associations such that objects of one colour were heavier than a second colour. In Experiment 2, we used wood and steel object, that is, surface textures that have a well-learned association with weight. To manipulate attention to features, participants either grasped and lifted the objects or touched the object with their knuckle, thus making features more or less task-relevant. We then compared the spatiotemporal EEG patterns between pairs of conditions via Mahalanobis distance to generate representational dissimilarity matrices (RDMs) at each time point. In both experiments, expected shape, colour and action RDM models significantly predicted actual RDMs. Moreover, models built from a priori hypotheses of colour and shape representation interactions with action uniquely explained variance as early as 100 ms after stimulus presentation. Taken together, this suggests that task-related attention modulates representation at intermediate latencies.

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Title: Behavioral and neuronal effects of large-scale bilateral optogenetic inactivation of the lateral prefrontal cortex during feature attention and working memory

Authors: *D. MENDOZA-HALLIDAY[1], H. XU[1], F. AZEVEDO[2], R. DESIMONE[3];
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Abstract: The lateral prefrontal cortex (LPFC) has been implicated in visual feature attention and working memory. However, demonstrating a causal role of LPFC in these cognitive functions requires temporally-specific inactivation of LFPC activity, which is a major challenge. Here we devised a method for large-scale bilateral optogenetic inactivation of LPFC in macaque monkeys. The animals performed a task requiring them to maintain in working memory the direction of motion of a sample full-screen random-dot surface and, after a 3.2 s delay period, attend to one of two overlapping, oppositely-moving, full-screen test random dot surface (a sample-matching target and an oppositely moving distractor) in order to report the occurrence of a small patch of speeding dots in the target surface. Large-scale bilateral LPFC optogenetic inactivation was accomplished by replacing the native dura with a transparent artificial dura over the lateral prefrontal cortex in each hemisphere and performing ~170 injections of the inhibitory opsin *Jaws* covering a surface area of ~50 mm^2 per hemisphere. Each LPFC was optogenetically stimulated with a high-power 635 nm laser 18 mm above the cortical surface in half of the trials, specifically during the target/distractor presentation. We found that bilateral LPFC optogenetic inactivation caused a remarkable deficit in task performance compared to trials with no inactivation. A decrease in task performance also occurred when optogenetic stimulation was delivered during the delay period, although this effect was less pronounced. Moreover, LPFC inactivation modulated neuronal responses to the test stimuli in several direction-selective areas along the dorsal visual pathway, far from the optogenetically-stimulated regions. Taken together, our results suggest that LPFC plays a causal role in visual feature attention and working memory, and that such role may involve the top-down modulation of activity in visual cortical neurons.

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Poster

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NIMH K99MH115082-01

Title: Holographic imprinting of novelty detection

Authors: *Y. SHYMKIV[1], S. BAIR[1], J. P. HAMM[2], R. YUSTE[1];
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Abstract: Perception of sensory information by the brain is highly dependent on the information context, where responses to the most informative, or “novel”, stimuli are selectively amplified. Deficits of novelty detection appear in patients with schizophrenia, suggesting its high importance for normal information processing and cognitive function. Here we use two-photon calcium imaging in awake mice undergoing the “oddball” paradigm and learn the neural activity structure encoding informational context in visual and auditory cortices. Analysis of trial to trial and averaged stimulus evoked responses reveals a low dimensional organization, consisting of independent, contextually selective subpopulations of neurons (“ensembles”). One major ensemble includes cells selectively responding to stimuli that are novel, i.e. novelty detectors, number of which increases from primary to secondary sensory cortex. Imaging in schizophrenia mouse models revealed that the low dimensional context specific structure is disorganized in disease. Further we use two-photon holographic stimulation along with go/no-go deviance detection behavioral readout to assess the functional importance and stability of novelty detection ensembles. We optically manipulate the low dimensional activity patterns in the primary sensory cortex in conjunction with the oddball paradigm to imprint an altered context specific activity and behavioral response. Furthermore, with optical imprinting in in schizophrenia mice we attempt to enhance the deviance detection behavior aiming at improving the functional phenotype of the disease.

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Topic: H.02. Human Cognition and Behavior

Support: NRF-2017M3C7A1031976

Title: Attention maintains the neural-representational structure of primary visual cortex across the cortical hierarchy

Authors: *J. CHUNG, D.-J. YI;
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Abstract: Attention enhances the neural activity of task-relevant stimulus in sensory processing. Moreover, attention sharpens the neural population coding of attended features in sensory regions. But, attentional modulations on neural population coding across the cortical hierarchy still remains unclear. Here, we investigated attentional modulation on neural representational structure of visual stimulus across the cortical hierarchy. We used the working memory task fMRI from Human Connectome Project (HCP) dataset. The task tested n-back working memory

using within-category objects from four categories. Working memory is conceptualized as internally oriented attention, thus we compared characteristics of the structure between 0- and 2-back working memory conditions to investigate the attentional modulation. We specified cortical regions of interest from primary visual to prefrontal cortex participating in visual working memory process by using the general linear model analysis. We constructed inter-stimulus neural representational distance (IS-RD) matrix by calculating 1-Pearson correlations between multi-voxel fMRI activity patterns of all stimulus pairs in each cortical region. We separated IS-RD matrix into within- (task relevant) and cross-category (task irrelevant) parts. Based on the matrix, we measured two characteristics of the neural representational structure of visual stimulus. We calculated mean IS-RD to estimate the size, and inter-regional similarity of IS-RD matrices between primary visual cortex and the other regions to estimate the shape similarity across the cortical hierarchy. We assumed that primary visual cortex, which is at the lowest cortical hierarchy, represents the most primitive shape of visual stimulus in neural representational space most directly reflecting inter-stimulus distance in the physical space. We found that mean within-category IS-RD is increased in all regions. Mean cross-category IS-RD is rather decreased in the primary visual cortex and prefrontal regions, but only increased in the middle temporal region. We next found that Inter-regional IS-RD similarity is decreased along with the cortical hierarchy. All regions showed increased inter-regional similarities of within-category IS-RD matrix during 2-back. Interestingly, parietal and frontal regions also showed increased similarities of cross-category IS-RD matrix during 2-back. These results indicate that the attention modulates the size of task-relevant and -irrelevant neural representational structures in the opposite direction, while modulates the shape in the same direction to be similar with that of the primary visual cortex.

Disclosures: J. Chung: None. **D. Yi:** None.

Poster

664. Selective Attention

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Topic: H.02. Human Cognition and Behavior

Support: FWO grant GOA0913N
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Title: Incongruency between visual saliency and task-based relevance: Effect on intraparietal sulcus and inferior parietal lobule

Authors: T. JAMOULLE[1], P. DUPONT[2], *R. R. VANDENBERGHE[3];
[1]KU Leuven, Leuven, Belgium; [2]Lab. for Cognitive Neurol., KU LEUVEN, Leuven, Belgium; [3]Univ. Hosp Gasthuisberg, Leuven, Belgium

Abstract: The balance between exogenous capture and endogenous selection is a central theme in attention research. If stimulus saliency is aligned with a subject's attentional priorities, selection will be facilitated. In case of a misalignment, endogenous selection may be compromised (automaticity of attentional capture). Here we distinguished between task-congruent vs -incongruent saliency. We predicted that early saliency effects in posterior IPS would be independent of task congruency and that task incongruency would activate middle IPS and the endogenous control network.
16 healthy subjects participated in a change detection task. Eight stimuli (letters and numbers, size 0.75°) were presented on an imaginary circle at 3.5° eccentricity followed by a mask (combined duration of array + mask = 500ms). Depending on the run, the array contained two letters and six numbers, or inversely, and subjects were instructed to attend to the two letters or the two numbers, respectively. Following the mask and a delay (100 ms), a central probe stimulus (500 ms) was presented and subjects had to indicate by key press whether the probe matched one of the two targets. There were three conditions: [no-saliency] all stimuli were either red or blue; [saliency-congruent] the two targets were of one color and the distracters of the other color; [saliency-incongruent] two of the distracters were of one color and the remaining stimuli of the other. Gaze fixation was monitored with EyeLink 1000 Plus. Based on a prior behavioral session, the array durations were adapted to match performance between conditions, while the total duration of array plus mask was held constant. Significance was set at voxel-level $p<0.001$ and corrected $p<0.05$ at the cluster-level (voxel size = 3 x 3 x 3 mm).
Saliency minus no-saliency conditions revealed activation in the right IPL (x = 48, y = -45, z = 46, Z = 3.95, k = 48, p=0.006). This was mainly driven by the 'saliency-congruent minus no-saliency' contrast (x = 42, y = -57, z = 37, Z = 4.41, k = 72, $p<0.001$). In the saliency-incongruent minus -congruent condition, activity was bilaterally increased in the posterior IPS (L: x = -24, y = -72, z = 34, , Z = 4.19, k = 308, $p<0.001$; R: x = 33, y = -78, z = 31, Z = 3.96, k = 110, $p<0.001$), the middle IPS (x = 15, y = -51, z = 55, Z = 4.18, k = 135, $p<0.001$) and the upper premotor cortex (x = -30, y = -6, z = 49, Z = 3.86, k = 47, p=0.008). The saliency-congruent minus -incongruent condition did not yield a significant effect
To conclude, saliency incongruency enhances activity in posterior IPS as well as in regions involved in endogenous control.

Disclosures: **T. Jamoulle:** None. **P. Dupont:** None. **R.R. Vandenberghe:** None.

Poster

664. Selective Attention

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 664.21/J22

Topic: D.07. Vision

Support: NIH Grant R00 EY025768

NIMH Grant R01 MH118929
NIH Grant R01 EY022928
NSF Grant NCS 1734901 / 1734916

Title: A stable population code for attention in prefrontal cortex drives a dynamic code in visual cortex

Authors: A. C. SNYDER[1], B. M. YU[2], *M. A. SMITH[3];
[1]Univ. of Rochester, Rochester, NY; [2]Carnegie Mellon Univ., Pittsburgh, PA; [3]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: We recently found (Snyder et al., 2018, Nat. Comm.) that the population pattern of attention-related activity modulation in visual area V4 when visual stimuli are present substantially differs from when visual stimuli are absent but anticipated. Thus, the population code for attention in V4 is dynamic and context-dependent. This is sensible for a sensory population, for which read-out of cognitive factors (such as attention) should remain separable from stimulus-related signals until stimuli are actually processed. The question naturally arises whether the top-down attention signal from executive control areas is likewise dynamic, or rather is a stable code that impacts V4 differentially depending on the ongoing sensory context. We reasoned a stable executive code would support more reliable behavior than a dynamic code, which may be less robust to perturbation. To test this, we simultaneously recorded neural populations in V4 and dorsolateral prefrontal cortex (PFC; a known node in the endogenous attention network) in the same hemifield in two rhesus macaque monkeys while they performed a covert visual spatial attention task. Whereas the attention code in V4 differed substantially in the absence versus presence of visual stimuli, we found the attention code in PFC to be highly consistent across time and stimulus contexts. Moreover, the stability of this code had important functional consequences: stable PFC attention states predicted stronger attention signals in V4 at later time points, and also accounted for considerable variation in the animals' target-detection performance on a trial-by-trial basis. This shows a stable attention code in PFC drives the dynamic attention code in V4, and is important for reliable task performance.

Disclosures: **A.C. Snyder:** None. **B.M. Yu:** None. **M.A. Smith:** None.

Poster

664. Selective Attention

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Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 664.22/J23

Topic: D.07. Vision

Support: NIH R00EY025768
NSF/NCS 1734901/1734916

Title: Attentional bias is mediated by oscillatory communication between PFC and V4

Authors: *B. SAHOO[1], A. C. SNYDER[1,2,3];
[1]Brain and Cognitive Sci., [2]Neurosci., [3]Ctr. for Visual Sci., Univ. of Rochester, Rochester, NY

Abstract: Long range brain-wide coordination is essential for goal-directed behavior. In the context of selective attention, this network has been well characterized. Although attention has been mostly studied in the context where it is successfully deployed in the task, it would be crucial to understand what are the potential network level alterations where attentional control is faltered. For this, we investigated the coordination between PFC, which is an integral part of the attentional network, and a more sensory encoding area of the brain i.e. V4, during false alarms. We recorded local field potentials simultaneously from V4 and PFC with 96-channel Utah arrays in the same hemisphere of two adult male rhesus macaques performing a delayed non-match to sample task. The emerging view is that selective attention is non-stationary and nearly rhythmic in a theta frequency range i.e. 4-8 Hz. Also, oscillations in the alpha band have been shown to be a hallmark of attention. We estimated the strength of communication between V4 and PFC in these frequency bands using Canonical Coherence Analysis. We found that in correct-rejection trials the strength of communication between V4 and PFC in theta band is higher in the peri-stimulus period when the RF was attended compared to when it was ignored, whereas the opposite was true for the alpha band. During false alarms, we observed an increase in V4 and PFC communication in the theta and lower alpha band in the pre-stimulus period when the RF was attended compared to when it was ignored. Also, the V4 and PFC communication was higher in the theta and lower alpha band during false alarms compared to correct rejections. We present our evidence in a framework where false-alarms are caused by an unwarranted increase in top-down bias and that this bias manifests as coordination with PFC in the theta band.

Disclosures: B. Sahoo: None. **A.C. Snyder:** None.

Poster

664. Selective Attention

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 664.23/J24

Topic: D.07. Vision

Title: Feature based attention modulates BOLD signals of parvocellular layers in human lateral geniculate nucleus

Authors: W. LIN, ***P. ZHANG**;
Inst. of Biophysics, CAS, Beijing, China

Abstract: Attention can be directed to non-spatial features such as orientation, color or direction of motion. The lateral geniculate nucleus (LGN) is the earliest stage of the visual pathway where magno- and parvo-cellular visual processing remain clearly segregated. Cells in the dorsal parvocellular (P) layers of the LGN encode color information and spatial details, while magnocellular (M) cells in the ventral layers are highly sensitive to achromatic contrast and motion. Previous studies showed that activities of the LGN can be strongly modulated by spatial attention. Although there have been found M,P and K stream-specific feedback connections from deep layers of V1 to the LGN, whether feature-based attention can selectively modulate layer-specific activities of the LGN has not been clearly demonstrated. Using high-resolution fMRI at 7T and carefully designed functional localizer stimuli to isolate the magno- and parvo-cellular layer activities of the human LGN, we investigated the modulation of layer-specific activities of the LGN by feature-based attention. For the functional localizer, the P biased stimulus was a low spatial frequency (0.375 cpd), high contrast isoluminant red and green concentric ring grating, expanding or constricting at low speed (0.5 Hz). The M biased stimulus was a low luminance contrast (30%), low spatial frequency radial grating (4 spokes), rotating at high speed (15 Hz). During the feature-based attention task, the chromatic concentric ring and the luminance defined radial gratings were superimposed on one another at the same spatial location. Subjects were asked to either pay attention to the chromatic grating to detect occasional color contrast changes, or to the luminance defined motion to detect speed changes. Color and motion tasks were performed in alternation with a central fixation task. For each subject (n=9), a small cluster of voxels selectively biased to the P stimulus can be clearly identified in the dorsal lateral part of the LGN, consistent with the anatomical location of parvocellular layers. The fMRI signals of the parvocellularlayerswere significantly stronger when subjects attended to color contrast than to motion speed. The entire LGN also showed stronger activity when subjects attended to the stimulus than to the fixation, suggesting a modulation effect of spatial attention. Similar spatial and feature based attention effect were also found in cortical area hV4.These results clearly demonstrate that feature-based attention can selectively modulate parvocellular layer activities of the human LGN, the earliest stage of feature selective processing in visual hierarchy.

Disclosures: **P. Zhang:** None. **W. Lin:** None.

Poster

664. Selective Attention

Location: Hall A

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Topic: H.02. Human Cognition and Behavior

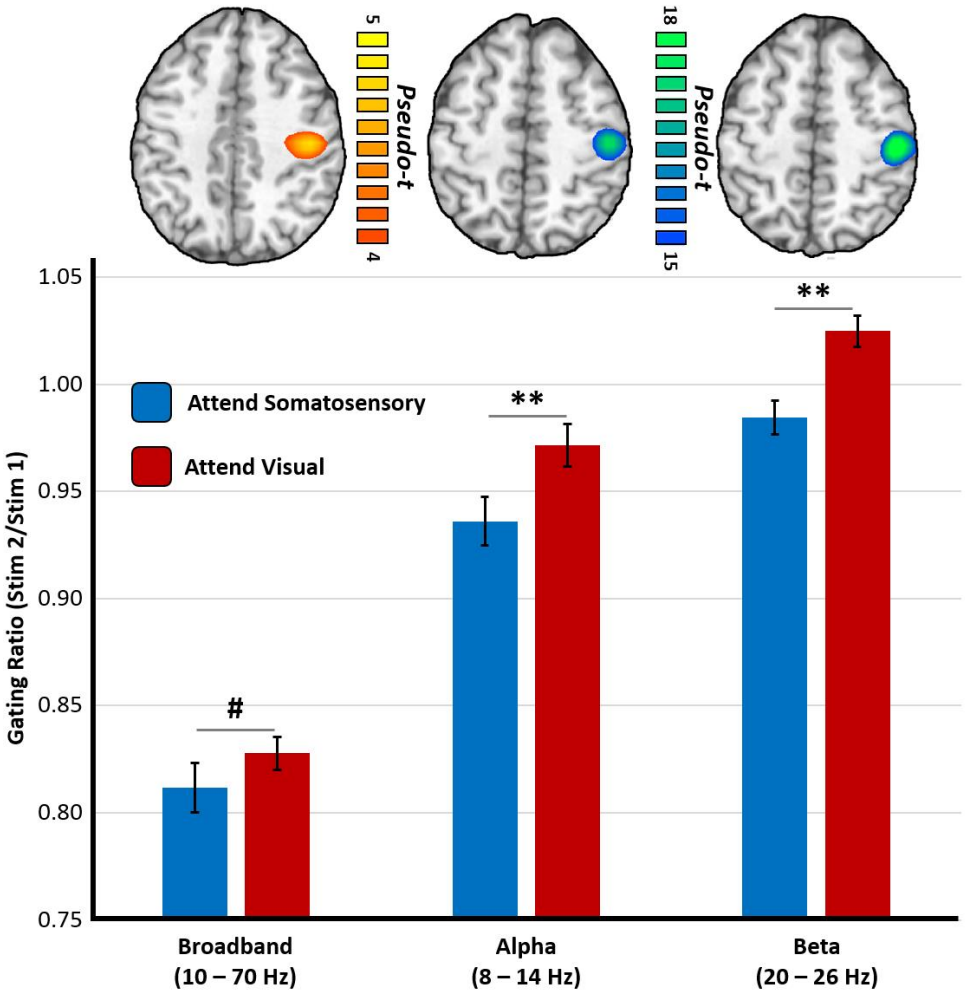
Support: NIH Grant MH103220
NIH Grant MH116782
NIH Grant AG055332

NSF Grant 1539067

Title: Frequency-specific effects of directed attention on the gating of somatosensory responses

Authors: *A. I. WIESMAN, T. W. WILSON;
Neurolog. Sci., Univ. of Nebraska Med. Ctr., Omaha, NE

Abstract: Sensory gating (SG) is the process in which population neural responses to similar stimuli are reduced when presented in succession. SG is thought to represent the functional gating of primary sensory inputs that are at least partially redundant in nature, which would spare shared neural resources from processing less salient stimulus features. Traditionally, SG has been considered “pre-attentive,” but very little is known about the effects of attentional state on this process. In this study, we investigate the impact of directed attention on SG in the somatosensory system using high density magnetoencephalography (MEG). Healthy young adults (n = 26) performed a novel multisensory paired-pulse oddball paradigm, in which attention was directed towards or away from paired-pulse stimulation of the left median nerve. The temporal, spectral, and spatial properties of oscillatory neural responses to the paired-pulse stimuli were quantified using advanced source imaging and virtual sensor analyses, and tested for interactions between attentional state and SG. Expectedly, we found that three stereotyped somatosensory oscillatory responses were significantly gated on the second stimulation: an early broadband response (10 - 70 Hz), and later alpha (8 - 14 Hz) and beta (20 - 26 Hz) responses. SG of these responses was significantly altered when attention was directed away from the somatosensory stimuli, and this reduction was stronger within the frequency bands commonly associated with attention and somatosensory processing (i.e., alpha and beta). These findings highlight the dynamic effects of attentional modulation on somatosensory processing, and suggest that, although SG might be pre-attentive, it is not attention-invariant. This is particularly important, as a number of SG studies in neurologic and psychiatric populations have demonstrated aberrant SG without controlling for attention. Many of these same populations have been found to exhibit attentional deficits, and so controlling for the effects of attentional state on SG is essential.



Disclosures: **A.I. Wiesman:** None. **T.W. Wilson:** None.

Poster

664. Selective Attention

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 664.25/J26

Topic: D.07. Vision

Support: NEI IRP at NIH

Title: In through the out door: Inactivation of primate superior colliculus alters spatial preferences of neurons in the caudate nucleus

Authors: *J. P. HERMAN[1], F. ARCIZET[2], R. J. KRAUZLIS[1];
[1]Lab. of Sensorimotor Res., Natl. Eye Inst., Bethesda, MD; [2]Visual Information Processing, Inst. De La Vision, Paris, France

Abstract: Neuronal activity in the head of the caudate nucleus (CDh) is strongly influenced by the behavioral relevance and spatial location of visual stimuli. The prevailing view is that descending inputs to CDh provide information to distinguish relevant from irrelevant stimuli; this signal is then transmitted to the superior colliculus (SC) via the substantia nigra as inhibition which suppresses saccades to irrelevant visual field locations. In contrast to this implicitly feedforward and serial circuit, with caudate as input and SC as output, anatomy suggests that the SC is also the source of input signals for the caudate, forming a possible recurrent subcortical circuit. Specifically, we hypothesized that this recurrent loop might link the spatial preferences observed in both the SC and CDh for behaviorally relevant visual stimuli. To test this, we recorded extracellular activity from populations of CDh neurons before and during unilateral muscimol inactivation of SC while monkeys performed a covert spatial attention task. During inactivation, many fewer caudate neurons showed a significant preference for the side of presentation of the spatial cue, compared to before inactivation (24 during vs. 51 before). The magnitude of cue-side preference was also significantly diminished during inactivation compared to before. Finally, we found that both the mean and the variance of pairwise spike-count correlations amongst caudate neurons were significantly reduced during inactivation. Importantly, these effects were only observed during unilateral inactivation of SC ipsilateral to the caudate neurons, not during contralateral inactivation. These findings are consistent with the interpretation that inactivation of the SC attenuates the influence of a shared input to CDh neurons. We conclude that SC neuronal activity facilitates transmission of spatially-specific visual information to neurons in the CDh. Considered together with the caudate's well-established influence on SC activity, our results provide evidence that a previously unappreciated subcortical loop is important for defining the location of behaviorally relevant visual information.

Disclosures: J.P. Herman: None. **F. Arcizet:** None. **R.J. Krauzlis:** None.

Poster

665. Cross-Modal Processing in Humans I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 665.01/J27

Topic: D.09. Multisensory Integration

Support: Mitacs IT13711

Title: The neurophysiological priming effect of vibro kinetic stimulation during a digital multisensory entertainment experience- A NeuroIS study

Authors: *J. BOASEN[1,2], F. GIROUX[1], M.-O. DUCHESNEAU[1], J.-F. MÉNARD[3], M. PAQUETTE[3], P.-M. LEGER[1];
[1]Tech3lab, HEC Montréal, Montréal, QC, Canada; [2]Hokkaido Univ., Sapporo, Japan; [3]D-Box Technologies Inc., Longueil, QC, Canada

Abstract: **Intro**: Vibro kinetic (VK) technology is advancing, and increasingly used to create multisensory entertainment experiences. A goal of Neuro-Information-Systems (NeuroIS) science is to ascertain the validity of this kind of VK application. Research has demonstrated that temporally coincident VK stimuli are crossmodally neuronally integrated, and can enhance processing associated with aural and visual sensory modalities. VK stimulation has furthermore been shown to have a priming effect on sensory processing, in which the theta-band is a key brain rhythm. However, evidence regarding the neurophysiological effects of VK stimulation during cinematic experiences is scant. Here, we addressed this shortcoming by using a VK enhanced chair in a multisensory cinematic viewing experience to test the extent to which VK stimulation primed downstream neurophysiological responses. We hypothesized that VK priming would enhance theta power in areas of the brain associated sensory integration processing. **Materials/Methods**: Electroencephalograms (EEG) (BrainVision, 32 ch.) were recorded on 20 middle-age opera aficionados while experiencing a high-definition digital reproduction of Act I of Bizet's Carmen. All subjects sat in a VK enhanced seat (D-Box). During seven selected scenes of the experience, 10 subjects received high fidelity VK (HFVK) stimulation in precise temporal synchrony with musical elements such as the rhythm and melody of the auditory stimuli. The envelopes of source EEG theta-band (5-7 Hz) activity were extracted from the first two minutes after the selected scenes. Theta power was then averaged over time and across epochs for each subject, and normalized based on average baseline theta power two minutes prior to commencement of the experience. Comparisons of source EEG activity were then made between subjects who did or did not receive HFVK stimulation. **Results/Discussion**: Although our analyses are ongoing, preliminary results indicate that the theta-band rhythm is a relevant neurophysiological target to examine the priming effect of HFVK stimulation on sensory integration processing during multisensory cinematic experiences. Further analyses will need to assess changes in theta responsiveness to specific audio/visual events during the experience. Ultimately, we expect these results to create a foundation of evidence in the NeuroIS literature that serves to guide the development of VK technology, and increase its effectiveness in the entertainment sector.

Disclosures: **J. Boasen:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); D-Box Technologies Inc. **F. Giroux:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); D-Box Technologies Inc. **M. Duchesneau:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); D-Box Technologies Inc. **J. Ménard:** A. Employment/Salary (full or part-time):; D-Box Technologies Inc. **M. Paquette:** A. Employment/Salary (full or part-time):; D-Box Technologies Inc. **P. Leger:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); D-Box Technologies Inc..

Poster

665. Cross-Modal Processing in Humans I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 665.02/J28

Topic: D.09. Multisensory Integration

Title: Tech3lab adaptive systems group for the research and development of neuroadaptive information systems (neuroIS)

Authors: *A. J. KARRAN, S. SENECAL, T. DEMAZURE, A. SURI, E. FREVE-GUERIN, E. DE-CELLES, M. FREDETTE;
HEC Montreal, Montreal, QC, Canada

Abstract: We report progress from a program of research which aims to create frameworks and software artefacts for neuroadaptive information systems. The goal of these projects is to utilise measures of real-time user brain activity to adapt the information systems (IS) to augment user performance, automate elements of the system, share the burden of decision making, allowing greater task flexibility for users. The first project combined neuroscience, design science and IS to create a passive brain-computer (BCI) interface artefact capable of augmenting the ability of a user to self-modulate sustained attention using a real-time biofeedback mechanism. Users performed an ecologically valid IS task that involved the simulated management of a supply chain. The task involved monitoring an information dashboard for long periods, followed by brief periods in which supply decisions are made. Three groups, control, threshold and continuous utilised the IS, receiving none, level dependent and continuous feedback respectively from the system. A between groups analysis showed a decrease in on-task error for the continuous group. Additional analysis via GLM and wavelet coherence analysis and showed significant differences in brain activity between the groups. The results revealed that neuroadaptive systems have the potential to increase task performance and decrease on-task error, by allowing IS users to self-modulate their level of sustained attention to better meet task demands. The second project aims to develop a reactive BCI as a neuro-adaptive system that adapts components of an IS based on the cognitive load of the user. The artefact operates as a recommender system that supports decision-making through the classification of cognitive load and the dynamic allocation of the information displayed on a web interface. For interface and UX designers, this artefact may present a new and innovative means to configure the right balance of information presented on an interface.
The goal of the final project is to create onboard vehicular IS driven by the classification of cognitive workload and decisions involving risk using a combination of psychophysiological and telemetric data and machine learning methods. We aim to create a multimodal classification model of “decisions involving risk”, and then apply the model to automatically classify those types of decision in both an automotive and aerospace context during simulated driving and

high-fidelity helicopter flight. Classifications will also be integrated into post-flight debriefing processes to highlight problematic manoeuvres, allowing instructors to better train pilots. We look forward to receiving feedback.

Disclosures: **A.J. Karran:** None. **S. Senecal:** None. **T. Demazure:** None. **A. Suri:** None. **E. Freve-guerin:** None. **E. De-celles:** None. **M. Fredette:** None.

Poster

665. Cross-Modal Processing in Humans I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 665.03/J29

Topic: D.09. Multisensory Integration

Support: NSERC PGS-D 600791

Title: An ERP approach to measuring mind wandering during learning multimedia use

Authors: *C. CONRAD[1], A. J. NEWMAN[2];
[2]Psychology & Neurosci., [1]Dalhousie Univ., Halifax, NS, Canada

Abstract: Interactive learning multimedia are employed in many different contexts, ranging from public education to corporate training. Though their low marginal costs make them efficient education tools, there is growing recognition that learning multimedia tools are yet to live up to their full potential, due to their inability to incorporate users' cognitive context. For instance, recent research in the role of mind wandering in the classroom suggests that students who report increased mind wandering observed reduced learning outcomes. By incorporating physiological user feedback from electroencephalography (EEG) that are correlated with mind wandering, learning multimedia tools might be improved. In this presentation we describe two studies which observed the P1-N1-P2 complex and P3 event related potential (ERP) responses elicited by auditory oddball stimuli that were played during online lecture videos. In the first experiment, 16 participants were recruited and asked to report when they experienced mind wandering by pressing a button. Amplitudes of responses to standard and oddball stimuli onset at 125 ms (P1), 225 ms (P2) and 275 ms (P3) were compared for periods 10 s before and after self-reported mind wandering events, using linear mixed effects analysis. Oddball amplitudes were significantly different from standard stimuli in the 10 seconds before a button press (when mind wandering was reported to occur) but not in the 10 seconds following (when people were back on task). In the second experiment, we attempted to replicate the observed results using a different reporting method in which participants (n=50) were prompted at pseudo-random intervals during a video to report the degree to which they are currently experiencing mind wandering. ERP responses from 10 seconds before prompts that resulted in high degrees of reported mind wandering were contrasted with 10 seconds before reports of high degrees of on-task thought. Component

amplitudes of responses to oddball stimuli onset at 75 ms (N1) and 125 ms (P2) were analyzed using linear mixed effects and found to be significantly different from standard stimuli when reporting on-task thought, but not when reporting mind wandering and no distinct P3 response was observed. These results suggest two distinct ERP correlates of mind wandering which might be used to passively measure the mind wandering state during learning multimedia use. Future work may yield further evidence to support the use of these correlates to validate the effect of various multimedia in preventing mind wandering or facilitating learning outcomes.

Disclosures: C. Conrad: None. **A.J. Newman:** None.

Poster

665. Cross-Modal Processing in Humans I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 665.04/J30

Topic: D.09. Multisensory Integration

Title: Exploring the association between belief in misinformation and neural correlates of System 1: An EEG study

Authors: *M. MIRHOSEINI[1], S. BAKHTIARI[4], S. EARLY[2], N. E. SHAMY[1], G. CALIC[1], **K. HASSANEIN**[3];
[1]Information Systems, McMaster Univ., Hamilton, ON, Canada; [2]Information Systems, McMaster Univ., Burlington, ON, Canada; [3]McMaster Univ., Hamilton, ON, Canada; [4]Neurosci., McGill Univ., Montreal, QC, Canada

Abstract: Recent public discourse about the phenomenon of "fake news" has exposed the vulnerability of people to the widespread broadcast of misinformation on social media. Fake news is a type of misinformation that is presented as originating from reliable sources (Bronstein et al. 2018). Building upon dual system theories of cognition (Kahneman 2011), this research aims at predicting users' belief in misinformation based on the EEG measure of system 1. System1 is a fast, unconscious, and intuitive process that relies on long-term memory to retrieve similarity-based information and form an impression about a stimulus. On the other hand, system2 processing mode is a slow and conscious process, which is under our deliberate control and has much fewer cognitive resources than the associative mode (Evans 2014). System2 thinking is associated with frontal (Fz) theta rhythms (4-6 Hz) while system1 activities are correlated with increased parietal (Cpz) alpha (10-12 Hz) (Williams et al. 2019). 40 subjects (20 male and 20 female) participate in an experiment to 1) measure the neural correlates of system1 and system2 and 2) predict subjects' bias based on system 1 activations. Subjects are presented with 60 headlines, 20 of which are easy to identify as true or false (e.g., Democrats Criticize Trump's Border Policy). The remaining 40 headlines consist of more difficult to judge statements of which 50% are true, and 50% are false. Participants are asked to confirm or reject

the news headlines using two arrows of the keyboard. The news headlines are presented in a mimicked Facebook page similar to news shared on users' feed. EEG is being recorded from 20 electrodes using the Cognionics (Cognionics Inc., CA) quick-20 dry EEG headset. We then use a supervised machine learning technique (e.g. random forest) to predict subjects' bias using the EEG correlates of system1 and system2. Different EEG-based features that we expect to be informative for detecting correct/wrong subjects' decisions (different frequency bands and different brain lobes) will be fed to our machine learning method. The trained model selects a combination of EEG features that can best separate wrong and right trials. Within the selected EEG features by the model, we expect that higher system1 activation (Parietal Alpha) is associated with an increase in confirmation bias and belief in misinformation while more system 2 activities (Frontal Theta) results in more accurate identification of misinformation. This study advances our understanding of the neural correlates of the belief formation biases on social media.

Disclosures: **M. Mirhoseini:** None. **S. Bakhtiari:** None. **S. Early:** None. **N.E. Shamy:** None. **G. Calic:** None. **K. Hassanein:** None.

Poster

665. Cross-Modal Processing in Humans I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 665.05/J31

Topic: D.09. Multisensory Integration

Support: Kennesaw State University Coles College of Business Research and Development Committee

Title: Short-term training with a mu-based brain-computer interface indicates enhancement of motor skills

Authors: A. INGRAHAM, ***A. B. RANDOLPH**;
Information Systems, Kennesaw State Univ., Kennesaw, GA

Abstract: Brain-computer interface (BCI) researchers have been using neural input devices for communication and control for almost three decades. More recently, the field has explored using BCIs for neuro-rehabilitation. Neuro-rehabilitation is an attempt to restore lost function due to a neurologic disability such as due to stroke. Unfortunately, only a small portion of stroke patients experience success in regaining lost motor function even with intensive rehabilitation. Hence, further exploration into various and complementary techniques for neuro-rehabilitation is still needed.
Here, we examined mental training using a mu-based BCI based on motor imagery for its ability to enhance motor skills in humans. We conducted a study of eighteen (10 male, 8 female)

healthy individuals aged 18 to 50 years-old who played a virtual match of tennis on the Nintendo Wii gaming platform at the start and end of a four-to-five day mental training period. Individuals used a mu-based BCI developed by the Wadsworth Center on the BCI2000 platform.
We conducted a paired t-test to determine if there was a significant difference in Wii scores before and after mental training with the mu-based BCI. The mean before playing the Wii was 78.71 while the mean after playing the Wii was 80.33. Because there was little variation between the two administrations, we concluded that although there is no statistically significant difference in the Wii scores before and after mental training, there is a practical difference; hence, we found there was a slight improvement in Wii scores after just three sessions of mental training. Although there was only a slight improvement in motor skills overall as measured based on play with a sports video game, there was a practical level of improvement observed which supports future research. Gameplay on the Wii console provides evidence that even short-term mental training with a BCI can help increase the proficiency and effectiveness of the brain and motor skills. This work contributes to the growing evidence that mental training with a BCI has both cognitive and physical benefits.

Disclosures: A. Ingraham: None. **A.B. Randolph:** None.

Poster

665. Cross-Modal Processing in Humans I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 665.06/J32

Topic: D.09. Multisensory Integration

Support: NSF Grant 1814721

Title: Attentional habituation to non-essential computer notifications generalizes to security warnings: An fMRI study

Authors: *B. KIRWAN[1], B. ANDERSON[1], D. EARGLE[2], J. JENKINS[1], A. VANCE[3]; [1]Brigham Young Univ., Provo, UT; [2]Univ. of Colorado, Boulder, Boulder, CO; [3]Temple Univ., Philadelphia, PA

Abstract: Repeated exposures to a stimulus results in habituation of neural and behavioral responses to that stimulus. Habituation may also generalize to similar stimuli. Previous literature has shown that in the realm of computer security, habituation of neural responses within visual-attention networks accounts for much of the decreased behavioral responding to computer security warnings and that manipulations to security warnings that diminish habituation also improve security behaviors. While previous literature has focused on habituation to security warnings, little research has been done on habituation to the far more common non-security notifications. Here we examine the extent to which habituation to non-security notifications

generalizes to security warnings and the neural underpinnings of that generalization. In a series of experiments, participants performed an image categorization task and received frequent feedback notifications and computer security warnings. In a large online field experiment, we show that habituation to frequent non-security-related notifications does carry over to a one-time security warning. Generalization of habituation is manifest both in (1) decreased attention to warnings (as measured through behavioral indices such as mouse cursor tracking) and (2) lower warning adherence behavior. The carry-over effect, most importantly, is due to generalization, and not fatigue. The degree that generalization occurs depends on the similarity in look and feel between a notification and warning. In an fMRI experiment, we demonstrate habituation in visual-spatial attention networks to the frequent non-security notification that is distinct from fatigue. We further demonstrate generalization of habituation that is modulated by the similarity between notifications and warnings in terms of appearance and mode of interaction.

Disclosures: **B. Kirwan:** None. **B. Anderson:** None. **D. Eargle:** None. **J. Jenkins:** None. **A. Vance:** None.

Poster

665. Cross-Modal Processing in Humans I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 665.07/J33

Topic: D.09. Multisensory Integration

Support: NIH R15HD093086-01A1
FP7-PEOPLE-2012-CIG-334201
Whitaker International Program Grant
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Erasmus+ KA 107 action (USA-ITALY)

Title: Impact of extended training on vibrotactile feedback guided reaching

Authors: *V. SHAH[1,2], A. THOMAS[1], G. BALLARDINI[2], M. CASADIO[2], L. A. MROTEK[1], R. A. SCHEIDT[1,3,4];
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Abstract: Our long-term goal is to enhance the planning and ongoing control of upper limb reaches through the integration of real-time vibrotactile cues. Previous studies using vibrotactile feedback (VTF) to enhance 2D targeted reaching found that the use of VTF initially requires involvement of significant cognitive resources. While short-term training (1 to 2 days) does improve target capture accuracy of VTF-guided reaches, movements do not reflect straight and

efficient point-to-point hand paths typical of visually-guided reaches. We hypothesized that long-term training with VTF would improve reaching in a way that reflects a normalization of movement kinematics and increased autonomy in the integration of VTF during reach planning and execution.
Four young participants with no known neurological impairment gave written consent to participate in 20 experimental sessions. Participants completed 5 session per week over 4 weeks. Four eccentric rotating mass motors were attached to the non-moving arm to create a VTF display that encoded information about the {X, Y} end effector's position of a custom-made 2D manipulandum grasped by the moving hand. During each session, participants performed targeted reaching under three different feedback conditions: visually-guided, VTF-guided, and no feedback. Participants were provided VTF-guided reach training for 30 mins during each session, for a total of 10 hrs of training. We analyzed target capture error, target capture time, and reach trajectory straightness prior to, during, and after training.
Repeated measures ANOVA found statistically significant differences in target capture error [$F_{(19,57)} = 5.20$, $p < 0.001$] and target capture time [$F_{(19,57)} = 5.38$, $p < 0.001$]. Post hoc, one-tailed paired samples t-test revealed that target capture error decreased significantly by 24.0% at the end of 5 hrs of VTF-guided reach training ($p < 0.05$) and by 37.4% after 10 hrs ($p < 0.05$). Target capture time decreased by 25.2% after 5 hrs of VTF-guided reach training and by 45.1% after 10 hrs ($p > 0.05$ in both cases). When VTF was first introduced, reach trajectories were decomposed into two sequential strokes performed parallel to the cardinal {X, Y} axes of the vibrotactile display; a measure of movement decomposition increased by 64.8%, on initial exposure compared to values from visually guided movements ($p < 0.05$). After 10 hrs of training, decomposition decreased to 37.4 % ($p > 0.05$, compared to baseline). These training related changes in reaching behavior indicate that 10 hrs of training with VTF advances users towards the autonomous use of supplemental VTF to guide smooth and efficient reaching in the absence of visual feedback.

Disclosures: V. Shah: None. **A. Thomas:** None. **G. Ballardini:** None. **M. Casadio:** None. **L.A. Mrotek:** None. **R.A. Scheidt:** None.

Poster

665. Cross-Modal Processing in Humans I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 665.08/J34

Topic: D.09. Multisensory Integration

Support: Natural Sciences and Engineering Research Council of Canada (RGPIN-2016-05211)

Title: Musicians show better auditory and tactile identification of emotions in music

Authors: *A. SHARP[1], M.-S. HOUDE[1], B.-A. BACON[2], F. CHAMPOUX[1];
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Abstract: Musicians are better at processing sensory information and at integrating multisensory information in detection and discrimination tasks, but whether these enhanced abilities extend to more complex processes is still unknown. Emotional appeal is a crucial part of musical experience, but whether musicians can better identify emotions in music throughout different sensory modalities has yet to be determined. The goal of the present study was to investigate the auditory, tactile and audiotactile identification of emotions in musicians. Melodies expressing happiness, sadness, fear/threat, and peacefulness were played and participants had to rate each excerpt on a 10-point scale for each of the four emotions. Stimuli were presented through headphones and/or a glove with haptic audio exciters. The data suggest that musicians and control are comparable in the identification of the most basic (happiness and sadness) emotions. However, in the most difficult unisensory identification conditions (fear/threat and peacefulness), significant differences emerge between groups, suggesting that musical training enhances the identification of emotions, in both the auditory and tactile domains. These results support the hypothesis that musical training has an impact at all hierarchical levels of sensory and cognitive processing.

Disclosures: A. Sharp: None. **M. Houde:** None. **B. Bacon:** None. **F. Champoux:** None.

Poster

665. Cross-Modal Processing in Humans I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 665.09/J35

Topic: D.09. Multisensory Integration

Support: IBS-R015-D1

Title: Decoding melodic contours in early visual areas

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Abstract: Although primary sensory cortices have traditionally been considered to be unimodal, recent work has shown that multisensory processing also occurs in early modality-specific areas involved in primary sensory analysis. In particular, neuroanatomical studies on nonhuman primates and human neuroimaging studies found anatomical and functional connections between the auditory cortex and the anterior portion of the primary visual cortex (V1) retinotopically mapped to the peripheral visual field, which could support multisensory integration at early

stages of cortical processing. However, the extent to which auditory information can be processed in visual cortex, from low-level acoustic features to high-level abstract representations, remains unclear. In the current study, using fMRI and pattern classification methods, we investigate whether high-level auditory information that is metaphorically associated with visual properties, such as a melodic contour associated with visual motion, can be decoded in visual cortex in the absence of visual stimulation. While fixating at the center of the screen, participants either listened to an ascending or descending melody (auditory) or viewed random dots moving upward or downward in a circular annulus (visual) and monitored those stimuli for occasional changes in their directions. Shepard tones were used to create different melodic contours, which were perceived as infinitely ascending or descending in pitch. The direction of visually presented motion was successfully decoded in early and extrastriate visual areas (V1, V2, and V3). More interestingly, activities of the same visual areas were also predictive of the melodic contour with comparable accuracy. The decoding accuracy of the melodic contour was higher in the regions of visual cortex that correspond to the peripheral visual field compared to the regions mapped to the central visual field, whereas there was no significant difference between the central and peripheral visual regions for decoding visual motion. When the classifier was trained on the auditory data and tested on the visual data or vice versa, generalization performance was at chance level. Our results suggest that high-level auditory information that has an abstract association with visual properties, can be represented in visual cortex via cortical feedback facilitating multisensory integration in an abstract space, and this high-level auditory representation might not share a common neural code but is unique in nature.

Disclosures: **J. Ha:** None. **I. Kim:** None. **W. Shim:** None.

Poster

665. Cross-Modal Processing in Humans I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 665.10/J36

Topic: D.09. Multisensory Integration

Title: The neural basis of olfactory-trigeminal interaction

Authors: P. KARUNANAYAKA[1], L. JIAMING[2], Q. X. YANG[1], *K. SATHIAN[3];
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Abstract: Olfactory co-stimulation enhances the localization of chemosensory (Tremblay and Frasnelli, 2018, Chem Senses 43: 611-616) and somatosensory (Karunanayaka et al., 2018, bioRxiv, http://dx.doi.org/10.1101/519439) stimuli, both of which stimulate the trigeminal nerve.

The neural mechanisms of such olfactory-trigeminal interaction remain largely unknown. Here, we used functional magnetic resonance imaging (fMRI) to investigate the neural basis of enhanced sensitivity to intranasal somatosensory stimulation during olfactory co-stimulation. We hypothesized that olfactory-trigeminal integration is mediated by the primary olfactory cortex (POC). Fifteen healthy human subjects with normal olfactory function performed a localization task for weak air-puff stimuli in the presence or absence of the pure odorant, phenyl ethyl alcohol (PEA; rose odor). Consistent with the prior literature, PEA could not be localized to a nostril above chance. Yet, there was a significant improvement in the localization accuracy of weak, but not strong, air-puffs in the presence of PEA when both stimuli were delivered to the same nostril, but not to different nostrils. Correspondingly, bimodal stimulation with PEA and weak, but not strong, air-puffs enhanced activation, as measured by the blood oxygenation level-dependent (BOLD) signal, in the POC and superior temporal cortex (STC), compared to air-puffs alone. These behavioral and fMRI data follow the principle of inverse effectiveness, where multisensory integration is inversely related to stimulus strength. Activity in the POC and STC was also significantly correlated with the behavioral enhancement of weak air-puff localization by concomitant PEA. These data provide clear functional evidence for central integration of olfactory and trigeminal somatosensory inputs.

Disclosures: **P. Karunanayaka:** None. **L. Jiaming:** None. **Q.X. Yang:** None. **K. Sathian:** None.

Poster

665. Cross-Modal Processing in Humans I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 665.11/J37

Topic: D.09. Multisensory Integration

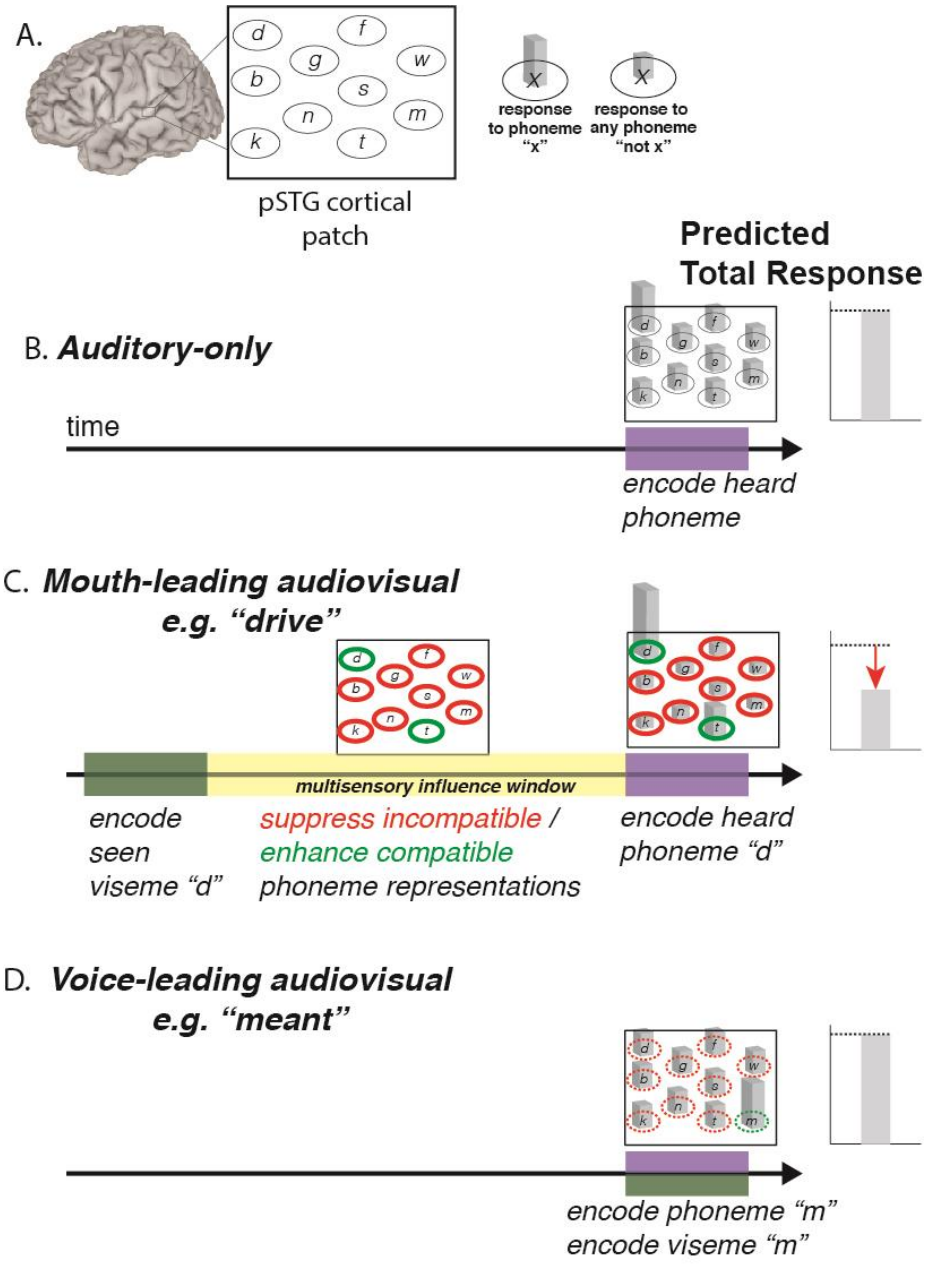
Support: NIH Grant R01NS065395
NIH Grant U01NS098976
NIH Grant R25NS070694

Title: Cross-modal suppression of auditory cortex by visual speech as a mechanism for audiovisual speech perception

Authors: *B. A. METZGER[1], E. A. NESBITT[1], J. F. MAGNOTTI[1], Z. WANG[2], P. J. KARAS[1], D. YOSHOR[1], M. S. BEAUCHAMP[1];
[1]Neurosurg., Baylor Col. of Med., Houston, TX; [2]Rice Univ., Houston, TX

Abstract: Humans perceive speech using visual info from the talker's mouth and auditory info from the talker's voice. For instance, viewing the talker's face enhances the intelligibility of noisy auditory speech. Key to this enhancement is the head start provided by vision, since most

speech is “mouth leading (ML)”, meaning that visual mouth movements begin before auditory vocalization. However, some speech (i.e. nasal consonant “m”) is “voice leading (VL)” with vocalization occurring before visible mouth movements. We constructed a model for audiovisual speech perception in which the early arrival of visual speech suppresses the representation of incompatible phonemes and enhances the representation of compatible phonemes in posterior superior temporal gyrus (pSTG), the cortical locus of speech perception (see Figure). Consistent with the model, a larger perceptual benefit of visual speech was observed for ML (28% accuracy increase) vs. VL words (4% increase). To examine the neural substrates of this benefit, we recorded from electrodes implanted on the pSTG of epileptic patients. Using broadband high-frequency activity (BHA) as a measure of neural activity, we observed smaller responses for AV *vs.* auditory-only ML words (34% difference, 118% increase from baseline *vs.* 152%) while VL words showed a smaller difference (5%, 129% *vs.* 134%). The model also predicts that any visual speech that precedes auditory speech should influence neural activity. To test this, we manipulated the timing of the visual relative to the audio component of naturally-spoken AV speech. ML stimuli were created by advancing the visual component by 300 ms. VL stimuli were created by delaying the visual component by 300 ms. Transformed ML speech should exhibit neural cross-modal suppression, while transformed VL speech should not. Consistent with this prediction, we observed smaller BHA responses for ML (116% increase from baseline) relative to VL speech (143% increase from baseline). Taken together, the data suggest cross-modal suppression of auditory cortex by visual speech plays a key role in AV speech perception.



Disclosures: **B.A. Metzger:** None. **E.A. Nesbitt:** None. **J.F. Magnotti:** None. **Z. Wang:** None. **M.S. Beauchamp:** None. **D. Yoshor:** None. **P.J. Karas:** None.

Poster

665. Cross-Modal Processing in Humans I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 665.12/J38

Topic: D.09. Multisensory Integration

Support: NIH R01 (DC016297)
SFI 15/CDA/3316

Title: Assessing the contribution of visual speech features to audiovisual speech perception in noise

Authors: *A. E. O'SULLIVAN[1], A. R. NIDIFFER[2], E. C. LALOR[2,1];
[1]Trinity Col. Dublin, Dublin, Ireland; [2]Univ. of Rochester, Rochester, NY

Abstract: Seeing the face of the speaker you are listening to benefits speech intelligibility - particularly in noisy situations (Sumby and Pollack, 1954). The neural mechanisms underlying this improvement in intelligibility remains unclear. Behavioral studies have found that listeners predominantly gaze at the lips of the speaker when the acoustics are noisy (Vatikiotis-Bateson et al., 1998). The use of lip information under such conditions is not surprising since the lips convey general dynamic information (which is correlated with the acoustic envelope, Chandrasekaran et al., 2009), as well as detailed articulatory movements which convey complementary information (Campbell 2008). Neuroimaging work has also found an enhancement of lip processing regions in visual cortex when the acoustics are missing (Ozker et al., 2018). Together, this suggests that the lips are an important feature of visual speech which the brain exploits to assist speech processing. Research on how the rest of the facial features contributes to speech comprehension is less clear, particularly with respect to natural speech. It has been shown that other features of the face such as jaw, eye, and head movements contribute to speech comprehension (Jiang et al., 2002; Yehia et al., 2002; Munhall et al., 2004). Yet it remains unclear whether the information that confers the improved intelligibility of noisy audiovisual speech is shared between mouth movements and other dynamic facial features or whether they carry complementary information. Here we present an experiment where we have modulated the amount of facial information available to listeners as they listen to audiovisual speech in noise (-9 dB). In particular, we have tested the effects of degrading the information available from the lips on speech comprehension - while the rest of the facial information remains intact. As well as this, we have tested if degrading all of the information except the lips affects the multisensory benefit obtained for speech in noise. Our results show that the behavioral benefits of visual speech depend on access to both visual speech dynamics and articulatory information. These results extend our understanding of the contribution of visual speech features to audiovisual speech perception.

Disclosures: **A.E. O'Sullivan:** None. **A.R. Nidiffer:** None. **E.C. Lalor:** None.

Poster

665. Cross-Modal Processing in Humans I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 665.13/J39

Topic: F.01. Neuroethology

Support: NSERC RGPIN-2016-04591

Title: Abcam monoclonal Egr-1 is an effective primary antibody replacement for Santa Cruz polyclonal Egr-1 in songbirds

Authors: E. N. SCULLY, J. M. SANCHEZ, *C. B. STURDY;
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Abstract: The immediate early gene protein product ZENK (acronym zif268, Egr-1, NGFI-A, krox24) has been widely used in the songbird neurobiology research community, as well as other research areas interested in assessing learning and memory. In much of songbird research, ZENK is used to measure neural activation and identify the cellular and molecular substrates involved in the first stages of memory formation. Previous songbird research revealed that neurons in the auditory areas involved in auditory perception, mainly the caudomedial nidopallium (NCM) and caudomedial mesopallium (CMM), respond with high levels of ZENK protein expression in response to presentation of biologically-relevant auditory stimuli. Santa Cruz Egr-1 primary antibody has been widely used in the immunohistochemistry protocols for visualizing ZENK. However, Santa Cruz Biotechnology has discontinued production of Egr-1. Thus, the current study is focused on analyzing the effectiveness of alternative primary antibodies: Abcam polyclonal c-Fos, Abcam monoclonal Egr-1, and Proteintech polyclonal Egr-1. Abcam monoclonal Egr-1 succesfully labeled ZENK positive cells in the songbird NCM and CMM at a concentration of 1:2000 and 1:5000. Abcam polyclonal c-Fos also labeled cells in the auditory nuclei; however, this labeling was non-specific. Abcam monoclonal Egr-1 was found to have labeling at similar levels to previous studies using Santa Cruz polyclonal Egr-1 in NCM and CMM. Abcam was also found to specifically label only cells in the areas known to express ZENK, and not label cells in areas known not to express ZENK.

Disclosures: E.N. Scully: None. **J.M. Sanchez:** None. **C.B. Sturdy:** None.

Poster

665. Cross-Modal Processing in Humans I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 665.14/J40

Topic: A.08. Development of Motor/ Sensory/ and Limbic Systems

Support: NSF Grant #: IIS-1637892

Title: Shape and texture detection using haptic sensation delivered through transcutaneous nerve stimulation

Authors: *L. VARGAS[1], Y. ZHU[3], H. HUANG[2], X. HU[4];
[1]NCSU/UNC Joint Dept. of Biomed. Engin., North Carolina State Univ. and Univ. of North Carolina-Chape, North Carolina State Univ. and Univ. of North Carolina-Chapel Hill, Chapel Hill, NC; [2]NCSU/UNC Joint Dept. of Biomed. Engin., North Carolina State Univ. and Univ. of North Carolina-Chapel Hill, Raleigh, NC; [3]Mechanical and Aerospace Engin., North Carolina State Univ., Raleigh, NC; [4]Univ. of North Carolina at Chapel Hill, Chapel Hill, NC

Abstract: Haptic perception is crucial for reducing the required cognitive burden and uncertainty that is currently existent during the open-loop control of many prosthesis and teleoperation devices. Using delivered haptic sensation to discriminate between different shapes, object locations, and textures allows for efficient and intuitive classification of a given interaction eliminating the need for high-level auditory or visual characterization. This study aimed to evaluate if percepts delivered using non-invasive transcutaneous nerve stimulation could feasibly be utilized to differentiate between object shape and location in hand along with various surface textures. Using a 2x8 electrode grid placed along the upper arm, charge-balanced bipolar stimulation is delivered to a pair of electrodes activating the median and ulnar nerves. Current sent to a select pair creates a specific electric field, which activates different portions of the sensory axon each of which innervate the hand at various locations. The encoding strategy implemented for object shape and location discrimination required the use of two electrodes pairs each of which corresponded to an elicited sensation in the median or ulnar portions of the hand. Based on the timing and the location of the individual perceptions, users were expected to determine the object's shape or location along a sensorized prosthesis. Alternatively, during surface texture trials, a single electrode pair was necessary as discrimination was encoded based on the frequency in which a change in sensation occurred as the prosthetic finger ran across surfaces with varying number of ridges. Subjects were able to discriminate object shape, object location, and surface texture with a success rate >85 percent. Our results demonstrated that transcutaneous nerve stimulation could be utilized to provide essential sensory information required to better interact with the world around us. The outcomes provide evidence of the efficacy of the current sensory feedback method and the strategies implemented to promote

increased intuitive interaction characterization and potentially improve user acceptance, control, and overall quality of life.

Disclosures: L. Vargas: None. **Y. Zhu:** None. **H. Huang:** None. **X. Hu:** None.

Poster

666. Cross-Modal Processing in Humans II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 666.01/J41

Topic: D.09. Multisensory Integration

Support: NIH Grant EY025018

Title: Audio-visual interactions in the primary visual and auditory cortex

Authors: *A. M. WONG-KEE-YOU, S. NICHOLAS, A. LOTZE, H. SIMON, C. HOU; Smith-Kettlewell Eye Res. Inst., San Francisco, CA

Abstract: The primary visual cortex is considered to play an active role in multisensory processing (e.g., Murray et al., 2016). This view is supported by human imaging studies demonstrating connectivity between the primary visual cortex and primary auditory cortex (Beer et al., 2011, 2013), and ERP studies reporting task related multisensory neural interactions over the posterior scalp (e.g., Molholm et al., 2004). In the current study, we aimed to further examine and identify audiovisual interactions across the primary visual and auditory cortex in humans, by using source-imaged steady-state visual/auditory evoked potentials. Visual (2 cpd gratings, on/off modulated at 6Hz) and auditory (440 Hz pure auditory tone, on/off modulated at 3.75Hz) stimuli were presented simultaneously or alone, and were tagged with distinct temporal frequencies. The responses associated with the individual visual and auditory stimulus (self-terms), and the interactions between both stimuli (intermodulation terms) were quantified in the frequency domain. Self-term responses revealed that both the primary visual (V1) and auditory (Brodmann areas 41 and 42) cortex respond to visual and auditory stimuli, whether they are presented simultaneously or presented alone. However, responses to the auditory stimuli were weaker than those to the visual stimuli. In addition to self-term responses, intermodulation responses were also observed in V1 and Brodmann areas 41 and 42, when the visual and auditory stimuli were presented simultaneously. Overall, our results support the view of connectivity between the primary visual and auditory cortex. Moreover, given that intermodulation responses are believed to represent non-linear integration of neural signals (Regan & Regan, 1988), our findings provide further evidence of multisensory interactions across the early visual and auditory cortex.

Disclosures: **A.M. Wong-Kee-You:** None. **S. Nicholas:** None. **A. Lotze:** None. **H. Simon:** None. **C. Hou:** None.

Poster

666. Cross-Modal Processing in Humans II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 666.02/J42

Topic: D.09. Multisensory Integration

Support: JSPS KAKENHI 19K21492

Title: Contribution of subjective body midline to estimating body orientation in space

Authors: K. TANI[1], *S. UEHARA[2], S. TANAKA[1];
[1]Lab. of Psychology, Hamamatsu Univ. Sch. of Med., Hamamatsu, Japan; [2]Fujita Hlth. Univ., Toyoake, Japan

Abstract: The body midline forming a basis for the egocentric representation of an external object seems to contribute to the estimation of spatial orientation of the body in space. Given the fact that the body midline is erroneously perceived tilt when the body is tilted (e.g. Ceyte et al. 2007), the misperception of body midline during body tilt may influence the estimation of gravitational direction or body orientation. To elucidate this possibility, we conducted two human behavioral experiments. In the first experiment, 14 healthy subjects (7 females and 7 males, aged 21- 41 years) were asked to verbally report the subjective angle of body tilt relative to gravity (subjective body tilt; SBT), and to adjust a visual line with the perceived direction of gravity (subjective visual vertical; SVV) or body midline (subjective body longitudinal axis; SVBA) at upright, or the leftward or rightward tilt position. As a result, partial correlation analysis for each subject revealed the significant positive correlation [$p < 0.05$] between the SBT and SVBA angles among 13 subjects. On the other hand, the significant correlations between SVV and SVBA angles were found among only 3 subjects. To further investigate the causal relationship between SVBA and SBT, we manipulated SVBA by providing false feedback and evaluated its effect on SBT. We asked 9 subjects (3 females and 6 males, aged 21- 31 years) to answer the SBT angle, at the leftward or rightward tilt position, after they received the manipulated visual feedback for the SVBA angle. 2-way ANOVA (2 body angles × 3 feedback conditions) showed a significant main effect of feedback condition [$p = 0.01$], indicating that SBT was influenced by the manipulated direction of SVBA even when the body tilt angles were identical. These results suggest that the CNS would estimate the body orientation in space based on the internal body midline, as well as sensory signals such as vestibular or somatosensory inputs.

Disclosures: **K. Tani:** None. **S. Uehara:** None. **S. Tanaka:** None.

Poster

666. Cross-Modal Processing in Humans II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 666.03/J43

Topic: D.09. Multisensory Integration

Title: Seeing a face in a crowd of emotional voices: Changes in perception and cortisol in response to emotional information across the senses

Authors: *S. C. IZEN[1], H. E. LAPP[1], D. A. HARRIS[2], R. G. HUNTER[1], V. M. CIARAMITARO[1];
[1]Psychology, Univ. of Massachusetts Boston, Boston, MA; [2]Epidemiology, Univ. of Toronto, Toronto, ON, Canada

Abstract: Background: Correctly interpreting emotions is essential for social interaction. While emotional state can be expressed through several modalities (body posture or movements, body odor, touch, facial expression, or voice intonation), most research has focused on faces and emotional processing within one sensory modality or the transfer of processing from one modality to another. Less is known regarding how emotional processing interacts across the senses. Further, while one literature considers how emotional exposure yields a contrastive perceptual after-effect, another literature considers how emotional exposure induces mood changes. It is unclear if cortisol changes correlate better with perceptual or mood changes.
We examined if visual and auditory emotions of matched valence (congruent) conferred stronger perceptual and physiological effects compared to emotions of unmatched valence (incongruent). We quantified how exposure to angry faces and congruent versus incongruent sounds, altered perception, using a psychophysical adaptation paradigm, and how it altered a physiological proxy for stress or arousal, using salivary cortisol.
Methods: Adapting stimuli included 30 unique angry face images (NimStim database) gray-scaled to 50%. Test images included a subset of eight unique identities morphed along an angry to happy emotional continuum (neutral, 10%, 20%, 40%, and 80% happy and angry). Eighty-one participants (mean age=22.6) first judged 64 test faces as either happy or angry to obtain their baseline point of subjective equality (PSE), or unique neutral point. Next, after 3 minutes of exposure to either congruent (100% angry faces/negative sounds), incongruent (100% angry faces/positive sounds), visual only (100% angry faces), or auditory only (negative sounds) conditions, participants judged the test faces again. To determine the strength of interactions between seen and heard emotions, pre- and post-exposure to a given condition, we quantified changes in PSE and changes in salivary cortisol.
Results: While we found no significant perceptual advantage for congruent over incongruent emotions, effects on perception and cortisol were weakest for heard emotions. Furthermore, cortisol changes correlated significantly with perceptual changes, such that larger decreases in

cortisol post-exposure to negative emotions correlated with more positive perceptual after-effects.
Conclusions: Our results suggest that the more exposure to negative emotional information biases neutral faces to be perceived as happier, the greater the decrease in stress or arousal.

Disclosures: S.C. Izen: None. **H.E. Lapp:** None. **D.A. Harris:** None. **R.G. Hunter:** None. **V.M. Ciaramitaro:** None.

Poster

666. Cross-Modal Processing in Humans II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 666.04/J44

Topic: D.09. Multisensory Integration

Support: NRF (Korea) Grant 2018R1A2B2007227

Title: Distinct light dependent human magnetoreception in geomagnetic food orientation

Authors: *K.-S. CHAE[1], S.-C. KIM[2], H.-J. KWON[1];
[1]Kyungpook Natl. Univ., Daegu, Korea, Republic of; [2]Hankyong Natl. Univ., Anseong, Korea, Republic of

Abstract: It is well established that dozens of magnetoreceptive animals, from worms to mammals, use the Earth's magnetic field (geomagnetic field, GMF) to navigate short- or long-distance and modulate body alignment to fulfill biological needs, depending on species. For humans, it is largely thought that GMF cannot be sensed, even though some previous studies suggested that human may sense magnetic fields including the GMF. Very recently, using a self-rotatory chair experiment, we reported that human males can sense the GMF and use it to search for food direction in a blue light-dependent manner under starved condition. Here, we provide additional behavioral mechanistic evidence for human magnetoreception of the GMF. In a two-alternative forced choice paradigm, starved men showed a distinct light wavelength-dependent magnetic orientation, which may not be consistent with conventional role of light in magnetoreception. The exact reversal of the GMF resulted in orientation toward the magnetic north, indicating that orientation is mediated by axial direction but not polarity of magnetic field. The results confirm that humans can sense the GMF and use it for magnetic food orientation in a light- and inclination compass-dependent manner. Further, the results suggest that magnetite may not be involved in the observed human magnetoreception.

Disclosures: K. Chae: None. **S. Kim:** None. **H. Kwon:** None.

Poster

666. Cross-Modal Processing in Humans II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 666.05/J45

Topic: D.09. Multisensory Integration

Support: NIH (T32AR007505)
DARPA HAPTIX (N66001-15-C-4014)
VA RR&D Center Grant (C3819)
VA RR&D Merit Review (I01 RX00133401)

Title: Peripheral nerve stimulation is processed at a preconscious level

Authors: *N. CHOWDHURY, D. J. TYLER;
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Abstract: Upper limb amputees rely on sight alone while using a prosthetic arm. While attempting to a grasp, they are guessing as to how much to close their hand on an object while not crushing it. This single sensory feedback bottlenecks the user's functional ability to purely focusing on the task at hand while using a device. This is one of the main contributing factors reported for why upper limb amputees abandon use of their prosthesis. Current literature suggests that haptic feedback diverts some of this visual effort to the tactile system, but the feedback becomes less effective the further from the hand it is implemented. Direct stimulation of the somatosensory cortex was used to fill this gap, but counterintuitively it has shown to provide information which is processed slower than visual feedback despite being perceived on the hand. This suggests that for tactile feedback to be used effectively, conscious perception may be less important than the preprocessing by subcortical areas. Our group's solution is to send stimuli through the peripheral nerves of the amputee's arm so that the signal is naturally directed by physiology to the correct areas of the brain before conscious perception occurs. In order to do this, we used an external stimulator to apply different intensities of tactile feedback to create an attentional blink task. By backmasking a threshold level stimulus with a medium intensity stimulus, we were able to shift the subject's conscious reaction back in time compared to when the masked stimulus had not occurred. This implies that the stimulus was used preconsciously to trigger a preplanned motor output. We also compared the reaction times due to stimulated tactile feedback with reaction times due to visual and vibrotactile feedback. Our results show that stimulated reaction times are consistent with tactile reactions times seen with able-bodied individuals and this once again confirms that the artificial tactile information is used similarly if not the same as for an able-bodied individual. These results taken together suggest peripheral nerve stimulation is used more intuitively than existing methods and could provide feedback resulting in intuitive control of a prosthesis.

Disclosures: **N. Chowdhury:** None. **D.J. Tyler:** A. Employment/Salary (full or part-time):; Case Western Reserve University.

Poster

666. Cross-Modal Processing in Humans II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 666.06/J46

Topic: D.09. Multisensory Integration

Title: Thinking outside the neurotypical box: Synesthesia and creativity

Authors: *C. DABBY[1], T. A. DOTY[2], D. L. LARRANAGA[3], R. MORALES[4], J. GLUCK[1], D. LEVATON[1], M. R. LEITAO[5], A. M. RUTCHICK[1], S. A. DREW[5];
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Abstract: Synesthesia is a neurological condition in which people experience a sensory concatenation when exposed to a specific stimuli. For example, some people may hear colors. Past research has shown that synesthetes tend to exhibit more creativity through music, art, and verbal tasks. The present line of research investigates whether synesthetes elect to use differing levels of figurative language as compared to neurotypical participants. Participants completed three separate writing tasks (describing a childhood memory, writing a creative short story using three words, and describing a picture) which three coders rated for occurrence of figurative language. Figurative language was operationalized as language that is not interpreted in the literal sense, such as idioms, similes, and metaphors. Lexical choices were also measured. Preliminary data shows that synesthetes display different rates of figurative language in some but not all of the tasks, suggesting a correlation between synesthesia and creativity. Implications will be discussed.

Disclosures: **C. Dabby:** None. **T.A. Doty:** None. **D.L. Larranaga:** None. **R. Morales:** None. **J. Gluck:** None. **D. Levaton:** None. **M.R. Leitao:** None. **A.M. Rutchick:** None. **S.A. Drew:** None.

Poster

666. Cross-Modal Processing in Humans II

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Program #/Poster #: 666.07/K1

Topic: D.09. Multisensory Integration

Support: NIH R15 HD092086
National Science Foundation under an Individual Research and Development Plan
Erasmus+ KA 107 action (USA-ITALY)

Title: Human vibrotactile discrimination thresholds for sequential and simultaneous stimuli at four different locations on the body

Authors: *E. L. CORRIGAN[1], V. A. SHAH[1,2], A. THOMAS[1], J. MAJ[1], M. CASADIO[2], L. A. MROTEK[1], R. A. SCHEIDT[1,3,4];
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Abstract: Body-machine interfaces (BMIs) can be used to enhance control of movement, whether of the body itself or of an external device. BMIs can be used by healthy individuals as well as patients (e.g. survivors of stroke), who may have better somatosensation at specific body locations. Vibrotactile feedback (VTF) is one mechanism that BMIs can use to augment intrinsic sensory information about the ongoing movement. We examined VTF perception at four body locations to determine suitable application sites for future multi-channel BMIs that use VTF cues to guide motion planning and control. Seventeen healthy adults (age 18-66 years) had a pair of small vibration motors affixed to the skin at each of four location pairs. The motors were placed on soft tissue on the right forearm (dermatome C7/T1), on both shoulders (dermatome C5), near the midline on the chest/back (dermatome T2), and on the medial and lateral sides of the right lower leg, just distal to the knee (dermatome L4/L5). Each pair of motors was spaced at least 8cm apart. The motors applied pairs of vibrotactile stimuli and participants verbally indicated (discriminated) which stimulus felt more intense, where greater intensity was defined as being greater in vibration frequency and/or amplitude. Each pair of stimuli included a standard (186 Hz; 750 ms duration) and a probe intensity (ranging from 100 Hz to 235 Hz; 750 ms). Standard and probe intensity pairs were presented sequentially or simultaneously. Stimuli order was counterbalanced across tactors and body locations. Probabilities that the probe felt more intense than the standard were computed and fit with a cumulative normal distribution function. The discrimination threshold was defined as one standard deviation of the underlying distribution. Two-way repeated measures ANOVA revealed that threshold magnitudes depend on both inter-stimulus timing ($F_{(1,48)} = 9.126$, $p = 0.004$) and locations ($F_{(3,48)} = 5.967$, $p = 0.002$).

Discrimination thresholds were best if stimuli were applied sequentially to the shoulders. Overall, discrimination thresholds were worst when stimuli were applied simultaneously to the chest. In this sample population, discrimination capability was impacted by location, and impacted by vibrotactile information timing. Thus, multiple body locations appear to be viable options for BMI applications. Future research will focus on vibrotactile discrimination capability in patient populations (i.e. survivors of stroke).

Disclosures: E.L. Corrigan: None. **L.A. Mrotek:** None. **R.A. Scheidt:** None. **V.A. Shah:** None. **M. Casadio:** None. **A. Thomas:** None. **J. Maj:** None.

Poster

666. Cross-Modal Processing in Humans II

Location: Hall A

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Program #/Poster #: 666.08/K2

Topic: D.09. Multisensory Integration

Support: DFG, SFB 936/A3
DFG, TRR 169/B1

Title: Multisensory associative learning by classical conditioning of unique audiovisual stimulus combinations in the MEG

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Abstract: Learning of new associations between sensory modalities can be beneficial, if the input of a single modality alone is not sufficiently predictive of upcoming events. The question how the brain resolves this crossmodal learning, i.e. the forming of new associations between sensory modalities, is not yet fully unraveled. We investigated crossmodal learning in a classical conditioning experiment in which only a combination of auditory and visual stimuli was sufficiently predictive of aversive unconditioned stimuli using magnetoencephalography (MEG). Simple auditory (sinusoidal tones) and visual stimuli (Gabor patches) served as conditioned stimuli (CS) and mildly aversive pain stimuli (electric stimulation of the finger tip) as unconditioned stimuli (UCS). Only unique audiovisual feature combinations (CS+) were predictive of UCS, while stimuli in each of the single modalities had no predictive value for UCS. Other unique audiovisual feature combinations (CS-) were predictive for the absence of UCS. We recorded neuronal activity in N=34 human participants (22 female, age range: 21-35 yrs.) using MEG during a crossmodal aversive conditioning paradigm. Pain thresholds were individually titrated and UCS were administered at 1.5 times the pain threshold. Participants rated the valence of CS and the expectancy of UCS revealing that new associations between

sensory modalities were learned and used for the prediction of UCS. Analysis of event-related fields revealed early differences between CS+ and CS- audiovisual stimulus combinations already between 60 to 120 ms following CS onset. Statistics were computed using cluster-based permutation tests. The results are interpreted as signs of early integration between sensory inputs and the formation of memory traces between sensory modalities.

Disclosures: T.R. Schneider: None. **K. Müsch:** None. **A.K. Engel:** None.

Poster

666. Cross-Modal Processing in Humans II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 666.09/K3

Topic: D.09. Multisensory Integration

Support: National Eye Institute (grant 1R21EY020662)
Children's Hospital of Philadelphia
Department of Ophthalmology of the University of Pennsylvania

Title: Impact of auditory cross modal plasticity on vision restoration

Authors: *T. G. MOWAD[1], A. E. WILLETT[2], A. DOUGAL[1], M. MAHMOUDIAN[1], M. DUONG[1], M. LIPIN[1], A. MAGUIRE[1], J. BENNETT[1], M. ASHTARI[1];
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Abstract: In subjects with long-term visual deprivation, the visual cortex supports functions of other sensory inputs, a process known as the cross modal plasticity (CMP). The reorganization of the visual cortex during CMP has been considered as an impediment for vision restoration therapies. The goal of this study was to shed light on the largely unknown impact of this adaptive plasticity of the visual cortex on the success of vision restoration. Participants consisted of 8 LCA2 patients and 8 matched controls. The patients received retinal gene therapy (GT) in the left (n=7) or right (n=1) eye. All subjects underwent vision, auditory, and resting-state fMRI (rsfMRI); the patients received same tests 3 years after GT. fMRI tasks consisted of alternating active (30 s) and rest (15 s) blocks. Visual stimuli consisted of contrast-reversing checkerboards[1]. Auditory stimuli consisted of a random sequence of various tones. Auditory and visual stimulation were delivered using Resonance Technology Audio/Video apparatus[2]. Functional connectivity between the primary auditory (BA41) and the primary visual (BA17) areas were evaluated using the region of interest (ROI) based rsfMRI analysis. All fMRI analyses were performed in BrainVoyager20[3](BV). Statistical group comparisons were performed using fixed and random effect analysis as implemented in BV. Consistent with previous reports, the auditory stimuli activated the primary auditory and visual cortices in LCA2

patients, and rsfMRI showed a strong functional connectivity between BA41 and BA17 and vice versa in controls and LCA2 patients. Surprisingly, GT significantly enhanced auditory response in both auditory and visual cortices. Furthermore, GT significantly increased functional connectivity between BA41 and BA17 in LCA2 patients. Controls depicted similar activation patterns observed in LCA2 patients in and around the auditory cortex with no response in the primary visual cortex. After GT, the visual stimuli induced strong and widespread occipital lobe activations, thus demonstrating a significant improvement of the visual functions. The results indicate that primary visual cortex in LCA2 patients processes both visual and auditory stimuli 3 years after vision restoration. The enhanced auditory CMP activations after GT may stem from the increased functional connectivity between the BA41 and BA17 areas, supported by the rsfMRI results. In summary, our results are suggestive of the fact that the cross modal plasticity does not hinder the success of future retinal interventions to reinstate vision.
1. Ashtari M, et al (2011) J. Clin. Invest. 121(6) 2160-2180.2.
www.mrivideo.com/3.www.brainvoyager.com

Disclosures: **T.G. Mowad:** A. Employment/Salary (full or part-time):; Center for Advanced Retinal and Ocular Therapeutics at University of Pennsylvania Perelman School of Medicine. **A.E. Willett:** A. Employment/Salary (full or part-time):; Center for Advanced Retinal and Ocular Therapeutics at University of Pennsylvania Perelman School of Medicine. **A. Dougal:** A. Employment/Salary (full or part-time):; Center for Advanced Retinal and Ocular Therapeutics at University of Pennsylvania Perelman School of Medicine. **M. Mahmoudian:** A. Employment/Salary (full or part-time):; Center for Advanced Retinal and Ocular Therapeutics at University of Pennsylvania Perelman School of Medicine. **M. Duong:** A. Employment/Salary (full or part-time):; Center for Advanced Retinal and Ocular Therapeutics at University of Pennsylvania Perelman School of Medicine. **M. Lipin:** A. Employment/Salary (full or part-time):; Center for Advanced Retinal and Ocular Therapeutics at University of Pennsylvania Perelman School of Medicine. **A. Maguire:** A. Employment/Salary (full or part-time):; Center for Advanced Retinal and Ocular Therapeutics at University of Pennsylvania Perelman School of Medicine. **J. Bennett:** A. Employment/Salary (full or part-time):; Center for Advanced Retinal and Ocular Therapeutics at University of Pennsylvania Perelman School of Medicine. **M. Ashtari:** A. Employment/Salary (full or part-time):; Center for Advanced Retinal and Ocular Therapeutics at University of Pennsylvania Perelman School of Medicine.

Poster

666. Cross-Modal Processing in Humans II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 666.10/K4

Topic: D.09. Multisensory Integration

Support: Puelma scholarship

Title: Modulation of bistable visual perception by auditory stimuli in a multisensory environment with controlled attention

Authors: *G. BUCCI[1], M. CONCHA-MIRANDA[1], C. JOANA[2], P. MALDONADO[1]; [1]Neurosci., Univ. de Chile, Santiago, Chile; [2]Univ. of Louvain, Leuven, Belgium

Abstract: The integration of the multiple stimuli presented by the environment facilitates coherent perception and shapes our behavior. Understanding how the characteristics of stimuli influence sensory integration is important to understanding this phenomenon. Evidence has shown how one stimulus in one sensory modality can influence the perception of another stimulus in a different modality, especially when the latter stimulus is ambiguous and therefore difficult to perceive. However, it is not yet clear what characteristics a stimulus must present in order to allow the disambiguation in a different sensory modality and generate a perception that is coherent with the environment, especially in stimuli that present movement. We set out to investigate how the direction of a stimulus in one sensory modality could influence the perception of the direction of another one in a different sensory modality. For this, we observed whether the direction of a sound was able to generate a change in the visual perception of people. The subjects had to sit 70 centimeters from a screen in a totally dark room. On the screen, a bistable visual stimulus was presented with "structure from motion" movement. This bistable stimulus can be perceived in two possible ways: rotating to the right or to the left. Subjects had to respond each time they perceived a change in the direction of the stimulus. Simultaneously, the subjects heard a directional white noise (that could have a right or left direction). The direction of the sound was presented randomly. Changes in the level of arousal and attention evoked by auditory stimuli were controlled so that they could not explain the results. To date, 14 subjects have been recorded, 6 men and 8 women, with an average age of 27.57 years. We evaluated the effect of the direction of sound on the visual perception reported by the subjects. So far, no significant differences were observed between coherent audiovisual and incoherent audiovisual events. These results show that in the absence of significant changes in arousal, the direction of the sound does not affect the perceptual change of the subjects. This finding supports the hypothesis that a minimum level of attention is required for audiovisual sensory integration to occur.

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Poster

666. Cross-Modal Processing in Humans II

Location: Hall A

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Program #/Poster #: 666.11/K5

Topic: D.09. Multisensory Integration

Support: Universidad Alberto Hurtado, 2018 Research Fund for Collaborating Professors

Title: The contribution of consciousness in the multisensory integration of sound with a bistable visual stimulus

Authors: *S. VICENCIO[1,2,3], G. BUCCI[1,2,4], M. CONCHA-MIRANDA[1,2,4], N. SANTANDER[2], F. DANNEMANN[2], N. PONCE-ROBLES[2];
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Abstract: The environment around us fills us with a multitude of sensory signals that differ in their physical nature and in the way they are processed by our senses and our brains. However, we do not perceive the objects of the world as a series of separate stimuli or as the mere sum of their sensory signals. The brain constructs a unique and coherent perception by integrating the different sources of information that come from our sensory pathways. This multisensory nature of our perception opens the question of how the various senses are integrated to form a single percept. In this regard, while there is evidence that conscious sensory processing is important for the integration of different sensory modalities, most of these studies have been conducted with brief or acute stimuli. In contrast, the role of consciousness on interactions that occur when sensory stimuli are coupled for a longer period of time has not been explored in detail. With this in mind, we set out to evaluate the effect of conscious perception on the sensory integration of moving and prolonged stimuli. We used a structure from motion stimulus, which consisted of moving dots that could be perceived either as a sphere turning to the left or to the right. This stimulus was paired with a battery of sounds that varied in direction (left or right) and intensity. The threshold at which subjects were able to differentiate a directional sound from a neutral one was evaluated, as well as the threshold at which they could correctly identify the orientation of that direction. With all of this, we analyzed the effect that the direction of conscious and subliminal sounds had on the direction of the visual stimulus reported by the subjects. We found that conscious directional sounds have a significant effect on the perception of the bistable visual stimulus, increasing the number of reports that are congruent with the direction of the auditory stimulus. On the other hand, we did not find this effect on subliminal directional sounds. These results show that in the absence of conscious perception, the direction of sound has no effect on the visual perception of subjects.

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Poster

666. Cross-Modal Processing in Humans II

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Topic: D.09. Multisensory Integration

Support: Ramalingaswami fellowship (BT/RLF/Re-entry/31/2011)
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NBRC core fund
SERB National Postdoctoral Fellowship (Grant No. PDF/2016/003188)

Title: Posterior superior temporal sulcus is involved in segregative and integrative cortical information processing underlying cross-modal perception, but not necessarily multisensory processing

Authors: *S. SINGH, A. MUKHERJEE, D. RAY, P. RAGHUNATHAN, A. BANERJEE;
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Abstract: In a naturalistic environment, brain is accustomed to integrate multiple sensory inputs into a coherent perceptual object. Over the years, the study of McGurk effect, a phenomenon in which visual stimulus shapes speech perception, provided insights on the multimodal integration in brain. However, an equivocal interpretation on its mechanism is still at large. Our study aims to reveal the role of posterior superior temporal sulcus (pSTS) during audiovisual (AV) illusory perception. A critical question is how does pSTS guide network modulations while processing for the sensory components of the signal? An associated question is, whether the role of pSTS extends beyond the sensory processing level to rather a representative of the cross-modal perceptual experience.
Forty-two healthy right-handed volunteers participated in the fMRI study, approved by the Institutional Human Ethics Committee of NBRC, India. Inside the scanner, AV stimuli were presented in a block design, comprising 28 activation blocks of 10 similar stimulus videos interspersed by rest blocks. There were 7 stimulus videos: 6 incongruent AV objects (/pa-/ka) corresponding to -300, -150, 0, 150, 300, and 450 ms audio signal lags, and 1 congruent AV object (/ta-/ta, or pure /ta). Participants reported their perceptual hearing experience of either /pa, /ta, or other during the presentation. Finally, 34 participants were categorized as McGurk perceivers based on the threshold that at least 60% of /ta being perceived in any lag condition. Cortical activation pattern and functional connectivity (FC) changes across AV lags, as well as across three other perceptual conditions, were analyzed among the McGurk perceivers. At group level, we then explored the interrelation between the changes in brain and the degree of illusory perceptual experience.
Illusory /ta perception was maximal during 0 lag, and it gradually decreased with more AV

separation. Cortical regions activated during different task conditions were also found to be very similar, however the degree of activation increased with decreasing AV separation as well as with increasing cross-modal /ta perception. We also observed more bilateral activation of cortical areas (including pSTS) at 0 and 150 ms AV lags. The degree of pSTS activity for large AV lags as well as the pure /ta condition were very similar. Further, seed-based FC analysis revealed that inferior frontal gyrus, precentral gyrus, pSTS, insular gyrus, and cingulate gyrus were crucial during AV illusory perception. Thus, pSTS region in both hemispheres played important role in segregative and integrative aspects of cortical information processing during McGurk illusory perception.

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Poster

666. Cross-Modal Processing in Humans II

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Program #/Poster #: 666.13/K7

Topic: D.09. Multisensory Integration

Support: Dissertation completion grant 2019, Temple University

Title: Vestibular training promotes adaptation of the vestibular system in postural control among healthy adults

Authors: *K. O. APPIAH-KUBI[1], A. GALGON[2], R. TIERNEY[1], R. LAUER[1], W. WRIGHT[1]; [1]Temple Univ., Philadelphia, PA; [2]Univ. of the Sci., Philadelphia, PA

Abstract: **Purpose:** Postural stability depends on the integration of multisensory inputs to drive motor outputs. When visual and somatosensory input is available and reliable, this reduces the postural control system's reliance on the vestibular system. Despite this, vestibular loss can still cause severe postural dysfunction. One form of sensory training is vestibular adaptation/habituation achieved through rhythmic head-shaking activities. We hypothesized that the effect of a concurrent weight shifting and head-shake training will significantly alter the pattern of sensory weighting and vestibular role in maintaining postural stability as measured by vestibular reflexes (VOR, VCR and VSR).
Methods: Forty-two young healthy individuals (22 females; 23.0±3.5 years; 1.7±0.1 meters) were randomly assigned into four groups: 1) visual feedback weight shifting training (WST) coupled with an active rhythmic horizontal head-shake (HHS, n=11), 2) same WST with rhythmic vertical head-shake (VHS, n=10), 3) WST with no head-shake (NHS, n=11) and 4) no training/head-shake control (CTL, n=10) groups. Training was performed for 5 days/week for 20 minutes/session. Pre- and post- assessments were Sensory Organization Test (SOT), video head

impulse test (vHIT) and ramp perturbation trials. A between- and within-group repeated measures ANOVA was used to analyze the data. Alpha was set at $p<0.05$.
Results: Following training, the VOR gain showed a Group-by-Session effect, with HHS and VHS showing the biggest change (p=.040). The second ramp down perturbation trial showed a Group-by-Session effect in the COP sway area, especially in VHS (p=.004). The vestibular (head-shake) groups (HHS, VHS) also showed a faster automatic postural response (COP sway velocity, p=.010) during the ramp up trials. The medial gastrocnemius muscle showed reduced muscle activation in the SOT, with HHS showing the greatest change (p=.017). For the ramp up trials, medial gastrocnemius and rectus femoris showed significant changes in peak amplitudes, with decreased amplitude mainly for the vestibular groups ($p<0.05$). The SOT equilibrium, composite scores, sensory ratios and COP variables did not show significant changes ($p>0.05$).
Conclusion: Combined vestibular activation and WST show evidence of modifying vestibular responses in the vestibular groups. The change in VOR gain, postural control and muscle activation after training may be as a result of vestibular re-weighting via VOR, VCR or VSR adaptation and habituation. **Clinical relevance:** Findings may be used to guide the development of a vestibular rehabilitation intervention in populations with vestibular disorders.

Disclosures: K.O. Appiah-Kubi: None. **A. Galgon:** None. **R. Tierney:** None. **R. Lauer:** None. **W. Wright:** None.

Poster

666. Cross-Modal Processing in Humans II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 666.14/K8

Topic: D.09. Multisensory Integration

Title: Memory consolidation and aesthetic judgments in sound-form symbolism (bouba-kiki)

Authors: V. RAMACHANDRAN, P. BHATTACHARYYA, Z. MARCUS, R. SEN, K. VON-KLEIST, *C. CHUNHARAS;
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Abstract: When naïve subjects are shown an amoeba shape and a jagged shape and asked, 'which of these is kiki and which is bouba', 95% pair the amoeba with bouba and the jagged shape with kiki. Despite the fact that neural populations activated by the shape (photons hitting the eye in parallel) are utterly different from sound-driven sequentially activated hair cells in the ear, the brain extracts the abstract property of sharpness or undulation in Fourier space.
When presented with a congruent sound-shape pair (e.g. amoeba(shape)=bouba(sound)) vs. incongruent sound-shape pair (amoeba=kiki), the former is remembered better. We showed participants a series of shapes paired with either congruent names or incongruent names, and after 10 minutes, asked them to pick the correct name for each shape from two name choices. In

the case of congruently named shapes (e.g. amoeba=bouba), they were asked to choose from two congruent names – one which was originally paired with that precise shape in the learning phase, and a second one (also congruent and bouba-like), which was presented with a different shape in the learning phase (e.g., when presented with an amoeba, they were asked to choose between "bouba" and "maluma"). The same procedure was used for incongruent name-shape pairs. Participants were better at remembering the correct name for congruent name-shape pairs than for incongruent name-shape pairs, even when they had to choose it over another equally congruent, but different name.
Attractive faces paired with unattractive names are less well remembered than those paired with attractive names. Likewise – words with mismatched colors (e.g., "red" printed in green ink) – even after being learned to criterion, may decay more readily than congruent ones (e.g. "red" printed in red ink).
We conclude: 1) Establishing congruence may continue into the consolidation period – not merely during acquisition. 2) Features that have an inherent affinity to be bound (amoeba+bouba), bind more strongly, persisting as a pair longer during the consolidation of memory (which involves not merely a stabilization of synapses, but editing, caricaturizing, binding, prioritizing etc.). 3) Even congruence derived from aesthetic judgment (e.g. pretty name+pretty face) might enhance memory consolidation. These observations have obvious implications for the emergence of language and the cognitive neural apparatus involved in consolidating memories.

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Poster

666. Cross-Modal Processing in Humans II

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Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 666.15/K9

Topic: D.09. Multisensory Integration

Support: NRF-2017M3C7A1047225

Title: Effects of dominant eye and head direction on locomotion trajectory

Authors: ***H. JOO**[1], S. KIM[1,3], J.-K. RYU[2], K.-M. LEE[1,4];
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Abstract: Background
Self-orientation is the basis of human behaviors such as walking, grasping, and navigation, etc. To construct the relationship between the self and the surrounding environment, recognizing

self-orientation is required. Since human has limited cognitive resource capacity, aligning self-orientation to the so-called "cyclopean-eye" would take additional computational effort. Here, we hypothesized that self-orientation would follow the visual information of the dominant eye not the converged information of binocular vision.
Method
There were 9 conditions in total: three head rotation conditions(front, left, right) X three eye conditions(binocular, dominant eye, non-dominant eye). The dominant eye test was done prior to the experiment. Participants were asked to walk in a straight line ten times in each condition. To calculate the drifted walking tendency while walking under different conditions, participants wore a cap type motion tracker. There was no practice session before the test to prevent motor adaptation. The baseline was set by each participant's front head direction X binocular vision condition. The angle differences were analyzed, and the positive value means that the walking path was drifted to the direction of the dominant eye.
Result
In a binocular eye condition, we observed the tendency that walking path drifted to the direction of the head rotation. In dominant/non-dominant head rotation and eye conditions, the variance appeared smaller in the dominant head rotation and the dominant eye combination compared to the non-dominant head rotation and the non-dominant eye-condition. Analysis indicated that there was a significant main effect for head direction($F(2, 203)=13.173$, $p=.000$). There was no significant main effect for eye condition level($F(2, 203)=.385$, $p= .681$) and no significant interaction effect of head directions and eye conditions($F(2, 203)=2.175$, $p=.116$).
Conclusion
If self-orientation depends on the dominant eye's visual information, locomotion trajectory of the dominant eye condition will not differ from that of the binocular eye condition. In this study, however, we found only the head direction condition have significant effects on locomotion trajectory, and this is in line with our previous research. Thus, we can expect that there is an information processing mechanism to make a reference frame other than the visual information from the initial perceptual level.

Disclosures: **H. Joo:** None. **S. Kim:** None. **J. Ryu:** None. **K. Lee:** None.

Poster

666. Cross-Modal Processing in Humans II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 666.16/K10

Topic: D.09. Multisensory Integration

Support: National Key R&D Program of China 2017YFA0205904
National Science Foundation of China and the German Research Foundation NSFC 61621136008/DFG TRR-169

Title: Functional connectivity between 'visual' and language areas in the blind predicts braille reading performance

Authors: *R. WANG[1], J. GONG[2], C. ZHAO[1], Y. XU[2], B. HONG[1];
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Abstract: Prior studies have implicated activations in 'visual' cortex of the blind during language processing, including speech comprehension (Bedny, 2011; Röder, 2002) and verbal memory tasks (Amedi, 2003). It has been shown that blind subjects with higher activation in V1 perform better in verbal-memory tasks (Amedi, 2003). While there remains an outstanding question about how the functional connectivity between these 'visual' areas and language nodes contributes to linguistic behavior, which may help elucidate the reorganization of language network in the blind. With fMRI scan of 12 skilled blind Braille readers (mean age 22.55 years, 6 males) , we found that 'visual' areas including V1 and extrastriate cortex (V2) showed similar involvement to classic language areas including inferior frontal gyrus (IFG) and reading-specific visual word form area (VWFA) in the Braille reading task. We next analyzed resting-state functional connectivity (RSFC) to explore the altered neural network among these active nodes in the blind. Compared with the sighted group, the blind showed enhanced RSFC in left V2 - IFG (unpaired t-test, $P < 0.005$), left V2 - VWFA ($P < 0.05$) and left V1 - IFG ($P < 0.005$). We further investigated the correlation between RSFC and Braille reading performance. The left V2 - IFG and left V2 - VWFA connectivity strengths were positively correlated with the blind subject's Braille reading speed (character/per minute) respectively (left V2 - IFG: $P < 0.001$, $R^2 = 0.72$; left V2 - VWFA: $P < 0.05$, $R^2 = 0.42$). No such association with Braille reading performance was found in V1 connectivity. We postulated that with visual deprivation and Braille learning experience of the blind, additional language-sensitive neural connectivity developed to the left 'visual' area, especially lateral occipital region V2, which may explain the language-related brain activity of 'visual' areas in previous work. This study further revealed the causal role of extended language-related neural connectivity in 'visual' cortex in superior Braille reading performance of the blind.

Disclosures: R. Wang: None. **J. Gong:** None. **C. Zhao:** None. **Y. Xu:** None. **B. Hong:** None.

Poster

666. Cross-Modal Processing in Humans II

Location: Hall A

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Program #/Poster #: 666.17/K11

Topic: D.09. Multisensory Integration

Support: NIH Grant DC013828

Title: The causal role of the pSTS in auditory-visual speech integration: A voxel-based lesion-symptom mapping study

Authors: *O. G. WIESE[1], S. KAKAIZADA[3], C. VALDIVIA[3], S. HERVEY-JUMPER[4], D. BRANG[2];
[2]Psychology, [1]Univ. of Michigan, Ann Arbor, MI; [3]Neurosurg., [4]Univ. of California San Francisco, San Francisco, CA

Abstract: Auditory receptive speech abilities are important for social and emotional health in hearing individuals. However, the reliability of auditory signals varies widely in every-day settings (e.g., at a crowded party), requiring supplemental processes to enable accurate speech perception. The principle way this occurs is by auditory-visual (multisensory) compensatory mechanisms restoring auditory content using lipreading and other visual cues (i.e., speaker identity, rhythmic entrainment of visual speech, among others). Research suggests that the posterior region of the superior temporal sulcus (pSTS) is critical for multisensory compensatory mechanisms to modulate speech perception. Previous research using transcranial magnetic stimulation demonstrated that transient impairment of the left pSTS inhibited auditory-visual speech integration. However, a case study describing a patient five years after complete destruction of their left pSTS due to stroke reported intact auditory-visual integration using the McGurk effect. These discrepant results indicate that the case study was either a usual instance of the right pSTS supporting auditory-visual speech integration prior to the stroke, or, more likely, that functional reorganization due to neural plasticity allowed the individual to recover auditory-visual speech integration processes over the course of the five-year period. To discriminate between these possibilities, we examined auditory-visual speech integration abilities in patients with brain tumors in various locations. Specifically, we identified 8 patients with a tumor that extended into the left pSTS and 31 patients with tumors in other regions. Next, we compared these two groups' performance on a McGurk effect task to estimate their auditory-visual speech integration abilities. Preliminary results indicate that tumors located in the left pSTS are associated with significantly ($p<.05$) reduced strength of the McGurk effect, consistent with non-invasive data indicating the causal role of this structure in integrating auditory and visual speech information. Longitudinal tracking of these participants' behavioral performance will enable a better understanding of if (and when/how) compensatory structures re-enable auditory-visual speech integration processes.

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Poster

666. Cross-Modal Processing in Humans II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 666.18/K12

Topic: D.09. Multisensory Integration

Support: The Swedish Research Council
Göran Gustafssons Stiftelse

Title: Motor interference in the rubber hand illusion correlates with the perception of the real hand disappearing

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Abstract: Background
A sense of ownership over the body arises through multisensory integration, whereby a combination of sensory cues provide a coherent experience of an owned body distinct from the world around us. However, our sense of body ownership is malleable, as shown by the rubber hand illusion (RHI): synchronous stroking of a fake hand and a participant's real hidden hand can induce a sense of ownership over the false limb, and cause the perceived position of the real hand to drift towards the fake one (proprioceptive drift). Some individuals also report a feeling of the real hand disappearing, which might reflect a feeling of disownership for the real hand.
It is still unclear if movement is reliant on a sense of ownership over our body, though the RHI may alter parietal-motor cortical connectivity and reduce corticospinal excitability. With this in mind, we examined if the RHI has functional consequences for basic movement.
Methods
We recruited 58 participants (mean age = 26.3 years, 29 female) who took part in two blocks (synchronous or asynchronous stroking of the real and false hand) of ten trials. The position of the right index finger was motion-tracked. In each trial stroking was performed for 30 seconds. After stroking, a tone signalled participants to rapidly abduct their index finger, providing measures of reaction time (RT), peak acceleration (PA), and peak velocity (PV). We also recorded proprioceptive drift and questionnaire statements (feelings of rubber hand ownership, real hand disappearance) for the synchronous and asynchronous conditions.
We predicted that, should the RHI alone interfere with movement, then RT would be greater in the synchronous than in the asynchronous condition, and PA and PV would be reduced. We also examined if specific components of the RHI (proprioceptive drift, sensations of rubber hand ownership and real hand disappearance) were correlated with changes in kinematic variables.
Results
Neither the RHI alone, nor proprioceptive drift or sensations of rubber hand ownership interfered convincingly with movement. However, individuals reporting a greater feeling of the real hand disappearing performed movements with smaller PA (r_τ=-.285, p=.004, BF_{10}=23.2) and PV (r_τ=-.270, p=.007, BF_{10}=13.7) following illusion induction. Though most participants did not affirm this feeling, the correlation was supported by effects observed in the subset (n=15) that did (BF_{10}>3).
Conclusion
Although it may not be an essential component of the RHI, a feeling of losing the real hand may have functional consequences for movement. This supports the idea that body ownership may mediate the capacity of the motor system for basic movement.

Disclosures: **A.T. Reader:** None. **H.H. Ehrsson:** None.

Poster

666. Cross-Modal Processing in Humans II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 666.19/K13

Topic: D.09. Multisensory Integration

Title: Visual selection is influenced by natural auditory dynamics

Authors: ***M. K. SMITH**[1], M. GRABOWECKY[2], S. SUZUKI[2];
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Abstract: We often find ourselves in environments containing multiple multisensory objects that vie for our attention. Our auditory system has the ability to play a crucial role in the visual selection process because it is good at rapidly identifying temporal regularities in our environment as well as detecting salient, transient events. The aim of this study was to investigate the role of dynamic auditory features in influencing visual selection. Participants engaged in a novel paradigm in which they experienced dynamic audiovisual combinations consisting of natural auditory soundscapes (nature, urban, and music) paired with visualizer displays containing distinct elements each of which represented the amplitude modulation changes of a given auditory frequency band as luminance changes. The visual elements were circles arranged in a 4x4 matrix. As the soundscape-visualizer combinations played, participants visually searched for a visual element that appeared to be an optimal match for what they heard at any point in time. By assigning the visual elements to correspond to dynamic changes within a particular frequency band, we probed whether specific frequency ranges provided useful information for visual selection. Across all auditory scenes we found a tendency for participants to fixate the visual elements that represented the auditory frequency bands with the highest pulse clarity ($t(50) = -4.14$, $p < 0.001$) rather than the visual elements representing the frequency bands with the highest intensity ($t(50) = 0.61$, $p = 0.54$). This result demonstrates that the auditory systems ability to identify the periodic dynamics in a chaotic signal can bias visual selection towards objects that may be plausible sources of those sounds.

Disclosures: **M.K. Smith:** None. **M. Grabowecky:** None. **S. Suzuki:** None.

Poster

666. Cross-Modal Processing in Humans II

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Topic: D.09. Multisensory Integration

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Title: Integration of simultaneous artificial sensory percepts to identify prosthetic hand postures

Authors: *I. CUBEROVIC[1], J. L. SEGIL[3], E. L. GRACZYK[2], R. F. F. WEIR[3], D. J. TYLER[2]; [2]Biomed. Engin., [1]Case Western Reserve Univ., Cleveland, OH; [3]Univ. of Colorado Boulder, Boulder, CO

Abstract: Skilled prosthesis use requires both high degree-of-freedom control and sensory feedback. However, current prostheses do not restore somatosensation, forcing users to rely only on visual and auditory feedback to regulate movements. Prostheses are rarely used for complex motor tasks like tool manipulation, since these tasks divert attention away from the prosthetic device. Instead, they are adopted for supporting tasks, used passively, or not used. To provide sensory feedback to upper limb amputees, peripheral nerve interfaces are used to electrically activate the residual somatosensory nerves of the hand. In the intact system, multiple sources of sensory information are integrated to develop hand posture percepts. However, the extent to which prosthesis users can integrate patterns of artificial sensory information has not been studied. Here, we report on a case study of a person with transradial amputation.
We found that the participant was able to successfully integrate five simultaneous, electrically-evoked sensory percepts to identify prosthetic hand postures. He achieved 95.0% success in identifying 4 postures and 75.7% in identifying 7, significantly above chance ($p \leq 0.001$). Further, we studied how artificial somatosensation and the extant body schema are integrated in the decision-making process by varying the mapping between the prosthetic sensor and the location of the sensory percept. Two mappings were used across experimental conditions: 1) a congruent mapping (index finger sensor evokes perception on the index finger), and 2) an incongruent mapping (index finger sensor evokes perception on the ring finger). We found that the participant was able to learn postures more accurately ($p \leq 0.04$) and more quickly ($p \leq 0.022$) in the anatomically congruent condition. Further, we showed that his strategy in identifying postures and error types ($p \leq 0.011$) changed with mapping. Finally, we investigated how prior knowledge is applied in novel decision-making tasks by expanding the task to identifying seven

postures and found that he was only able to successfully generalize to novel postures in the anatomically congruent condition (p=0.018 and p=0.989, anatomically congruent and incongruent conditions, respectively).

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Poster

666. Cross-Modal Processing in Humans II

Location: Hall A

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Program #/Poster #: 666.21/K15

Topic: D.09. Multisensory Integration

Support: STW 14906

Title: Stiffness-dependent sensory weighting of position and force feedback during pinching

Authors: *J. E. GEELEN[1,2], A. C. SCHOUTEN[1], N. F. RAMSEY[2], F. C. T. VAN DER HELM[1], W. MUGGE[1];
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Abstract: During daily activities, complex tasks such as opening a bottle, writing a note, and playing the piano reveal the dexterity and the high number of degrees of freedom of our fingers. When controlling finger movements, the central nervous system (CNS) has to cope with the redundancy of hand muscle activation and the uncertainty in the sensory feedback. The integration of multiple afferent inputs includes interrelations beyond the simple addition of inputs. Sensory weighting can be found within the proprioceptive system of the shoulder, more specifically between the two sensory modalities: muscle length and muscle force (Mugge et al. 2009). When pinching an object between two fingers, information from both proprioceptive modalities are related. Interactions with stiffer objects result in smaller position changes and higher force changes. Thus force feedback is expected to be dominant in that situation. We hypothesize that similar stiffness-dependent sensory weighting exists in object manipulation by the fingers.
This exploratory study investigates the weight adjustment of proprioceptive inputs by the CNS that facilitates optimal control of the fingers. A robotic manipulator was designed to provide an adjustable dynamic environment, a virtual spring, over a range of stiffnesses. The robot accurately measures the force and position of the tip of the fingers in a pinching motion. The subjects (n=10) were trained to blindly reproduce a force against the virtual spring. In regular trials, the fingertip position was linearly related to the applied force, and thus the weights were indistinguishable. The virtual spring dynamics were altered into a non-linear spring for some

trials, catch trials, revealing the sensory weighting. A maximum likelihood estimation model predicts the optimal integration of the proprioceptive sensory information and explains the sensory weighting in pinching. Future experiments that compare the brain activity patterns for distinct weightings of position and force during finger movements require knowledge about the stiffness level at the crossing point of these weights. With the current study, we provide the essential information to analyse the multisensory integration in the CNS during pinching.
W. Mugge, J. Schuurmans, A. C. Schouten, and F. C. T. Van Der Helm, "Sensory Weighting of Force and Position Feedback in Human Motor Control Tasks," vol. 29, no. 17, pp. 5476-5482, 2009.

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Poster

666. Cross-Modal Processing in Humans II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 666.22/K16

Topic: D.09. Multisensory Integration

Title: Short term monocular deprivation in adult humans influences multisensory interactions

Authors: *C. OPOKU-BAAH[1], J. E. OLSEN[2], B. HOU[2], M. T. WALLACE[3];
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Abstract: Normal visual sensory experience plays a crucial role in the development of the visual and the multisensory systems. Even in the adult brain with limited plasticity, recent studies have shown that transient absence of visual input in one eye changes the dynamics of binocular rivalry to favor the deprived eye. This short-term experience-dependent plasticity is thought to likely reflect an upregulation of contrast-gain control mechanisms in the deprived eye. Here, we sought to extend this work into the multisensory (i.e., visual-auditory) arena, with the hypothesis that short term monocular deprivation will influence not only binocular interactions, but multisensory interactions as well. Participants were recruited to perform an audiovisual temporal numerosity judgment task using their deprived and non-deprived eyes in separate sessions. The sessions occurred before and after 90 minutes of monocular deprivation with an opaque eye patch. Each participant's pre and post deprivation results for the deprived and non-deprived eyes were obtained, analyzed and fit to a Bayesian Causal Inference (BCI) model with 9 parameters. Comparing the behavioral responses, we discovered that visual bias (which measures the influence of the more reliable modality (i.e. audition) on the perceived visual percept) tended to decrease for the deprived eye more than for the non-deprived eye. For the modeling results, two out of the nine parameters of the BCI model showed significant differences between the deprived

and non-deprived eye conditions. First, deprivation was found to decrease the variance (i.e., standard deviation) of the visual likelihoods of the deprived eye, demonstrating an improvement in visual sensory encoding. Second, after deprivation, the tendency to bind the audiovisual signals was reduced for the deprived eye but was increased for the non-deprived eye. Changes in visual likelihood and binding tendency were found to be strongly positively correlated, such that larger improvements in visual sensory encoding were associated with weaker binding tendency. Together, our findings support the hypothesis that short-term monocular deprivation can affect multisensory perceptual processes through a change in visual sensory encoding and the tendency to bind audiovisual signals. This indicates that changes in visual experience in the adult can influence the way the visual system interacts with other sensory modalities, and thus such changes in multisensory perception may contribute to the overall compensatory behaviors observed in patients with adult-onset visual deprivation.

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Poster

666. Cross-Modal Processing in Humans II

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Topic: D.09. Multisensory Integration

Support: Supported by NRF-2017M3C7A1029659

Title: Audio-visual interactions during motion adaptation modulates the perceived duration of the motion aftereffect and the brain activity in hMT+

Authors: *M. PARK[1], C.-Y. KIM[2];
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Abstract: The perceptual system forms a unified, coherent percept by integrating sensory inputs from multiple modalities each of which is processed through a distinct neural pathway. In our previous psychophysical study exploiting the motion aftereffect (MAE; an illusory motion caused by adaptation to physical motion), adaptation to visual motion accompanied by auditory motion with the congruent direction enhanced the intensity of the subsequent visual MAE, suggesting audio-visual interactions relatively early in the visual pathway. In the present study, we used functional magnetic resonance imaging (fMRI) to examine the neural mechanisms underlying such audiovisual congruence effect. Specifically, we focused on the motion sensitive area hMT+ since neural adaptation arising from direction-selective neurons in hMT+ has been considered as the neural basis of the MAE. During the 30-sec initial adaptation and the 12-sec top-up adaptation phases, MAE was induced by the 100%-coherence random-dot kinematograms (RDKs) moving either leftward or rightward. Leftward or rightward moving sound was

simulated by cross-fading the intensity of the white noise presented between binaural channels of noise-cancelling headphones. According to the audio-visual direction congruence, there were congruent and incongruent sound conditions along with stationary, and no-sound conditions. During the 4-sec test phase, participants reported the duration and the direction of the MAE experienced on a stationary RDK. Behavioral results from the three participants clearly replicated our previous findings that the duration of visual MAE was longer in the congruent condition and was shorter in the incongruent condition than in other conditions. fMRI results from the univariate analysis showed the greater activation in hMT+ in the congruent condition than in the incongruent condition, echoing the behavioral results. Results from the multivariate pattern analysis (MVPA) showed the difference in decoding accuracies between the congruent and incongruent conditions when a classifier discriminated the direction of the MAE after being trained to discriminate leftward versus rightward direction of physical motion. These results indicate that audio-visual interactions based on the direction congruence during adaptation lengthened the duration of the MAE, which was subserved by modulation of the intensity and the activity patterns of hMT+.

Disclosures: M. Park: None. **C. Kim:** None.

Poster

666. Cross-Modal Processing in Humans II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 666.24/K18

Topic: D.09. Multisensory Integration

Title: Defining the time course of multisensory object processing: A three stage model

Authors: *T. VERCILLO[1], E. G. FREEDMAN[1], S. MOLHOLM[2], J. J. FOXE[1];
[1]Neurosci., Univ. of Rochester Sch. of Med., Rochester, NY; [2]Neuroscience/Pediatrics, Albert Einstein Col. of Med., Bronx, NY

Abstract: The majority of objects that we interact with in the natural environment are multisensory, stimulating multiple sense organs and leading to representations in a distributed sensory cortical network. Multisensory objects that are frequently encountered lead to strong associations across this network, with the end result perception of a unitary object. However, we know relatively little about the cortical processes sub-serving multisensory object formation and recognition. This is surprising given their relevance to learning to read (e.g., associating graphemes with phonemes) and to ubiquitous other tasks. To advance our understanding in this important domain, the present study investigated the brain processes affected by the learning and identification of novel visual-auditory objects. Thirty adults were remotely trained for a week to recognize, with ~100% accuracy, a novel class of multisensory objects (3D shapes paired to complex sounds), while data were live streamed to the lab via an Andriod device. High density

event related potentials (ERPs) were recorded to the unisensory (shapes or sounds only) and the multisensory (shapes and sounds) stimuli, before and after the intensive training. We differentiated multisensory effects by comparing individual ERPs to the multisensory versus the unisensory stimuli, and the summation of the unisensory responses. Moreover, we compared ERPs before and after training, to map the evolution of multisensory cortical responses between initial exposure to full consolidation (post-training) of these audiovisual pairings into a well-learned class of multisensory object. We report three major multisensory effects: 1) an early multisensory effect (<100 ms) within occipital scalp areas, triggered by the detection of simultaneous audiovisual signals and not related to multisensory learning; 2) an intermediate object-processing stage (100-200 ms), involving a larger cortical network, sensitive to the learned multisensory associations and 3) a late conceptual multisensory processing stage (>250 ms) that does not appear to be learning-specific. Results from this study provide support for multiple stages of processing of multisensory object learning and recognition, subserved by an extended network of cortical areas. This innovative work significantly contributes to our understanding of multisensory object representations, and could shed light on developmental learning disorders associated with multisensory integration.

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Poster

666. Cross-Modal Processing in Humans II

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Topic: D.09. Multisensory Integration

Support: NIH R00 DC013828

Title: Characterizing auditory responses in human low-level visual cortex using ECoG

Authors: ***J. PLASS**[1], E. AHN[1], A. SHERMAN[2], V. TOWLE[3], W. STACEY[1], V. WASADE[4], J. TAO[3], S. WU[3], N. ISSA[3], M. GRABOWECKY[5], S. SUZUKI[5], D. BRANG[1];
[1]Psychology, Univ. of Michigan, Ann Arbor, MI; [2]Occidental Col., Los Angeles, CA; [3]Univ. of Chicago, Chicago, IL; [4]Henry Ford Hosp., Detroit, MI; [5]Northwestern Univ., Evanston, IL

Abstract: Sounds can facilitate the perception of simultaneous visual events. One mechanism thought to subserve these enhancements is crossmodal phase-resetting of subthreshold oscillations in low-level visual cortex. By placing visual cortex in a high-excitability state before visual input arrives, crossmodal phase-resetting is thought to enhance sensitivity for concurrent visual signals. Using intracranial electrocorticography (ECoG) in human epilepsy patients, we recently observed widespread auditory phase-resetting throughout visual cortex, including pericalcarine (putative V1/V2), lateral occipito-temporal (potentially V5/hMT+), inferior

occipito-temporal, and posterior parietal cortex. Here, we sought to further characterize the electrophysiological properties and stimulus selectivity of crossmodal responses in low-level (pericalcarine) visual cortex by analyzing additional indices of neural activity and responses to a wider variety of auditory stimuli. Consistent with research in non-human primates, pericalcarine electrodes exhibiting auditory phase-resetting demonstrated only weak or negligible neural firing, as indexed by high gamma (70-150 Hz) power. At lower frequencies (reflecting neural oscillatory activity), electrodes with the most pronounced phase-resetting effects (measured using inter-trial phase coherence; ITPC) exhibited increased power in the same frequency bands (theta/alpha), while electrodes with weaker ITPC exhibited broad power suppression. These results suggest that sounds primarily influence low-level visual cortex by modulating sub-threshold oscillations, potentially increasing theta/alpha power by synchronizing oscillations in targeted neural ensembles, while reducing neural variability overall. To characterize the stimulus selectivity of these responses, we examined whether they varied with the frequency (pure tones) or complexity of auditory stimuli. Crossmodal responses exhibited variable or no frequency preferences, and similar phase-resetting responses for pure tones, noise bursts, and speech. These results suggest that crossmodal responses in low-level visual cortex may primarily convey stimulus timing with minimal selectivity for stimulus content. Altogether, these results support the hypothesis that sounds enhance stimulus coding in low-level visual cortex by synchronizing subthreshold oscillations to the timing of auditory events.

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Poster

666. Cross-Modal Processing in Humans II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 666.26/K20

Topic: D.09. Multisensory Integration

Title: fMRI response to transcutaneous vagus nerve stimulation

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[1]Translational Neurocircuitry, [2]Synaptic Transmission in Energy Homeostasis, Max-Planck-Institute for Metabolism Res., Cologne, Germany; [3]Anat. II (Neuroanatomy), Univ. Hosp. of Cologne, Cologne, Germany

Abstract: Transcutaneous vagus nerve stimulation (tVNS) is known to have acute as well as long-term effects. The physiology of neither, however, is well understood. Classical block designs for the fMRI-analysis of acute brain activation in response to tVNS are difficult to

interpret due to time-varying effects of tVNS. Here, we used task-free functional MRI in humans to assess time-dependent effects of tVNS on brainstem neuronal responses. Specifically, we used a repeated- measures design with factors time (10 time points during a 7 minute stimulus- plus 3 minute post-stimulus interval), and group (sham vs. verum stimulation).
Activation of previously described downstream targets of vagal afferents like the dorso-vagal complex (DVC), parabrachial complex (PB) and substantia nigra (SN) showed significant (FEW brainstem cluster-level corrected under a cluster-defining threshold of $p < 0.001$) response to electrical stimulation in ROI-based analysis of the brainstem in 13 lean, healthy human subjects (8 females).
In the course of stimulation, we observed a linear increase in activation, which peaked during the 'off'-period after the 7 min stimulation phase, suggesting that carry over effects are particularly important when interpreting fMRI data with respect to the neurophysiology of tVNS.

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Poster

666. Cross-Modal Processing in Humans II

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Topic: D.09. Multisensory Integration

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Title: You or me? Defining the boundaries of self-other peripersonal space

Authors: *F. GARBARINI, C. FOSSATARO, M. GALIGANI, A. ROSSI SEBASTIANO, V. BRUNO, I. RONGA;
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Abstract: The concept of peripersonal space (PPS) captures the idea of a portion of space immediately surrounding the body (near space). Since the PPS representation is known to be highly plastic, changing with experience, here we asked whether it can be modulated by social-dependent contextual manipulations. In social contexts, the PPS can be defined as "my space" as opposed to "your space". Does the presence of someone else's hand modulate the boundaries of the self-related PPS? To answer this question, we capitalized on visuo-tactile multisensory integration, occurring when visual stimuli appear within the PPS boundary (i.e. close to the stimulated body district) and known to speed up the behavioural responses to tactile stimuli and to induce sub/super-additive responses in the neural activity (Visual Enhancement of Touch, VET). In two experiments, participants underwent a VET paradigm in which event-related

potentials (ERPs) and reaction times (RTs) to tactile stimuli were recorded. In both experiments, tactile (electrical) stimuli were delivered to the participants' hand, while visual stimuli (colored-led) could appear either near to the stimulated hand or far from it, at two different distances (i.e. 20 cm or 40 cm away from the stimulated hand). In the first experiment, we verified that, in both RTs and ERPs, significant differences between near and far conditions were found only when visual-stimuli in far position were coded as outside the PPS (40 cm away from the stimulated hand) and not when they were coded as inside (20 cm). In the second experiment, we demonstrated that, when another person's hand was present, so that the position far from the participant's hand was near to the co-experimenter's hand, visual-stimuli, previously coded as inside the PPS (at 20 cm), were coded as outside and significant differences between near and far conditions reappeared in both RTs and ERPs. Taken together, these findings show that the presence of someone else' body-parts reduces the self-related PPS boundary, within which integrated responses occur, and induces a social recoded of "my space" as "your space".

Disclosures: F. Garbarini: None. **C. Fossataro:** None. **M. Galigani:** None. **A. Rossi Sebastiano:** None. **V. Bruno:** None. **I. Ronga:** None.

Poster

666. Cross-Modal Processing in Humans II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 666.28/K22

Topic: D.09. Multisensory Integration

Support: EU Hz2020 PACE ITN Grant No 642961

Title: The effect of free manipulation on bimanual integration in the haptic perception of the size of boxes and pliers

Authors: Q. XU[1,2], G. RISSO[1,2], ***G. BAUD-BOVY**[1,3];
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Abstract: Many circumstances in daily life require people to use both hands to manipulate objects and gather information about their shape. While historically most studies have focused on the integration of information from different sensory modalities, within-modality sensory integration and bimanual integration in particular raise similar questions about when the brain should or should not integrate information. Intriguingly, previous studies have shown little evidence that proprioceptive information from the two hands is integrated when apprehending the size or shape of objects. In the present study, we investigated the influence of lifting the object on bimanual integration. To that end, we measured how precisely people estimate the size of objects (wooden boxes, actuated apparatus with two movable flat surfaces and large-size

pliers) when using one hand or two hands with the object grounded or lifted. Results indicate that subjects are able to discriminate the size of complex tools such as pliers, and that lifting the object can improve size discrimination performance. We propose that the physical interaction between the two hands occurring during free manipulation enhances bimanual integration by strengthening the assumption that information is coming from the same object. However, no factor can single-handedly explain all the results. Like in other sensory integration studies, a mix of structural factors and cognitive factors such as the familiarity of the object appears to matter.

Disclosures: **G. Baud-Bovy:** None. **Q. Xu:** None. **G. Risso:** None.

Poster

666. Cross-Modal Processing in Humans II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 666.29/K23

Topic: D.09. Multisensory Integration

Title: The optometric effects of virtual reality

Authors: ***C. MCGINNIS**[1], J. A. ARMENDARIZ[1], M. F. AWAD[1], A. KANGAVARY[1], D. VIDAMUERTE[1], J. HINKEL-LIPSKER[2], S. A. DREW[1];
[1]Psychology, [2]Kinesiology, California State University, Northridge, Northridge, CA

Abstract: As virtual reality head mounted display (VR-HMD) technology becomes more widely used in industry, research, and recreation, the oculomotor effects of continued use will become more prominent. This study aims to test the possible ocular effects caused by a new commercially available VR system. Participants were assigned to either a VR-training or real-world (RW) training condition. Researchers were trained to administer optometric tests by a licensed optometrist and measured vergence and accommodation facilities in both groups before and after a 30 minute session of dart throwing. Preliminary results indicate overall increase in the performance on the accommodation and vergence test, but no significant difference between the groups. This may show promising results to any individuals or organizations that would plan to implement VR in the future.

Disclosures: **C. McGinnis:** None. **J.A. Armendariz:** None. **M.F. Awad:** None. **A. Kangavary:** None. **D. Vidamuerte:** None. **J. Hinkel-Lipsker:** None. **S.A. Drew:** None.

Poster

666. Cross-Modal Processing in Humans II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 666.30/K24

Topic: D.09. Multisensory Integration

Support: This research was undertaken thanks in part to funding from the Canada First Research Excellence Fund
CSA Grant 15ILSRA1-York

Title: Visual reorientation illusions on earth - Comparison of different assessment techniques

Authors: *N.-A. BURY, M. HUSSAIN, M. MCMANUS, L. R. HARRIS;
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Abstract: Human spatial orientation uses three reference frames: gravity, allocentric (orientation and relationships of visual objects and features) and egocentric (orientation of the body). Usually these frames are redundant; however, in unusual environmental conditions, such as in microgravity, they can become dissociated which can evoke Visual Reorientation Illusions (VRI) in which the interpretation of up can suddenly switch directions. Here we compare different assessment techniques for identifying VRIs evoked by altering the relationship between visual, gravity and body cues by means of the York tumbled room. Twenty-eight participants (12 female; 20.3 ± 2.6 yrs.) were positioned in two rooms with the identical interior layouts. One was normally oriented, the other was tilted 90° relative to gravity. Participants were blindfolded when entering either room and were guided to adopt the same orientation relative to the features of each room: upright in the normally-oriented room, supine in the tilted room. Participants were exposed to each room for 5s and 180s. Before, in between, and after these exposure periods, they donned a head mounted display in which they were immersed in a featureless virtual cubic room with six differently colored surfaces (randomly rotated for each trial) and identified the “ceiling” / “floor” (group A) or the surface “above” / “below” them (group B) by verbally indicating the appropriate colored surfaces. Afterwards they were asked whether they perceived a VRI during either exposure period. The rate of VRI reporting in the tumbled room (defined as when the visual frame dominated) depended on the identification technique used. VRIs were less likely to be reported using the cubic room technique compared to verbal report. Surprisingly, the shorter exposure period to the tumbled room led to >20% more VRI reports than the longer exposure. However, this was only the case for verbal reports. Use of different wording (ceiling/floor vs. above/below) evoked no difference in reports. We conclude that caution should be used when generalizing findings on VRI incidence when only a single identification technique is used. Longer exposure seemed to allow gravity to become more salient when deciding on the perceived direction of up.

Disclosures: **N. Bury:** None. **M. Hussain:** None. **M. McManus:** None. **L.R. Harris:** None.

Poster

667. Basal Ganglia: Cellular and Systems Physiology

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 667.01/K25

Topic: E.03. Basal Ganglia

Title: Inputs to neurons in layer 1 of mouse cerebral cortex

Authors: *E. LAI, G. W. ARBUTHNOTT;
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Abstract: In rodents, a major output from the basal ganglia arrives in layer 1 (L1) of frontal cortex. Neocortical L1, the most superficial layer of cerebral cortex, is composed of a small number of GABAergic interneurons and received massive excitatory input fibers from the ventromedial thalamus and other cortical and subcortical areas. Electrophysiological results have identified that L1 fibres from ventral motor thalamus have monosynaptic access to layer 5 cortical output (pyramidal tract, corticofugal or corticostriatal) and layer 6 corticothalamic output. Understanding the synaptic organization in L1 interneurons circuitry is vital for understanding the mechanism involved in regulating movement. For this study we have compared the postsynaptic responses in interneurons of L1 to optogenetic activation of both thalamocortical (thalamocortical pathway, TC) and contralateral cortical inputs (intratelencephalic tract, IT) using in vitro whole-cell patch-clamp recordings of motor cortex in C57BL/6J mice. We discovered that L1 interneurons received excitatory inputs from at least two set of input fibres. Interestingly, they evoked different paired-pulse response; TC afferent exhibited paired-pulse depression while IT input fibres evoked paired-pulse facilitation. Furthermore, many L1 interneurons have inhibitory responses - presumably from other interneurons within layer 1. In particular, L1 interneurons received proportionally more inhibitory signals after TC stimulation than after IT fibres. Such differences in the probability of finding inhibition strongly suggest that the two inputs control different numbers of interneurons, and so differently affect layer 1 actions. Based on our results, we hope that a study of this less populated area of cortex will illuminate the detailed interactions of motor thalamus with cortical areas involved in mechanisms of motor control. Increasing speculation about the role of cortex in Parkinson’s Disease symptoms -or even in the cause of the disease- make these experiments important for the understanding of the influence of basal ganglia on motor behavior.

Disclosures: **E. Lai:** None. **G.W. Arbuthnott:** None.

Poster

667. Basal Ganglia: Cellular and Systems Physiology

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 667.02/K26

Topic: E.03. Basal Ganglia

Support: JSPS Kakenhi JP18H03134

Title: Involvement of choline metabolism in short latency afferent inhibition: MRS and TMS study

Authors: *D. SATO[1], K. YAMASHIRO[2], N. KODAMA[2], N. OTSURU[3], Y. YAMAZAKI[2], K. IKARASHI[2], H. ONISHI[2];
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Abstract: Short afferent inhibition (SAI) has been extensively studied to identify the experimental factors affecting the magnitude of the phenomenon, and to determine the underlying neural mechanisms. Current evidence indicates that sensory and motor pathways are involved in generating SAI, and that its modulation may depend on the inputs received via cholinergic neural activity to the GABAergic interneurons or pyramidal neurons. However, the correlation between cholinergic metabolism and SAI remains unclear. We aimed to identify the involvement of choline metabolism in SAI. We hypothesized that the involvement of the brain regions associated with choline metabolism is dependent on the stimulus paradigm of SAI, and that the choline metabolism in the primary somatosensory cortex (S1) and the striatum may be related to SAI with shorter and longer interstimulus interval (ISI). Sixteen right-handed, healthy adults participated in this study. On day 1, magnetic resonance spectroscopy (MRS) were conducted to evaluate the choline metabolism in the lower and upper part of the striatum, primary motor cortex (M1), and S1. Next, on day 2, SAIs were measured using a paired stimulation paradigm with electrical stimulation to the median nerve, and transcranial magnetic stimulation to the M1. According to the latency of the N20 component in somatosensory evoked potential, ISIs were set at N20 latency plus 2, 4, 6, 8, and 10 ms by each participant. Both MRS and SAI measurement were conducted between 0930 and 1200 h on different days. Pearson correlation analysis showed that SAI with an ISI of N20 plus 2 and 10 ms significantly correlated with choline concentration in S1 (r^2=0.256, p=0.04) and the lower part of the striatum (r^2=0.376, p=0.02), respectively. No other significant correlations between choline concentration and SAI were found. In line with our hypothesis, choline metabolism in S1 was involved in SAI with an ISI of N20 latency plus 2 ms. This supports previous studies indicating that S1 may modulate SAI with an ISI of N20 latency plus 2 ms, and identified the novel finding that higher choline concentration in S1 may be involved in lower SAI. Additionally, this is the first study to show

that choline metabolism in the striatum modulates SAI with an ISI of N20 latency plus 10 ms. This suggests that tonic cholinergic neural activity may modulate GABAergic neurons which inhibits the thalamo-cortical projection in the striatum, and which decreases SAI with an ISI of N20 latency plus 10 ms via the inhibited afferent input to M1. To conclude, SAI is modulated by distinct neural mechanisms that depend on ISI and choline metabolism in S1, and the striatum was involved in SAI with ISI of 2 ms and 10 ms.

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Poster

667. Basal Ganglia: Cellular and Systems Physiology

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 667.03/K27

Topic: E.03. Basal Ganglia

Support: Ministero dell'Istruzione, dell'Universita` e della Ricerca Grant PRIN 2015AWSW2Y_005

Title: Crossed corticostriatal projections in the macaque brain

Authors: E. BORRA, ***G. LUPPINO**;
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Abstract: Ipsilateral corticostriatal (CS) projections are the major source of input to the basal ganglia (BG) and it is largely agreed that different sets of functionally related cortical areas project to different parts of the striatum (striatal input channels), at the origin of largely segregated BG-thalamo-cortical loops. Indeed, we found that projections from inferior parietal, ventral premotor, and ventrolateral prefrontal areas involved in controlling goal-directed hand actions (lateral grasping network) overlap in two distinct putamen sectors and in one caudate sector, suggesting parallel BG processing and integration of different aspects of motor control. The striatum is also target of crossed projections from the contralateral hemisphere which have been so far somewhat neglected. In 2 macaques we analyzed the distribution of the direct and crossed CS projections based on 3 tracer injections placed at different dorso-ventral levels of the motor putamen and 1 in the mid-rostral caudate. In all cases, the labelling extensively and differentially involved mostly frontal motor (60-77% of ipsi + contra CS labeled cells), posterior parietal (8-18%) and cingulate areas (4-23%). The amount of labeling in the contralateral hemisphere largely varied according to the location of the injection site: quite low after the ventral putamen (5% of all CS labeled cells), higher after the middle putamen (14%), and even higher after the dorsalmost putamen and the caudate injection (23 and 29%, respectively). The distribution of the labeled cells in the contra- vs. the ipsilateral hemisphere showed clear

asymmetries. In some regions (e.g., parietal and ventral premotor cortex) the labeling in the contralateral hemisphere, compared to that in the ipsilateral one, was in all cases relatively scarce or almost negligible, whereas in other it was much richer. Indeed, in all cases, from 20 to 40% of area 24 (ipsi + contra) labeled cells was observed in the contralateral hemisphere; after the caudate injection 34% of area F3/SMA (ipsi + contra) labeled cells was observed in the contralateral hemisphere; after the dorsal putamen injection 36% of dorsal premotor area F2 (ipsi + contra) labeled cells was observed in the contralateral hemisphere. It is noteworthy that after the caudate injection, contralateral area F2 was the third strongest source of cortical input and after the dorsal putamen injection contralateral areas 24 and F1 (primary motor area) were the fourth and fifth strongest sources of cortical input, respectively. The present data provide evidence for potentially important contributions of crossed CS projections to information processing carried out in the macaque BG.

Disclosures: G. Luppino: None. **E. Borra:** None.

Poster

667. Basal Ganglia: Cellular and Systems Physiology

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 667.04/K28

Topic: B.09. Network interactions

Title: Weight related sex differences in insular and striatal connectivity

Authors: *L. A. MAAYAN[1], A. LARR[2], P. REISS[3], M. J. HOPTMAN[4], J. NIERENBERG[2], K. HERNANDEZ[5], A. TIMKO[1], B. LEVENTHAL[6];
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Abstract: Neural processes regulating intake are finely tuned to maintain homeostasis; yet the mechanisms underlying dysfunction are not known. Previously we showed the relationship of BMI to functional connectivity between insula (Ins), inferior temporal gyrus and lingual gyrus as well as less robust findings of connectivity between nucleus accumbens (Nac) and sensorimotor strip. Here we delve further to examine sex differences in connectivity in relationship to BMI. 204 subjects completed study procedures after overnight fast. Weight and height were assessed with a detecto scale and stadiometer, and participants were given 15 minutes to consume a multi item meal followed by a 10 minute resting state fMRI on a Siemens Magnetom 3T scanner. Images were pre-processed and processed using AFNI and FSL commands. Functional connectivity was determined to seed regions of interest in Nucleus accumbens (Nac), Insula (Ins), Orbitofrontal cortex (OFC) and Inferior frontal gyrus (IFG). Results were analyzed for connectivity in relation to BMI across all subjects as well in contrast between sexes.

Results:
102 right handed adults had a normal distribution of BMI and are reported on in the following. When thresholded with threshold free cluster enhancement and regressed against BMI Left insula seed (LtINS) showed increased connectivity to right middle(17.9, 37.2, 14.8) and inferior temporal gyri (13.4, 45.4,11.9) and right insula seed (RtINS) to superior temporal gyrus (25.1,16, 22.3).
Males had increased connectivity between RtINS with right lingual gyrus (28.4,17.5,23.8) (threshold z=2.3 and p=.05 for this and following results) Females had decreased connectivity between Left Nac seed (LtNAC) and right pre and post central gyrus (18.9, 32.7, 47.1). LtINS had decreased connectivity with right middle and inferior temporal gyrus (14.7, 40.3, 14.6) and Left OFC seed (LOFC) showed increased connectivity with right insula and superior temporal gyrus (15.4, 43.5, 27.2).
Gender contrast
At higher BMI females had greater connectivity than males between LtNAC and left middle frontal gyrus (41.3, 57.3, 28.6) as well as between LOFC and a region including right inferior parietal lobe, superior temporal gyrus and insula (1.8, 30.4, 31.9).
Males had greater connectivity than females between right IFG seed and left superior frontal gyrus (30.5, 58.4, 23.9).
Conclusions
We found differences in reward sensitivity between sexes suggesting that decreased sensory connectivity to reward regions is more relevant to female than male BMI. Women and men also contrast in connectivity to insula suggesting that interoception may play a differential role in eating behavior between sexes.

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Poster

667. Basal Ganglia: Cellular and Systems Physiology

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 667.05/K29

Topic: E.03. Basal Ganglia

Support: SIP 20180265
SIP 20196612

Title: Electrical activity of the thalamic reticular nucleus is controlled in a differential way by the globus pallidus

Authors: *A. ALATORRE[1], A. OVIEDO-CHÁVEZ[1], J. R. MARTINEZ-ESCUDERO[2], E. QUEREJETA[1];

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Abstract: The information that flows from different thalamic nuclei to the cerebral cortex (Ctx) is regulated by the electrical activity of the thalamic reticular nucleus (RTn) (Sherman et al, 1996). Through GABAergic projections, RTn neurons synchronize the overall electrical activity of thalamo-cortical (TC) neurons (Pinault, 2004). RTn receives glutamatergic afferents from layer six neurons of Ctx and TC collaterals. However, there is a GABAergic afferent pathway coming from the globus pallidus (external GP in primates) which effect in the electrical activity of RTn neurons have received scarce attention (Guillery et al, 2003). In the present work, we analyzed the electrical activity of RTn neurons in vivo in normal and lesioned ipsilateral GP Wistar rats by using unitary recordings. In normal conditions, we recorded two types of electrical behavior from the dorsal to the ventral pole in RTn: a tonic spiking and mixed spiking that consisted in a tonic firing alternating with burst activity. In lesioned rats the spontaneous frequency increased both tonic and mixed spiking (up to 3500%) as compared with normal rats (figures 1 and 2). Unlike that was observed in normal rats, we did not record mixed activity in the medial region of RTn; this fact allows us to arbitrarily divide the RTn into three regions: dorsal, medial and ventral pole. Mixed activity only was recorded in the dorsal and ventral pole. Burst index of the mixed neurons recorded in the ventral pole was similar as the mixed neurons recorded along the RTn in normal rats; BI in the neurons of the dorsal pole in lesioned rats was minor as compared with mixed neurons along the RTn in normal rats.
Our results showed that GP controls in differential ways different population of neurons in the RTn.
Figure 1. Electrical activity of RTn neuron in sham rat.
Figure 2. Electrical activity of RTn neuron in GP lesioned rat.

Disclosures: A. Alatorre: None. **A. Oviedo-Chávez:** None. **J.R. Martinez-Escudero:** None. **E. Querejeta:** None.

Poster

667. Basal Ganglia: Cellular and Systems Physiology

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 667.06/K30

Topic: E.03. Basal Ganglia

Title: Movement-related single unit activities in the external segment of the globus pallidus in a step-tracking movement task

Authors: *T. ISHIKAWA, S. KAKEI;
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Abstract: The basal ganglia are considered to be one of the most important subcortical regions for motor control. In fact, distinctive types of movement disorders are observed in Parkinsonism and other abnormal conditions characterized by anatomic and biochemical changes in the basal ganglia. However, neural mechanism by which the basal ganglia contribute to control of voluntary movement is still controversial. We know little about functional role of individual nuclei in the basal ganglia in control of movements. To address this issue, we examined movement-related activities of neurons in the external segment of the globus pallidus (GPe) in a monkey performing a step-tracking wrist movement for eight directions and compared them with corresponding activities in the primary motor cortex in the same experiment. According to previous anatomical studies, neurons in GPe receive two distinct inputs originated from the motor cortex: an excitatory input via the subthalamic nucleus, and an inhibitory input via the putamen. We analyzed single unit activities of 81 GPe neurons with movement-related modulation in the movement task and obtained two major findings. First, we found that there are three types of neurons in terms of modulation changes of activity at movement onset. The first group of neurons (n=22, 27%) showed only excitation, while neurons in the second group (n=17, 21%) showed only suppression at movement onset. Forty-two neurons in the third group (52%) showed both excitation and suppression of activity depending on movement direction. In addition, 40 neurons out of 81 (49%) showed significant directional tuning at movement onset as often observed in neurons in motor cortices in the same experiment. These results suggest that the timing and balance of inputs from the subthalamic nucleus and the putamen to individual GPe neurons may dynamically change corresponding to kinematics of movement to perform or muscles to activate. Second, we performed a population analysis of movement-related GPe activities and found that excitatory modulation was dominant as a whole. Considering that excitation of GPe neurons is thought to have an excitatory effect on neurons in the thalamus by suppressing inhibitory neurons in the internal segment of the globus pallidus, movement-related activity in GPe appears to contribute to facilitation of cortical motor areas.

Disclosures: **T. Ishikawa:** None. **S. Kakei:** None.

Poster

667. Basal Ganglia: Cellular and Systems Physiology

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 667.07/K31

Topic: E.03. Basal Ganglia

Support: NINDS Grant U01NS098961

Title: Movement related oscillatory activities within corticobasal ganglia circuit predict motor performance

Authors: *J. CHOI[1], M. MALEKMOHAMMADI[1], S. NIKETEGHAD[2], N. POURATIAN[1]; [1]Neurosurg., [2]Bioengineering, Univ. of California, Los Angeles, CA

Abstract: Reaction time (RT) is one of the most important behavioral responses to evaluate the motor performance reflecting the overall efficacy of sensorimotor processing. In general, RT shows trial-by-trial variation, suggested to be modulated by the cortico-basal ganglia (BG) motor circuit. However, how the BG-cortical networks contribute to this RT variability remains underexplored. Here, we investigate the difference in the oscillatory activities within and between BG and motor cortex between fast and slow motor responses.We took advantage of deep brain stimulation (DBS) surgery to obtain invasive cortical and BG recordings during undergoing DBS lead implantation surgery. From 13 patients with idiopathic Parkinson's disease, we recorded local field potentials in sensorimotor cortical region and BG including subthalamic nucleus (STN) or globus pallidus internus (GPi) during a simple go task. We split all correct 'Go' trials into 3 groups based on the RT, which were 'fast', 'median', and 'slow' trials, and statically compared the movement-related changes in local and global BG-cortical oscillatory activities between 'fast' and 'slow' trials (by cluster-based permutation test). Additionally, the correlations between BG-cortical activities and RT were explored (by Spearman correlation). During the motor execution period, the slow trials showed significantly delayed event-related desynchronization (ERD) before the motor responses in motor cortex (M1) and STN in both low- and high-beta bands (13-20 and 20-30 Hz, respectively). Also, the slow trials showed significantly delayed event-related increases in M1 in broad gamma-band (70-200 Hz). Likewise, at the same period, the suppression of M1-GPi coherence in the whole beta band (13-30 Hz) was significantly delayed for the slow trials. Interestingly, during the motor preparation period, the motor cortical low-beta ERD was significantly stronger for the fast trials, and the magnitude of ERD was negatively correlated to RT.
Overall, our findings suggest that the modulation of the timing and magnitude of the oscillatory activities within BG-cortical circuit might subserve the dynamics of motor performance. Our study provides new insight in an electrophysiological role of BG-cortical circuit in motor control, particularly with respect to motor initiation.

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Poster

667. Basal Ganglia: Cellular and Systems Physiology

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 667.08/K32

Topic: E.03. Basal Ganglia

Support: Auckland Medical Research Foundation 1116016

Brain Research New Zealand

Title: Preferential dopamine release in the caudolateral striatum from substantia nigra pars lateralis neurons receiving subthalamic nucleus input

Authors: *P. S. FREESTONE, K. L. TODD, J. LIPSKI;
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Abstract: The subthalamic nucleus (STN) is unique being the only glutamatergic nucleus in the basal ganglia and also receiving direct cortical motor input forming the hyperdirect pathway. Recent anatomical and behavioural studies suggest that the STN exerts control over a subset of dopamine neurons in the substantia nigra pars lateralis (SNL) that preferentially project to the caudolateral region of the striatum, as opposed to the better studied substantia nigra pars compacta (SNC) to rostromedial striatum projection. Here, we applied electrochemical detection of electrically evoked dopamine release *in vivo* to better understand the role the STN has in modulating dopamine pathways in the basal ganglia. Experiments were conducted in anaesthetized (urethane; 1.4g/kg i.p) Wistar rats (~290g). Fast-scan cyclic voltammetry (FSCV) was used to measure evoked dopamine release in the rostromedial (centre) and caudolateral (tail) striatum. Dopamine release was evoked following electrical stimulation (300µA, 2ms, 60Hz, 2s, twisted-bipolar) of the STN, SNC and SNL. Modified controlled adsorption FSCV was used to accurately measure basal dopamine in both striatal regions. Electrical stimulation of the STN evoked significant dopamine release in the caudolateral striatum (53.4±13.9nM, n=5 hemispheres), but negligible release in the rostromedial striatum (17.4.±4.5nM, n=5). Conversely, stimulation of the SNC failed to evoke dopamine release in the caudolateral striatum (6.5±2.3nM, n=5), but evoked significant release in the rostromedial striatum (87.0±29.7nM, n=5). Importantly, stimulation of the SNL evoked the largest dopamine release in the caudolateral compared to rostromedial striatum (51.8±17.8nM vs 10.9±5.8nM, n=4) - this profile of response being comparable to that of stimulating the STN, suggesting a common pathway. Measurements of basal dopamine revealed a much lower level in the caudolateral striatum compared to the rostromedial striatum of the same hemisphere (255±30nM vs 416±33nM, n=12). These findings confirm that the caudolateral striatum receives greatest input from the SNL, and those neurons in turn are strongly innervated by glutamatergic input from the STN.

Disclosures: P.S. Freestone: None. **K.L. Todd:** None. **J. Lipski:** None.

Poster

667. Basal Ganglia: Cellular and Systems Physiology

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 667.09/K33

Topic: E.03. Basal Ganglia

Title: Functional organization of basal ganglia thalamocortical projections

Authors: *A. D. LIEN, A. C. KREITZER;
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Abstract: Inhibitory basal ganglia outputs to the ventral anterior/ventral lateral (VA/VL) motor thalamus are thought to play an important role in motor behavior by influencing thalamic input to the cortex. A complete understanding of basal ganglia thalamocortical function requires knowledge of both the type of information being signalled by individual basal ganglia-recipient thalamus (BGThal) neurons during motor behavior and the cortical regions to which they convey this information. While primary sensory nuclei of the thalamus contain functional maps of sensory space that are recapitulated in their target cortical area through topographically organized thalamocortical projections, the functional organization of BGThal and its thalamocortical projections is poorly understood. We developed an optogenetic antidromic stimulation approach for mapping cortical projection targets of many simultaneously recorded BGThal thalamic neurons in head-fixed awake, behaving mice. We expressed ChR2 in VA/VL and transcranially photostimulated ChR2-expressing axons across an array of cortical locations covering the anterior half of the dorsal cortex (AP: -1 to 3 mm from bregma; ML: 0 to 3mm from midline) while recording single-unit spiking in VA/VL using silicon probes. For some units, photostimulation of cortical locations evoked reliable single spike responses with submillisecond jitter consistent with antidromic spike generation in distal axons. For each recorded unit we generated a cortical projection map based on the locations eliciting antidromic responses. Additionally, we used optogenetic basal ganglia indirect pathway stimulation, which should suppress BGThal firing, to identify the recorded neurons as basal ganglia-recipient. BGThal projections were found in almost all stimulated cortical locations and many individual projections were large, spanning several mm. To relate BGThal neuron cortical projection patterns to function, we obtained cortical projection maps of neurons recorded during locomotion while tracking limb position using high speed video and DeepLabCut. A subset of BGThal neurons fired preferentially at specific phases of the locomotor stride cycle. The projections of BGThal neurons that preferred the stance phase of the contralateral forelimb had more projections to posterior cortex while those preferring the swing phase tended to project more anteriorly. These results demonstrate that BGThal neurons encode highly specific information during movement that is conveyed to distinct cortical locations.

Disclosures: **A.D. Lien:** None. **A.C. Kreitzer:** None.

Poster

667. Basal Ganglia: Cellular and Systems Physiology

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 667.10/K34

Topic: E.03. Basal Ganglia

Support: NIH Grant R01NS094667
Pew Scholar
NIH Grant K99NS102520
NIH Grant F32NS098634

Title: Movement related activity in ventral pallidum and dopaminergic midbrain is gated by behavioral state

Authors: *R. CHEN, V. GADAGKAR, P. A. PUZEREY, J. H. GOLDBERG;
Cornell Univ., Ithaca, NY

Abstract: Dopamine (DA) neurons and their inputs from the ventral pallidum (VP) exhibit both reward and movement related firing, but it remains unknown if these signals can be gated by behavioral state. For example, movement-related dopamine signals have been observed in some studies but not others. One possibility is that some neurons are movement related and others are not. Another possibility is that a single neuron can be movement related under certain behavioral states but not others. We recorded single DA and VP neurons in birds transitioning between singing and non-singing states while monitoring body movement with microdrive-mounted accelerometers. The activity of many VP neurons was locked to body movements with millisecond timescale precision but only during non-singing states. During singing, these neurons switched off their tuning to movement and became instead precisely time-locked to specific song syllables. Similarly, many DA neurons exhibited phasic movement related activity but only during non-singing states; during singing these neurons lost their movement related signaling and instead encoded singing-related performance error. Changes in neuronal tuning could occur on 10 millisecond timescale at state boundaries. Our findings demonstrate that movement-related activity in single neurons can dramatically change with behavioral context.

Disclosures: R. Chen: None. **V. Gadagkar:** None. **P.A. Puzerey:** None. **J.H. Goldberg:** None.

Poster

667. Basal Ganglia: Cellular and Systems Physiology

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Program #/Poster #: 667.11/K35

Topic: E.03. Basal Ganglia

Support: NIH Grant F31DA047014

Title: Functional innervation of the dorsal striatum by the rostral intralaminar thalamus

Authors: *K. K. COVER, G. W. BUNCE, B. N. MATHUR;
Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: The striatum mediates the selection of actions for reward acquisition through the dynamic activation of medium spiny output neurons (MSNs). Excitatory drive of MSNs is modulated by dopamine and acetylcholine. We recently elucidated a microcircuit by which glutamatergic projections arising from the rostral intralaminar nuclei of the thalamus (rILN) stably elicit striatal dopamine release through a striatal cholinergic interneuron intermediary to support action reinforcement. Unknown, however, is how this thalamostriatal projection directly influences direct versus indirect pathway MSNs to produce behavioral reinforcement. Here, we employ whole-cell patch clamp electrophysiology to interrogate the functional connectivity of rILN projections with MSN subpopulations in striatal slice. These results stand to inform how the rILN contributes to basal ganglia function and resulting behavior.

Disclosures: K.K. Cover: None. **B.N. Mathur:** None.

Poster

667. Basal Ganglia: Cellular and Systems Physiology

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Topic: E.03. Basal Ganglia

Support: NSF Grant #1707405

Title: A nano-to-milliscale imaging pipeline for detailing how multiple brain regions communicate with the striatum

Authors: *S. SHIGENO, V. SAMPATHKUMAR, R. VESCOVI, H. LI, A. J. MILLER, S. M. SHERMAN, N. B. KASTHURI;
Neurobio., Univ. of Chicago, Chicago, IL

Abstract: The striatal system has an essential role in action planning, reward learning, and goal-directed behaviors. A fundamental question in the striatum is understanding how varied brain regions, from cortex to thalamus, communicate with striatum. However, most studies that study long range connectivity in striatum focus on either looking at the coarse output of multiple brain regions at the macro level (e.g. MRI) or on the projections of individual neurons (e.g. Golgi or GFP like staining) without minimal context of the behavior of other brain regions. An ideal imaging pipeline would provide both: nanoscale information about the behavior of individual cell type labeled neurons and mesoscale information about long distance projections from many brain regions. In order to address this gap, we have developed a multimodal multiscale imaging pipeline using synchrotron X-ray microscopy and automated serial electron microscopy with

genetic labeling of specific cell types. We find interesting and contradictory results about the organization of long range projections in striatum. At the mesoscale, we image large volumes of striatum stained with a combined gold chloride myelin-specific staining and reduced osmium method with synchrotron source X-rays. We find evidence of 'crosstalk': smaller bundles of myelinated axons (MA) 'mix' and 'match' frequently across striatum, creating transitory macro bundles whose composition is constantly changing. At the nanoscale, we express an EM dense dye, APEX2, in layer 5 pyramidal neurons in M1, S1, and thalamus (pMO) and reconstruct labeled axons along with every individual MA in large volumes of white matter or spongy tracts in striatum. We find that axons from a specific cortical region spatially segregate within white matter bundles in striatum: clusters of 2-6 MA from a specific brain region remain more spatially proximate to each than to other brain regions. Thus we conclude that the 'logic' of long range connections from different brain regions in striatum is complicated with evidence of both global mixing between myelinated tracts and evidence of brain region specific segregation within individual tracts.

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Poster

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HHMI-PF Medical Research Fellowship 2017-2018
2018 AΩA Carolyn L. Kuckein Student Research Fellowship
Northwestern University Weinberg Summer Research Grant

Title: Mouse external pallidum harbours complex neuron subtypes

Authors: *B. L. BERCEAU, Z. A. ABECASSIS, J. P. WIN, D. GARCIA, H. S. XENIAS, Q. CUI, A. PAMUKCU, V. M. HERNÁNDEZ, C. S. CHAN;
Physiol., Northwestern Univ., Chicago, IL

Abstract: The GPe, as part of the basal ganglia circuit, is critically involved in motor control. Alterations of GPe neuron activity are observed in both mouse models and human patients of Parkinson's disease (PD). Despite the clinical importance of the GPe, its neuronal composition remains elusive. Aside from $Foxp2^{+}$ neurons and $ChAT^{+}$ neurons that have been established as

unique neuron types, there is no consensus on the classification of GPe neurons. In this study, we leverage new mouse lines, viral tools, and molecular markers to better understand the molecular, anatomical, and intrinsic properties of the remaining GPe neurons. We found that Sox6 represents a novel, defining marker for GPe neuron subtypes. $Lhx6^+$ neurons that lack the expression of Sox6 were devoid of both parvalbumin and Npas1. This result confirms previous assertions of the existence of a unique $Lhx6^+$ GPe population. Furthermore, we identified the $Npas1^+$-$Nkx2.1^+$ population that lacks Foxp2 as a potentially distinct functional subclass. Both retrograde and anterograde tracing experiments revealed that $Npas1^+$-$Nkx2.1^+$ neurons represent the principal, non-cholinergic, cortically-projecting neurons; they project profusely in the frontal cortex and are part of a cortico-pallidal-cortical loop. Lastly, analysis of the spatial distribution and electrophysiological properties of a number of GPe neuron types further confirms the diversification of GPe subtypes. In summary, we provide improved descriptions of GPe neuron subtypes. By delineating different GPe neurons and their synaptic partners, our findings establish the circuit substrates that can be important for motor function and dysfunction. Our findings reconcile some of the discrepancies that arose from differences in techniques or the reliance on pre-existing tools.

Disclosures: **B.L. Berceau:** None. **Z.A. Abecassis:** None. **J.P. Win:** None. **D. Garcia:** None. **H.S. Xenias:** None. **Q. Cui:** None. **A. Pamukcu:** None. **V.M. Hernández:** None. **C.S. Chan:** None.

Poster

667. Basal Ganglia: Cellular and Systems Physiology

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R01 MH112768
R01 NS097901
R01 MH109466
R01 NS088528
R00 MH109569

Title: Pallidal PV+ neurons and Npas1+ neurons have distinct input and function

Authors: *A. PAMUKCU[1], Q. CUI[1], E. C. AUGUSTINE[2], I. B. FAN[1], B. L. BERCEAU[1], H. S. XENIAS[1], T. N. LERNER[3], S. C. CHAN[4];
[1]Northwestern Univ., Chicago, IL; [2]Northwestern Univerisity, Chicago, IL; [3]Physiol.,

Northwestern, Chicago, IL; [4]Dept. of Physiol., Northwestern University, Feinberg Sch. of Med., Chicago, IL

Abstract: The GPe is a critical node within the basal ganglia circuit. Phasic changes in the activity of GPe neurons during movement and their alterations in Parkinson's disease suggest that the GPe is important in motor control. PV^+ neurons and $Npas1^+$ neurons are the two non-overlapping, principal neuron classes in the GPe. The distinct electrophysiological properties and axonal projection patterns suggest that these two neuron classes should serve different roles in regulating motor output. However, this idea has not been systematically tested. Here we demonstrate that PV^+ neurons and $Npas1^+$ neurons promote and suppress locomotion, respectively. Moreover, PV^+ neurons and $Npas1^+$ neurons are under different synaptic influence from the subthalamic nucleus (STN). Lastly, the selective weakening in the STN input to PV^+ neurons in chronic Parkinsonian mice reinforces the idea that the reciprocal GPe-STN loop plays key roles in disease symptomatology and thus provide the basis for future circuit-based therapies.

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Poster

667. Basal Ganglia: Cellular and Systems Physiology

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Topic: E.03. Basal Ganglia

Support: ANR-16-CE37-0007-01

Title: Neuronal activity in the internal (GPi) and external globus pallidus (GPe) during proactive motor inhibition

Authors: F. HADJ-IDRIS, J. MUNUERA, I. AMEQRANE, M. ROUSTAN, M. GAY, C. KARACHI, *B. LAU;
Inst. du Cerveau et de la Moelle Épinière, Paris, France

Abstract: A crucial component of adaptive behavior is response inhibition, the capacity to refrain from reacting to external events or internal urges. In addition to reactive inhibition—initiated when specific stimuli are identified—responses can be inhibited proactively in the absence of explicit stimuli or triggered by particular contexts, acting to gate actions when fast or erroneous actions are highly undesirable. Cortico-basal ganglia interactions may be important for implementing proactive inhibition, and we recorded single neurons in the internal and external segments of the globus pallidus (GPi and GPi, respectively) while monkeys performed a behavioral task where we manipulated response uncertainty to change proactive inhibition.

Monkeys performed a Go/No-go task where the likelihood of No-go trials was centrally cued with visual stimuli that indicated either 0% or 50% likelihood of a No-go trial. Target location was randomly selected in the left or right hemifield with equal probability, and the visual target indicated whether the trial required a Go response. Analyses of reaction times, as well as commission and omission errors, indicated that monkeys proactively inhibited responses when faced with No-go uncertainty. We isolated single-unit activity from multi-channel single-unit recordings in the GPi and GPe. We used regression analyses to separate effects of movement from putative proactive inhibition and reward expectation. A significant proportion of neurons in both the GPi and the GPe responded in a manner consistent with encoding proactive inhibition, as well as encoding movement execution and movement direction. Neurons encoded proactive inhibition and movement direction with both positive and negative changes in relative activity in approximately equal proportions. We found that the fraction of neurons jointly encoding proactive inhibition and direction was close to that expected from independent coding of these two properties.

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Poster

667. Basal Ganglia: Cellular and Systems Physiology

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Program #/Poster #: 667.16/K40

Topic: E.03. Basal Ganglia

Support: NIH R01 NS104089

Title: Diminished dendritic excitability of indirect pathway striatal projection neurons in the Sapap3 knockout mouse model of compulsive behavior

Authors: *J. M. MALGADY[1], E. M. PRAGER[1], Z. B. HOBEL[1], Q. ZHANG[2], G. FENG[2], J. L. PLOTKIN[1];
[1]Dept. of Neurobio. & Behavior, Stony Brook Univ. Renaissance Sch. of Med., Stony Brook, NY; [2]McGovern Inst. for Brain Res. and Dept. of Brain and Cognitive Sci., MIT, Cambridge, MA

Abstract: The striatum is the main input nucleus of the basal ganglia and contains two distinct neuronal populations: direct pathway and indirect pathway spiny projection neurons (dSPNs and iSPNs). These neuronal populations act in parallel to regulate action selection, with dSPN activity predominantly leading to disinhibition of the thalamus and iSPN activity to inhibition of the thalamus. Under normal conditions, information flow through the striatum may be biased towards iSPNs since they are intrinsically more excitable than dSPNs. However, some circuit

models of compulsive behavior suggest that this bias may be reversed under pathological conditions. Furthermore, several studies have demonstrated pathway-specific corticostriatal synaptic dysfunction in mouse models of compulsive behavior, providing evidence for differences in dSPN vs iSPN activity in generating this pathological behavior. One such model is the Sapap3 knockout (KO) mouse. Sapap3 encodes for a scaffolding protein at glutamatergic synapses, is highly expressed in the striatum, and germ line deletion of Sapap3 leads to compulsive grooming. Using a cross between Sapap3 KO mice and a D2R (drd2-eGFP) reporter line (labeling iSPNs), we employed a combination of electrophysiology and 2-photon imaging in order to assess the dendritic excitability of iSPNs in the dorsal striatum, comparing Ca^{2+} transients at distal vs proximal dendrites in response to somatically-induced back-propagating action potentials (bAPs). Here we present evidence that somatically-generated action potentials propagate farther along iSPN dendrites of WT mice vs KO mice, suggesting that iSPN dendrites are intrinsically less excitable in Sapap3 KO mice. Preliminary data did not detect differences in measures of somatic excitability, such as rheobase or input resistance. Current experiments are ongoing to assess if there are parallel changes in dSPN excitability under the same pathological condition.

Disclosures: **J.M. Malgady:** A. Employment/Salary (full or part-time):; Stony Brook Dept. of Neurobiology & Behavior, Stony Brook Center for Inclusive Eduction. **E.M. Prager:** None. **Z.B. Hobel:** None. **Q. Zhang:** None. **G. Feng:** None. **J.L. Plotkin:** None.

Poster

667. Basal Ganglia: Cellular and Systems Physiology

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Topic: E.03. Basal Ganglia

Support: National Science Foundation, DMS1724240
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Title: Responses of substantia nigra pars reticulata neurons to direct and indirect pathway GABAergic projections depend on intracellular chloride dynamics:computational analysis based on mouse data

Authors: R. S. PHILLIPS, ***J. E. RUBIN**;
Dept. of Mathematics, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: The substantia nigra pars reticulata (SNr) is the primary output nucleus of the rodent basal ganglia (BG) and receives converging $GABA_A$-receptor mediated synaptic inputs from the direct and indirect pathways. The resulting $GABA_A$ current (I_{GABA}) is typically considered to be inhibitory; however, it may also be shunting, excitatory, or biphasic with inhibitory-to-excitatory

responses mediated by intracellular chloride dynamics, which affect the $GABA_A$ reversal potential (E_{GABA}). Direct pathway projections synapse on the distal dendrites whereas indirect pathway projections form basket-like synapses around the somas of SNr neurons. Due to differences in compartment size and the distribution of the Cl extruder KCC2, dendritic and somatic compartments may have different susceptibilities to Cl accumulation and to breakdown of E_{GABA}. We predict that GABAergic signals to SNr will induce the range of atypical responses described above, depending on Cl extrusion capacity, compartment size and input properties. To investigate the contributions of the factors involved in shaping SNr responses to synaptic inputs, we constructed a novel data-driven conductance-based model of an SNr neuron that includes dendritic and somatic compartments. Our model recapitulates published data from experimental studies of short term plasticity in striatonigral and pallidonigral pathways. Moreover, simulations of our model show that $GABA_A$- and KCC2-mediated fluctuations in intracellular Cl can explain many aspects of the SNr spiking responses to GABAergic inputs from the direct and indirect pathways observed in data from the mouse. Finally, we also explore the predictions of our model relating to SNr activity patterns in functionally relevant settings involving inputs from both pathways, including decision-making tasks. Integration of $GABA_A$ receptor-mediated synaptic inputs to somatic and dendritic compartments is not unique to SNr neurons; thus, these results may have implications for other brain regions as well.

Disclosures: **R.S. Phillips:** None. **J.E. Rubin:** None.

Poster

667. Basal Ganglia: Cellular and Systems Physiology

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Topic: E.03. Basal Ganglia

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Title: Altered intrinsic electrophysiological properties of spiny projection neurons in LRRK2 mutant mice

Authors: ***H. XENIAS**[1], C. CHEN[2], S. KANG[2], S. CHERIAN[1], S. CHAN[1], L. PARISIADOU[2]; [1]Dept. of Physiol., [2]Dept. of Pharmacol., Northwestern University, Feinberg Sch. of Med., Chicago, IL

Abstract: Missense mutations in leucine rich repeat kinase 2 (LRRK2) account for the most common genetic form of Parkinson's disease (PD). LRRK2 is highly expressed in spiny

projection neurons (SPNs) in the striatum. However, several aspects of LRRK2 function in the striatum remain elusive. As it is known that the firing of SPNs is altered in PD, we sought to examine if and how LRRK2 mutations affect the electrophysiological properties of SPNs and consequently impair motor output and learning. In particular, $LRRK2^{+/R1441C}$ represents one of the more common LRRK2 mutations with a genetic link to PD. We previously showed that $LRRK2^{+/R1441C}$ gives rise to pathological protein kinase A signaling in SPNs. Therefore, it is also possible that aberrant phosphoregulation and consequently altered channel protein trafficking and gating in $LRRK2^{+/R1441C}$ will result in altered intrinsic excitability of SPNs. This hypothesis was not previously tested in identified SPNs. In the present study, we examined the intrinsic and corticostriatal properties in $LRRK2^{+/R1441C}$ knock-in mice. Our data so far suggest altered responsiveness of SPNs to somatically-injected currents and an imbalance in the activity of dSPNs and iSPNs. We postulate that these alterations would also impair motor learning. The function and relevance of LRRK in motor learning and disease will be further discussed.

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Poster

667. Basal Ganglia: Cellular and Systems Physiology

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Topic: E.03. Basal Ganglia

Support: KIST Grant 2E29180
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Title: Topological diversity of cell types in the subthalamic nucleus using single-molecule fluorescence *in situ* hybridization (smFISH)

Authors: ***J. KIM**[1,2], H. JEON[1], H. LEE[1,2], L. FENG[1], K. TANAKA-YAMAMOTO[1,2], J. KIM[1,2];
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Abstract: The subthalamic nucleus (STN) which relays extensive inputs from a variety of cortical and subcortical structures serves as a convergence hub and a successful target for deep brain stimulation. However, there is little systematic investigation into fundamental characteristics including cellular and synaptic profiles as well as the functional anatomy. Indeed, the complexity of circuit organization in the STN, distinguished by its heterogeneous neuronal populations and the complex patterns of convergence and divergence which might occur at

individual cells, has long been underappreciated. In this study, we performed single-molecule *in situ* hybridization to detect the spatial distribution of major cell classes and further various neurotransmitter receptors in the STN. In addition, we developed a machine learning-based algorithm to analyze and integrate the expression patterns for multiple cell populations. Furthermore, using mammalian GFP reconstitution across synaptic partner (mGRASP) and electrophysiological recording, we characterized the basic neuronal properties of STN subpopulations such as synaptic connectivity and physiological features. Our results provide comprehensive distribution of diverse cell types of the STN and may enable cell type-specific functional studies to enhance our understanding of the basal ganglia circuitry.

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Poster

667. Basal Ganglia: Cellular and Systems Physiology

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Program #/Poster #: 667.20/L4

Topic: E.03. Basal Ganglia

Support: NIH Grant R01 DA045783

Title: Motivation-related dopamine release in nucleus accumbens correlates with cholinergic interneuron activity

Authors: *A. MOHEBI[1], A. HAMID[2], J. D. BERKE[1];
[1]Neurol., UCSF, San Francisco, CA; [2]Dept. of Neurosci., HHMI and Brown Univ., Providence, RI

Abstract: The mesolimbic dopamine pathway (ventral tegmental area, VTA, to nucleus accumbens, NAc) is closely involved in both learning from rewards, and motivation to work for rewards. How dopamine release is regulated to achieve these distinct functions is not fully known. In a rat decision-making task we recently demonstrated that some NAc dopamine fluctuations reflect VTA firing, while others do not (Mohebi, Pettibone et al., *Nature* 2019). Consistent with prediction error coding, salient cues evoked transient spike bursts in optogenetically-identified VTA dopamine cells and a corresponding increase in NAc dopamine (measured with either fast-scan cyclic voltammetry or the optical sensor dLight1). However, NAc dopamine release also increased as rats approached rewards, without any increase in VTA dopamine cell spiking. We argued that this motivation-related aspect of NAc dopamine likely results from local control over release from dopamine terminals.
One potential mechanism of such local control involves cholinergic interneurons (CINs), which have previously been shown to be capable of evoking dopamine in brain slices. We have

therefore been examining whether NAc CINs contribute to motivation-related dopamine release in our behavioral task. We expressed the calcium indicator GCaMP6f in NAc ChAT+ neurons, and measured activity using fiber photometry (n=9 placements in 7 rats). We consistently observed that CIN activity rapidly ramps up during motivated approach, at the same time as dopamine increases. This supports the hypothesis that CINs drive motivation-related dopamine release independently from dopamine cell firing.

Disclosures: **A. Mohebi:** None. **A. Hamid:** None. **J.D. Berke:** None.

Poster

667. Basal Ganglia: Cellular and Systems Physiology

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Topic: E.03. Basal Ganglia

Support: NIH Grant R01 NS069777
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P50 NS047085

Title: Dorsolateral striatum regulates movement oppositely to dorsomedial striatum via complex striatopallidal subcircuitries

Authors: *Q. CUI[1], X. DU[1,2], V. LILASCHAROEN[3], A. PAMUKCU[1], D. GARCIA[1], B. BERCEAU[1], D. HONG[1], V. CHALASANI[1], B. LIM[3], S. CHAN[1];
[1]Physiol., Northwestern Univ., Chicago, IL; [2]Physiol., Qingdao Univ., Qingdao, China; [3]Biol. Sci., UCSD, La Jolla, CA

Abstract: The dorsal striatum can be subdivided into dorsomedial striatum (DMS) that regulates locomotion and initial motor learning and dorsolateral striatum (DLS) that modulates habitual behavior and gradual motor skill acquisition. It is established that activation of direct-pathway spiny projection neurons (dSPNs) and indirect-pathway spiny projection neurons (iSPNs) in the DMS promote and suppress movement, respectively. However, the roles of dSPNs and iSPNs in the DLS in relation to locomotion remain to be fully investigated. Despite the increasing evidence that suggest a dSPN projection to the external globus pallidus (GPe), the cellular target of this input has not been fully examined. To fill this knowledge gap, we utilized a combination of behavioral, electrophysiological, and anatomical techniques. We found that optogenetic activation of dSPNs and iSPNs in the DLS decreased and increased locomotion, respectively, directly opposite to the role of dSPNs and iSPNs in the DMS. By employing cell-specific retrograde labeling and *in situ* hybridization, we found that both the DMS and DLS organize with the GPe in a highly cell-specific manner. While dSPNs preferentially target Npas1+ GPe neurons, iSPNs preferentially innervate PV+ GPe neurons. Furthermore, functional studies using

ex vivo patch-clamp recordings with optogenetics confirmed this conclusion. In a chronic 6-OHDA lesioned mouse model of Parkinson's disease (PD), only the DLS dSPN-Npas1 input was strengthened. An increase in the number of synaptic contacts underlies this alteration. As Npas1+ GPe neurons preferentially inhibit iSPNs, we postulate that DLS dSPNs suppress locomotor behavior through disinhibition of DMS iSPNs activity, which mediate the "No-Go" pathway. The enhanced DLS dSPN-Npas1 input in 6-OHDA lesioned mice could be a mechanism that underlies the hypokinetic symptoms observed in PD patients.

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Poster

667. Basal Ganglia: Cellular and Systems Physiology

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Topic: E.03. Basal Ganglia

Support: CHDI, NIH R01MH101697
the University of California, San Francisco

Title: Proactive behavioral inhibition engages increase-type neurons in substantia nigra pars reticulata

Authors: *B.-M. GU, J. BERKE;
Dept. of Neurol., UCSF, San Francisco, CA

Abstract: The ability to inhibit actions is central to adaptive behavioral control. Behavioral inhibition can be "reactive" - e.g. aborting imminent actions in response to a Stop signal - or "proactive" - e.g. restraining actions in anticipation of a possible Stop signal. In an earlier series of rat Stop-signal electrophysiology studies we found that reactive inhibition involves a sequence of mechanisms within the basal ganglia. First, a very rapid "Pause" operates via the subthalamic nucleus, exciting the substantia nigra pars reticulata (SNr) to retard movement initiation (Schmidt et al. Nat Neuro 2013). Then, a slightly slower "Cancel" engages arkypallidal neurons of the globus pallidus (GP), inhibiting striatum to terminate movement preparation (Mallet et al. Neuron 2016). However, we did not address proactive inhibition, which has been hypothesized to involve the GP-SNr indirect pathway (Aron, Biol. Psych. 2011).
We modified our Stop-signal task to probe selective proactive inhibition in rats. Subjects were cued that a Stop signal either would not occur (0%), might occur after a Leftward instruction cue (50%-Left), or might occur after a Rightward instruction cue (50%-Right). Consistent with selective proactive inhibition, reaction times when no Stop signal occurred were slower, but only

for the direction for which a Stop signal was possible.
During this proactive task we recorded from the SNr (n=270 single-units from 35 sessions from 7 rats). The SNr has previously been shown to contain cells that decrease firing in association with movements, that promote movement onset by disinhibiting downstream structures, and also cells that increase with movements. We hypothesized that proactive inhibition would involve altered firing of decrease-type cells: either a higher initial firing rate (greater distance to "threshold") or a more gradual decrease in firing (slower movement towards threshold). Neither prediction proved correct. Instead, increase-type neurons showed higher firing rates when a Stop cue was anticipated. These results identify a new potential function for a poorly-understood basal ganglia cell class, and a new potential mechanism for behavioral control.

Disclosures: B. Gu: None. **J. Berke:** None.

Poster

667. Basal Ganglia: Cellular and Systems Physiology

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 667.23/L7

Topic: E.03. Basal Ganglia

Title: Dopamine neurons multiplex components of goal-directed actions

Authors: Y. KREMER, ***J. FLAKOWSKI**, C. ROHNER, C. LUSCHER;
Univ. of Geneva, Geneva, Switzerland

Abstract: Does dopamine (DA) neuronal activity within the ventral tegmental area (VTA) in response to external cues or rewards represent a learning signal in freely moving animals? To find it out, we introduced a spatial task where the mice can trigger a reward-predicting cue by going to a specific location within an operant box. Simultaneous *in vivo* single-unit recordings revealed that a fraction of DA neurons exhibited activity that reflected various components of the goal-directed action (e.g. distance from location to reward, velocity and licking) along with phasic responses to cue and reward. Neuronal activity discriminated between rewarded and unrewarded trials, generating an error signal even in the absence of external cues in expert animals. Following a reversal protocol, mice readily learned to move to a different location, which became impossible if we jammed the internal error signal by optogenetic manipulations. We conclude that a multiplexed internal representation of the task determines the overall activity of VTA DA neurons, engaging a learning process that leads to the behavioral adaptations of goal-directed actions.

Disclosures: Y. Kremer: None. **J. Flakowski:** None. **C. Rohner:** None. **C. Luscher:** None.

Poster

667. Basal Ganglia: Cellular and Systems Physiology

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 667.24/L8

Topic: E.03. Basal Ganglia

Title: Nucleus accumbens neuronal population dynamics during cocaine associated behaviors

Authors: *R. VAN ZESSEN[1], J. FLAKOWSKI[1], C. LUSCHER[1,2];
[1]Basic Neurosci., Univ. of Geneva, Geneva, Switzerland; [2]Dept. of Clin. Neurosciences, Geneva Univ. Hosp., Geneva, Switzerland

Abstract: Drugs of abuse initially increase Nucleus Accumbens (NAc) dopamine levels, leading to input-specific synaptic potentiation of afferents onto NAc spiny projection neurons (SPNs). However, how this affects activity dynamics of identified SPN subtypes remains elusive. The NAc mainly contains spiny projection neurons (SPNs) that are characterized by their expression of dopamine 1 receptors (D1R) or dopamine 2 receptors (D2R), and has been suggested to be involved in motivated behaviors. Here we use miniaturized endoscopic imaging techniques in mice to record calcium activity of D1R and D2R SPNs during cocaine exposure and cocaine-associated behaviors. D1R-cre and D2R-cre transgenic mice were injected with a cre-dependent GCaMP6f virus and a gradient-index lens was placed above the NAc. Calcium activity was then monitored in freely moving animals while they were repeatedly exposed to cocaine in an open field. Calcium and locomotion data were recorded and analysed. While both classes of neurons show divergent responses directly after cocaine exposure, we find that specific activity profiles become more prominent with repeated cocaine exposure and while animals are behaviorally sensitized to the effects of cocaine. Moreover we investigate how these activity profiles relate to self-paced movement-related activity, cocaine cue-related activity and spatial ensemble activity maps of identified NAc SPNs. Insights into the drug-related activity dynamics provides a foundation for understanding the circuit-level pathogenesis that leads to addiction.

Disclosures: R. Van Zessen: None. **J. Flakowski:** None. **C. Luscher:** None.

Poster

667. Basal Ganglia: Cellular and Systems Physiology

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Program #/Poster #: 667.25/L9

Topic: E.03. Basal Ganglia

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Title: Unique contributions of parvalbumin and cholinergic interneurons in organizing striatal networks during movement

Authors: H. GRITTON[1], W. M. HOWE[6], M. ROMANO[1], A. G. DIFELICEANTONIO[7], M. A. KRAMER[2], V. SALIGRAMA[3], M. BUCKLIN[4], D. ZEMEL[5], X. HAN[1];
[1]Biomed. Engin., [2]Dept. of Mathematics and Statistics, [3]Electrical Engin., Boston Univ., Boston, MA; [4]Biomed. Engin., Boston Univ., Chelsea, MA; [5]Boston Univ., Boston, MA; [6]Neurosci., Icahn Sch. of Med. at Mt Sinai, New York, NY; [7]Yale Univ. Sch. of Med., New Haven, CT

Abstract: The dorsal striatum is critical for the control of behavior. Interneurons make up a small fraction of striatal cells, but are poised to play a major role in coordinating striatal output and function. However, the sparse distribution and heterogeneity of interneurons has made it difficult to assess their contributions to striatal network dynamics and behavior. We combined wide-field single cell calcium imaging with optogenetics to test the capacity of parvalbumin and cholinergic interneurons to affect MSN activity and influence the behavior of mice engaged in voluntarily locomotion. We found evidence that both interneurons subtypes have unique contributions to striatal network activity and dissociable roles in supporting movement. Parvalbumin neuron activity is coincident with motor initiation and facilitates movement by refining the activation of MSN networks responsible for movement execution. Cholinergic neurons are recruited throughout movement and show peak activity moments before reductions in motor output. These findings reveal that interneurons have the capacity to regulate broader striatal networks to facilitate distinct components of voluntary movement.

Disclosures: H. Gritton: None. **W.M. Howe:** None. **M. Romano:** None. **A.G. DiFeliceantonio:** None. **M.A. Kramer:** None. **V. Saligrama:** None. **M. Bucklin:** None. **D. Zemel:** None. **X. Han:** None.

Poster

667. Basal Ganglia: Cellular and Systems Physiology

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 667.26/L10

Topic: E.03. Basal Ganglia

Support: Swedish Medical Research Council
Knut and Alice Wallenberg Foundation

Title: Classification, characterization and connectivity of Chrna2-expressing striatal interneurons

Authors: *A. TOKARSKA, G. SILBERBERG;
Neurosci., Karolinska Inst., Stockholm, Sweden

Abstract: The striatum is composed almost entirely of GABAergic neurons, most of which are projection neurons: the medium spiny neurons (MSNs), which are strongly modulated by a small yet heterogeneous population of GABAergic interneurons. In addition to the previously described fast-spiking interneurons (FS) and low-threshold spiking cells (LTS), recent studies emphasize the significance of newly observed cell-types such as 5Ht3a-, NPY-, TH- expressing interneurons.
In this study, we used a newly generated transgenic mouse line that labels striatal interneurons expressing the gene coding for the α2 nicotine receptor subunit (Chrna2). Using ex vivo whole-cell recordings combined with optogenetics, we obtained a detailed characterization of the electrophysiological, morphological and synaptic properties of Chrna2 cells. Hierarchical clustering based on electrophysiological properties revealed the existence of three distinct subtypes of Chrna2 cells with strikingly different morphologies, suggesting possible different network functions. Based on the expression of molecular markers, connectivity, and nicotine sensitivity, type I consists of FS-like cells, while type II and type III form new populations. Chrna2 interneurons receive glutamatergic cortical inputs from motor cortex, mediated by both AMPA and NMDA glutamate receptors. Paired recordings from different subtypes of Chrna2 interneurons revealed differences in the dynamics and strength of cortical inputs in the respective subtypes. Surprisingly, striatal Chrna2 interneurons do not resemble Chrna2 interneurons form hippocampus (CA1) or neocortex (Chrna2+ Martinotti cells) in terms of their intrinsic properties or molecular markers.

Disclosures: A. Tokarska: None. **G. Silberberg:** None.

Poster

667. Basal Ganglia: Cellular and Systems Physiology

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Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 667.27/L11

Topic: E.03. Basal Ganglia

Support: R01-DA034696
T32-DA007234

Title: Presence and relevance of GIRK channel activity in parvalbumin interneurons in the mouse nucleus accumbens

Authors: *T. ROSE, E. MARRON, K. D. WICKMAN;
Pharmacol., Univ. of Minnesota, Minneapolis, MN

Abstract: The nucleus accumbens (NAc) integrates motivation with motor action, and its dysregulation has been linked to neuropsychiatric disorders. The NAc harbors diverse microcircuits that fine-tune output from medium spiny neurons (MSNs) to regulate behaviors related to reward and reinforcement. Despite comprising only 1-2% of NAc neurons, fast-spiking interneurons (FSIs) - often defined by parvalbumin (PV) expression - exert a powerful inhibitory influence over MSN output. FSI manipulations alter behavioral responding to drugs of abuse, and exposure to addictive drugs can alter FSI excitability. While NAc FSIs receive multiple excitatory inputs that influence addiction-related behaviors, less is known about the role of inhibitory inputs and relevant postsynaptic signaling pathways in these neurons. The goal of this exploratory study was to probe the presence and relevance of a common inhibitory G protein-dependent signaling mediator in NAc PV neurons. G protein-gated inwardly rectifying potassium/K+ (GIRK) channels mediate G protein-dependent postsynaptic inhibition throughout the nervous system, but are expressed at or below the level of detection in the NAc. Indeed, GIRK channel activity is not seen in the vast majority of NAc MSNs. Here, we show that the GABAB receptor agonist baclofen (200 mM) evokes a reliable inhibitory current (Vhold = -60 mV) in NAc PV neurons in slices from PV-tdTomato mice. The baclofen-induced current was accompanied by a decrease in input resistance and was blocked by 0.3 mM Ba2+, consistent with a GIRK-mediated response. Furthermore, ablation of the GIRK2 subunit using a viral CRISPR/Cas9 approach in PVCre(+):Cas9GFP(+) mice eliminated the baclofen-induced current in NAc PV neurons. To probe the relevance of GIRK-dependent signaling in NAc PV neurons to reward-related behavior, we are evaluating cocaine-induced locomotor activity in the CRISPR/Cas9 loss-of-function model, as well as a gain-of-function model involving the viral-mediated, Cre-dependent overexpression of GIRK2 in PVCre(+) mice. Male and female mice are being used in this study, with subjects aged 7 wk at the time of viral infusion surgery and 11-12 wk at the time of electrophysiological or behavioral analysis. Our preliminary data shows that strengthening of GIRK channel activity in NAc PV neurons enhances, while suppression of GIRK channel activity attenuates, the acute motor-stimulatory effect of cocaine. Thus, GIRK-dependent signaling in NAc PV neurons may contribute to behavioral sensitivity to cocaine in mice, and could be a promising target for therapeutic intervention in addiction.

Disclosures: T. Rose: None. **E. Marron:** None. **K.D. Wickman:** None.

Poster

667. Basal Ganglia: Cellular and Systems Physiology

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 667.28/L12

Topic: E.03. Basal Ganglia

Support: NS003134

Title: Dendrite specific inhibition facilitates rebound firing in SNc dopamine neurons

Authors: *R. C. EVANS[1], E. TWEDELL[1], Z. M. KHALIQ[2];
[1]NIH, Bethesda, MD; [2]NIH/NINDS, Bethesda, MD

Abstract: Dopamine neurons in the substantia nigra pars compacta (SNc) are often inhibited by aversive events. A subset of these neurons fire rebound bursts of action potentials or show rebound calcium activity following the aversive pause in activity. The functional circuit underlying both the aversive inhibition and the rebound bursting are currently unknown. Retrograde viral tracing studies have been used to generate a comprehensive list of inputs to dopaminergic neurons, revealing diverse inhibitory inputs from nearly all nuclei in the basal ganglia. However, the functional strength, specific receptors activated, and dendritic location of each input have not yet been tested. Here we use two-photon imaging and local optogenetic activation to functionally map the inhibitory inputs from basal ganglia nuclei onto dopamine neuron dendrites. We compare the strength and location of five (5) separate genetically-defined inhibitory subpopulations in the striatum (striosome and matrix), globus pallidus (Pvalb and Lhx6), and substantia nigra pars reticulata (SNr). We find that the striosomal inputs selectively inhibit the ventrally-projecting “SNr dendrite” of the dopamine neurons. Although isolated to the SNr dendrite, this connection exerts strong control over the entire cell, pausing action potentials and facilitating rebound firing. By contrast, activation of the Lhx6-positive inputs from the globus pallidus leads to inhibition of dopamine neurons at the soma and proximal dendrites, but does not result in rebound spiking. We find that striosomal input facilitates rebound firing because it activates GABA-B receptors, which strongly hyperpolarize the SNr dendrite. Because the globus pallidus inputs selectively activate GABA-A receptors, they pause firing through shunting inhibtion without recruiting rebound mechanisms (such as T-type calcium channels and the Ih current). Finally, we use a computational model in Genesis simulation software to show that dendrite-specific inhibition more effectively generates rebound action potentials than either somatic inhibition or broad inhibition of the entire dendritic arbor. Therefore, inhibition from striosomes onto SNc dopamine neurons is optimally placed to produce rebound firing.

Disclosures: R.C. Evans: None. **E. Twedell:** None. **Z.M. Khaliq:** None.

Poster

667. Basal Ganglia: Cellular and Systems Physiology

Location: Hall A

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Program #/Poster #: 667.29/L13

Topic: E.03. Basal Ganglia

Support: NIH/CCB Fellowship
NIH/NINDS IRP Funding

Title: Direct axonal recordings identify a role of GABA-A receptors on subthreshold and suprathreshold control of axonal action potentials and dopamine release

Authors: *P. F. KRAMER, E. L. TWEDELL, Z. M. KHALIQ;
NIH/NINDS, Bethesda, MD

Abstract: Decades of electrophysiological research have examined the circuit and cellular-level mechanisms that control striatal dopamine release using methods like voltammetry and microdialysis. However, the indirect nature of these methods leaves open questions about the presence of axonal receptors and their influence over axonal excitability and ultimately dopamine release. Specifically, GABA-A receptors modulate transmitter release in some neurons, including potentially dopamine neurons, but the mechanisms of this modulation are varied and debated.To address this knowledge gap, we performed direct recordings from the cut ends of dopaminergic neuron axons, including from branching axons within the dorsal striatum. Our results provide definitive evidence for the existence of GABA-A receptor-mediated conductances. First, in contrast to their function at the soma, we found axonal GABA-A receptors were depolarizing. Perforated patch experiments showed that the chloride reversal potential was always depolarized (~-56 mV) relative to rest (~-68 mV). Second, activation of GABA-A receptors decreased the amplitude of a propagating action potential through shunting inhibition. In the dorsal striatum, calcium imaging experiments suggest that this shunting effect increases the probability of propagation failures. Third, we were surprised to see that electrical stimulation in the striatum resulted in a depolarizing, GABA-A mediated, post-synaptic potential (EPSP) in the axon. Finally, we found that diazepam, a broad-spectrum benzodiazepine, decreased the input resistance of striatal dopamine neuron axons, suggesting an underappreciated mechanism of action for these drugs.In conclusion, direct recordings from dopamine neuron axons demonstrate that GABA-A receptors are important modulators of axonal action potential propagation and dopamine release. In addition, these receptors are targets of benzodiazepines, as well as potentially other drugs that target GABA-A receptors like ethanol and barbiturates.

Disclosures: P.F. Kramer: None. **E.L. Twedell:** None. **Z.M. Khaliq:** None.

Poster

667. Basal Ganglia: Cellular and Systems Physiology

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Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 667.30/L14

Topic: E.03. Basal Ganglia

Support: NIH Grant P50-NS098685; The content is solely the responsibility of the authors and does not necessarily represents the official views of the National Institutes of Health.

Title: Reversal potential of GABA-A synapses in neurons of basal ganglia receiving motor thalamus

Authors: *E. K. BICHLER, D. JAEGER;
Dept. Biol., Emory Univ., Atlanta, GA

Abstract: GABA-A receptors are chloride channels and therefore can have different reversal potentials in neurons with different internal chloride concentration due to differential function of chloride transporters. An interesting question is posed by the similarity of firing rates across cerebellar input and basal ganglia input receiving motor thalamus (CBMT and BGMT) in vivo, despite CBMT receiving excitatory cerebellar and BGMT receiving inhibitory basal ganglia input. One potential explanation of this difference could be regulation of the chloride reversal potential (E_{Cl}) to more positive values in BGMT, thus weakening the inhibitory effect of GABAergic input. For example, E_{Cl} was found to be -45 mV in thalamic reticular nucleus, which is more depolarized than -80 mV found in sensory thalamic nuclei. However, the chloride equilibrium potential has not been measured in BGMT neurons to date.
We used whole-cell gramicidin perforated patch-clamp recordings from BGMT neurons in adult mice to address this question. In one set of experiments, AAV-Syn-EF1a-DIO-hchR2-EYFP vector was injected into SNr in slc32 GAD-Cre mice. 14-18 weeks later, GABA-A-mediated IPSCs were evoked in BGMT neurons by 2ms light flashes using a 480 nm filter on an 120W X-Cite light source. In an additional data set GABA (100 μM) was directly puffed onto the cell bodies of neurons in the same anatomical location in motor thalamus via a glass pipette.
In order to isolate GABA-A signaling, excitatory synaptic transmission was blocked with DNQX and D-AP5, and GABA-B IPSCs were blocked with CGP 55845. GABA-A-induced membrane current was recorded at different holding potentials. A peak-current voltage relationship was plotted, and the x-intercept of the linear fit was taken as GABA-A reversal potential.
In our preliminary data set we find that the average chloride reversal potential was -71 mV (N=8) which would indicate a ~10 mV depolarizing shift compared to sensory thalamus.
We will further investigate if chloride equilibrium potential is yet more depolarized in 6-

hydroxydopamine- lesioned mice as a potential homeostatic adaptation due to increased nigral inhibitory input as posited by classic Parkinson's disease models.

Disclosures: E.K. Bichler: None. **D. Jaeger:** None.

Poster

668. Sensorimotor Learning II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 668.01/L15

Topic: E.04. Voluntary Movements

Title: Top-down attentional modulation of steady-state somatosensory evoked potentials characterizing individual optimal attentional strategy for motor learning

Authors: *T. SAKURADA[1,2], K. NAGAI[1];
[1]Ritsumeikan Univ., Shiga, Japan; [2]Jichi Med. Univ., Tochigi, Japan

Abstract: Focus of attention is an influential factor for improving motor performance. Previous studies have found that directing attention to movement outcome (external focus; EF) results in greater improvement in motor performance than directing attention to body movement (internal focus; IF). On the other hand, we recently have found that the EF did not always lead to a better motor performance compared to the IF in both healthy and stroke populations. In a neuroimaging study, although we reported that the frontoparietal network is one of the neural bases of the individual optimal attentional strategy, it remains unclear whether sensory cortexes also associated with the individual differences. In this study, we aimed to explore the involvement of the early sensory cortexes for the individual optimal attentional strategy by recording steady-state somatosensory/visual evoked potentials (SSSEP/SSVEP). Firstly, twenty-five participants performed a visuomotor learning task with reaching movement under the IF and EF conditions. Fourteen participants showed higher motor learning effect in the EF condition (EF-dominant), whereas the others showed the opposite trend (IF-dominant). Subsequently, we recorded the SSSEP from the somatosensory cortex during presenting vibration stimuli on the fingertips (22 Hz and 25 Hz) and the SSVEP from the visual cortex during presenting flickering visual stimuli (12 Hz and 15 Hz). When the IF-dominant individuals actively directed their attention to vibration stimuli the amplitude of SSSEP markedly got stronger. On the other hand, the top-down attentional modulation of SSSEP amplitude was not observed in the EF-dominant individuals. Regarding the SSVEP amplitude, there was no difference in attentional modulation between IF- and EF-individuals. These results suggest that somatosensory cortex relates to the individual optimal attentional strategy. Furthermore, the top-down modulation of the SSSEP amplitude depending on the dominance of attentional strategy implies that the cognitive ability of attention control rather than response characteristic of sensory processing to focused stimuli characterize the individual attentional optimality.

Disclosures: **T. Sakurada:** None. **K. Nagai:** None.

Poster

668. Sensorimotor Learning II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 668.02/L16

Topic: E.04. Voluntary Movements

Support: NSERC Canada (RGPIN-2014-04361)

Title: Visuomotor adaptation and retention during balance-challenged reaching and walking tasks

Authors: ***A. BAKKUM**, J. M. DONELAN, D. S. MARIGOLD;
Simon Fraser Univ., Burnaby, BC, Canada

Abstract: The ability to adapt to our surroundings and retain what is learned is essential for performing many daily activities. Studies on reaching adaptation demonstrate that learning two opposing mappings shortly after one another interferes with consolidation of the motor memory. However, most of these studies focus on isolated upper-limb movements while the participant is in a seated position and balance is not a major concern. Yet, balance challenges are inherent to everyday reaching and walking, where the ability to complete these tasks depends critically on the control of the whole body. Interestingly, learning during walking appears less susceptible to interference. Could the balance challenges encountered during more complex, whole-body movements, provide an explanation for the differences observed in motor learning? In this study, we test the hypothesis that challenging balance during standing-based reaching and walking tasks (i.e., whole-body movements) leads to better learning, reflected by greater retention. Four groups (n=12 each) adapted to a new visuomotor mapping induced by prism lenses while performing either a precision reaching or walking task, with or without a balance manipulation. In balance-challenged groups, participants performed the task with inflatable rubber hemispheres (radii: 8.5cm) attached to the soles of their shoes to reduce the control afforded by shifting the center of pressure under the base of support. This manipulation challenged balance, reflected by increased effort (muscle activity: reaching, p=2.22e-6; walking, p=0.003), instability (trunk acceleration variability: reaching, p=0.0007; walking, p=4.81e-6), and motor variability (end-point error variability: reaching, p=0.008; walking, p=9.31e-6). Across all groups, the balance-challenged walking group demonstrated the greatest effort, instability, and motor variability. All groups adapted to the new mapping with similar adaptation rates. To assess retention, participants repeated the adaptation protocol one week later. Neither reaching group showed significant retention of the mapping. However, both walking groups showed retention (balance-unchallenged, p=4.51e-5; balance-challenged, p=0.001). Additionally, the walking balance-

challenged group showed greater retention (Retention Index, p=0.025). Overall, our results support the idea that challenging walking balance enhances visuomotor retention.

Disclosures: A. Bakkum: None. **J.M. Donelan:** None. **D.S. Marigold:** None.

Poster

668. Sensorimotor Learning II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 668.03/L17

Topic: E.04. Voluntary Movements

Support: NWO TTW OTP 15989

Title: Does factorization facilitate reward-based motor learning?

Authors: *K. VAN DER KOOIJ[1], N. M. VAN MASTRIGT[2], J. B. SMEETS[3];
[1]Vrije Univ. Amsterdam, The Netherlands, Amsterdam, Netherlands; [2]Human Movement Sci., Vrije Univ., Amsterdam, Netherlands; [3]Human Movement Sci., Vrije Univ. Amsterdam, Amsterdam, Netherlands

Abstract: In reward-based motor learning, errors can be reduced by varying the motor output and repeating successes. When multiple factors may underlie success (reward), it is unknown how we link success to these factors. Here, we ask whether a single factor is learned more rapidly when the total number of factors is restricted and further test whether learning of two factors is facilitated by practicing the them sequentially. Participants performed a novel 3D drawing task in which they viewed a virtual slanted line and were asked to copy this line with movement of a controller. Performance feedback was limited to binary reward (success) information. Two factors could contribute to reward: vertical slant and length of the drawn line. We based the feedback either on a single factor or on the combination of the two factors. A ‘slant first’ group first received feedback on slant, then on length and finished with combined feedback, a ‘length first’ group first received feedback on length, then on slant and finished with combined feedback, and a ‘combined’ group received feedback on the combined error in all learning blocks. Results show that learning of a single factor (slant or length) was not facilitated by restricting the total number of factors. Consistently, learning of the two factors was not facilitated by practicing them sequentially. This suggests that the nervous system can explore and exploit two parameters in parallel.

Disclosures: K. Van Der Kooij: None. **N.M. van Mastrigt:** None. **J.B. Smeets:** None.

Poster

668. Sensorimotor Learning II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 668.04/L18

Topic: E.04. Voluntary Movements

Title: Strategic compensation in mirror-reversal adaptation tasks

Authors: *S. A. WILTERSON, J. A. TAYLOR;
Psychology, Princeton Univ., Princeton, NJ

Abstract: Re-aiming strategies appear to dominate learning for visuomotor adaptation tasks (Taylor et al., 2014) and we have recently observed that strategies can take on different forms depending on task conditions (McDougle and Taylor 2019). When there are only a few training targets (low set size) participants preferentially employ a discrete or rule-based strategy. This type of strategy may involve holding a stimulus-response pairing in working memory. However, when there are many training targets (high set size), participants employ a parametric or algorithmic strategy such as performing a mental rotation. We recently found that strategies also account for the lion's share of learning in a mirror-reversal task, but that the particular form of strategy employed by participants is unclear. Participants may preferentially use a discrete strategy, such as flipping across the y-axis, or a parametric strategy, such as mentally rotating or scanning from the target to the solution. It is also possible that participants must combine both strategies, such as flipping and rotating sequentially. Our first experiment systematically varied both horizontal distance and angular perturbation size to expose constraints on strategy use in the mirror-reversal task. Surprisingly, reaction time was constant across all imposed perturbations. This suggests that participants are employing a discrete strategy to solve the mirror reversal. We further investigated this possibility with a 2 (set-size: 2 vs 12 targets) x 2 (perturbation-type: rotation vs mirror) design. Under visuomotor rotation, we replicated the set-size findings of McDougle and Taylor, 2019, demonstrating a discrete strategy with low set-sizes and a parametric strategy with high set-sizes. Reaction times were significantly faster under mirror reversal than under either visuomotor rotation condition. Additionally, there was only a slight difference in mirror reversal reaction times under different set sizes, echoing Hick's Law as opposed to a difference in strategy. These findings suggest that strategy use in mirror-reversal tasks is closer to a discrete strategy which holds stimulus-response pairings in working memory. We conclude that strategies appear to dominate learning in both visuomotor rotation and mirror-reversal tasks, and that the form of the strategy differs depending on the particular task demands with important implications for how motor learning proceeds.

Disclosures: S.A. Wilterson: None. **J.A. Taylor:** None.

Poster

668. Sensorimotor Learning II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 668.05/L19

Topic: E.04. Voluntary Movements

Title: Lateralization in motor learning of a *de novo* shuffleboard task

Authors: *J. YUK[1], J. B. DINGWELL[1], J. P. CUSUMANO[2], R. L. SAINBURG[1]; [1]Kinesiology, Pennsylvania State Univ., University Park, PA; [2]Dept. of Engin. Sci. & Mechanics, Penn State Univ., University Park, PA

Abstract: We have previously proposed a hypothesis of motor lateralization that attributes predictive control of limb trajectory to the dominant hemisphere and control of limb impedance to the non-dominant hemisphere. This model is supported by studies demonstrating sensorimotor adaptation during visuomotor rotations in patients with focal cortical lesions. However, it is not known whether specialization of the dominant system will also be reflected in learning of a de novo task. We now ask whether lateralization of motor learning will occur during learning of a task that requires predictive control of hand trajectory. In our de novo task, participants hit a virtual puck from a central location toward a 180° arc located 35 cm from the initial puck position. Participants were free to start each trial anywhere behind a horizontal line located 10 cm posterior to the puck. Hand velocity was transferred to the puck at impact depending on the location of impact, and the magnitude and direction of the hand velocity vector. Thus, accurate performance required coordinated control of hand velocity and impact location. Six right-handed young adults performed the task with both arms: 3 with their dominant arm first and 3 with their non-dominant arm first. Both arms showed similar adaptation early (fast) learning phase. However, over the slow, asymptotic phase of learning, the dominant arm continued to improve performance, while the non-dominant arm did not. Interestingly, variance in hand start positions was higher for the dominant arm earlier in learning. We propose the dominant hemisphere-limb system developed a model of control through exploration of state space early in learning that was more extensive than that learned by the non-dominant hemisphere. As a result, the dominant arm showed a greater reduction in error throughout the slow phase of learning. We suggest this asymmetry in learning a de novo task reflects dominant hemisphere specialization for predictive control of trajectory.

Disclosures: J. Yuk: None. **J.B. Dingwell:** None. **J.P. Cusumano:** None. **R.L. Sainburg:** None.

Poster

668. Sensorimotor Learning II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 668.06/L20

Topic: E.04. Voluntary Movements

Support: JSPS KAKENHI JP16H06566

Title: Learning and retrieving motor memories depending on gaze-reach coordination

Authors: *N. ABEKAWA, H. GOMI;
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Abstract: We can learn and execute multiple motor skills that are engaged in different behavioral contexts. To facilitate learning, each context should have linkage with different internal states that are inherently represented in sensorimotor processing (e.g. Howard et al., 2013). Meanwhile, it is known that the brain computes the spatial coordination between gaze and reaching target in motor planning (Buneo et al. 2002). Additionally, an fMRI study (Prado et al., 2005) showed neural activities in different cortical area for hand-reaching to foveal and peripheral targets. These reports can raise an advanced hypothesis that leaning of multiple motor skills is facilitated when each memory is linked with different gaze-reach coordination. We tested this hypothesis using learning paradigm including visuomotor rotation (Exp.1), force-field perturbation (Exp.2), and learning generalization (Exp.3). In Exps. 1 and 2, participants reached a target while looking at the target (Foveal reach: FOV) or at elsewhere (Peripheral reach: PER). We applied visuomotor rotations (Exp.1) or velocity-dependent forces (Exp.2). The direction of perturbation (CW or CCW) varied randomly across trials, but was individually coupled with FOV or PER. In both Exps., we found decrease in reaching error with training, and clear aftereffects for both FOV and PER. The results suggest that the brain can form and retrieve distinct internal models of kinematic and dynamic control that are linked to the different gaze-reach coordination. In Exp.3, we examined generalization of learning in visuomotor rotation across different gaze-reach coordination. We found that after participants completed learning in PER, adaptation gain was maintained in reaching to the target in the same visual field as in learning trials, whereas it was partially generalized for reaching to foveal target and opposite visual field. Unlike learning in PER, generalization pattern of learning in FOV highly depended on reaching directions. For reaching along sagittal axis, learning was fully generalized to every gaze location we tested, but for reaching in oblique axis, learning gain decreased as the gaze location separated from adapted one. Our findings indicate that different gaze-reach coordination forms partially separated representation in motor learning even if the location of reaching target is same across conditions. Several generalization patterns also suggest different learning mechanisms depending on gaze-reach coordination and reaching directions. Taken together, our

data give a new insight into the sensorimotor representation of gaze-reach coordination, which essentially contribute to motor learning.

Disclosures: **N. Abekawa:** None. **H. Gomi:** None.

Poster

668. Sensorimotor Learning II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 668.07/L21

Topic: E.04. Voluntary Movements

Title: Learning and generalization of complex visuomotor priors are context specific

Authors: *C. L. HEWITSON, M. J. CROSSLEY, D. M. KAPLAN;
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Abstract: Visuomotor adaptation tasks perturb the relationship between motor commands and their visual consequences. Humans can reliably learn to compensate for this type of perturbation by implicitly re-tuning their motor system. However, there is an apparent paradox in the literature regarding when the sign of the perturbation is randomly changed from trial to trial (e.g., leftward shift vs rightward shift). According to a simple state-space model, which is consistent with a large body of empirical data, this paradigm should prevent any appreciable re-tuning of the motor system since adaptation to leftward perturbations will be cancelled by adaptation to rightward perturbations on average. However, some work suggests that, at least in versions of this paradigm, humans can adapt to complex probability distributions of visuomotor perturbations including bimodal distributions with oppositely signed peaks (Körding and Wolpert, 2004). Although there is an apparent tension between these two results, drawing strong conclusions of any type is currently limited by the paucity of data bearing on this issue. To begin to address this, we investigated adaptation to a bimodal visuomotor prior with oppositely signed peaks and then tested generalization of this learning to novel reach directions. Our preliminary results indicate that initial learning does in fact occur and that this learning generalizes as two distinct unimodal distributions, selected according to movement context. Specifically, the positively signed component of the imposed bimodal distribution generalizes to rightward target directions, while the negatively signed component generalizes to leftward target directions. These findings raise important questions for conventional and Bayesian models of sensorimotor learning. They also suggest that the brain might employ distinct processes for visuomotor learning when operating in probabilistic versus non-probabilistic regimes.

Disclosures: **C.L. Hewitson:** None. **M.J. Crossley:** A. Employment/Salary (full or part-time):; Senior Lecturer, Macquarie University. **D.M. Kaplan:** A. Employment/Salary (full or part-time):; Deputy Head, Department of Cognitive Science, Macquarie University.

Poster

668. Sensorimotor Learning II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 668.08/L22

Topic: E.04. Voluntary Movements

Support: R01NS078311
R01NS095706
1DP2NS083037
R01NS100066
1U19NS104649
F32NS092350
National Science Foundation (1723967)

Title: Holding the arm still through integration of cortical commands

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Abstract: “Posture [accompanies] movement like a shadow.” - Sir Charles Sherrington. In other words, every movement ends in a period of stillness. When we make a reaching movement, it is thought that a cortical system produces motor commands that move our arm towards a desired goal. Curiously, when the motor cortex is transiently inhibited mid-movement, the arm maintains its current position, rather than falling to the side under the weight of gravity (Guo et al., eLife, 2015). How does the brain maintain the position of the arm despite inactivity in the motor cortex?Current models of reaching assume that to maintain a posture, the cortex translates the sensory location of a target into a set of motor commands that hold the arm in place. Here we consider a different possibility; perhaps the motor commands that hold the arm still are produced by a different, potentially subcortical, system whose output depends on the sequence of motor commands that the cortex produced in order to move the arm. Notably, the oculomotor system is designed in this way; the gaze-holding system uses distinct “move” and “hold” controllers that are serially linked. The hold circuitry resides in brainstem structures that mathematically integrate the commands that moved the eyes. Might the brain use a similar process of neural integration in the control of reaching?To test this hypothesis, we performed point-to-point reaching experiments in humans (n=246) and non-human primates (n=2). We found a clear relationship between the motor commands that held the arm, and those that moved the arm: irrespective of reach direction, reach duration, and reach endpoint, holding motor commands

were proportional to the time-integral of the reaching motor commands that preceded them. This relationship was causal; when we imposed changes on the reach commands with force field perturbations, what followed were precise alterations in the hold commands. Finally, we found that following damage to the corticospinal tract, the reach commands were severely impaired, but the holding system continued to faithfully integrate the now imperfect reach commands.Together, these findings suggest that the eye and the arm may share a common design principle of control: moving and holding use different neural circuits, but are causally linked to one another through a neural integrator. In this way, the way we hold still does not directly depend on the location of the target, but rather the integral of the commands that moved our body towards that target.

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Poster

668. Sensorimotor Learning II

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Program #/Poster #: 668.09/L23

Topic: E.04. Voluntary Movements

Support: Argentinian Ministry of Defense PIDDEF
Argentinian Agency for the Promotion of Science and Technology FONCyT
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NIH NS-095706

Title: Anterograde interference develops from a transient reduction in error sensitivity

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Abstract: When we experience an error during a movement, we adapt our future movements to improve our accuracy. The strength and duration of these motor adaptations provide insight into the mechanisms underlying memory formation in the brain. A memory is thought to be consolidated when it is no longer susceptible to interference from new information. Here we

aimed to track the time course of motor memory formation using anterograde interference as a marker for stabilization.Anterograde interference refers to an impairment in learning in Environment B after prior exposure to Environment A, where A and B are dissimilar perturbations. When A and B are experienced in close succession, consolidation of the A memory occludes the ability of the nervous system to adapt to the B perturbation. The dissipation of anterograde interference may signal the progress of consolidation.In order to monitor the duration of anterograde interference, we varied the time interval elapsed between adaptation to opposing rotations from 5 min through 24 hr (n=93 total participants). We fit a state-space model of error-based learning to differentiate between potential sources of interference: a lingering bias of performance towards the original A perturbation, an increase in the rate of memory decay, or a decrease in the sensitivity to error.We found that prior learning affected two specific parameters of our learning model: the initial bias of learning towards the memory of A, and the sensitivity to error in the B period. The initial bias in learning was strong, and persisted even if perturbations were separated by 24 hours. On the other hand, error sensitivity was reduced at 5 min and 1 hr but returned to control levels by 6 hours. Our findings suggest that anterograde interference is caused by a transient reduction in the sensitivity to error that recovers within a relatively short time window. Our work provides insight into the timeline of memory stabilization.

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Poster

668. Sensorimotor Learning II

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Topic: E.04. Voluntary Movements

Support: NIH Grant R00 HD073240.

Title: Exposing chronic, severe/moderate stroke survivors to startle during reach training improves voluntary reaching distance, final position error, and muscle activity

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Abstract: StartReact (SR), startle-evoked-movement, has recently been posed as a potential therapeutic target for individuals with stroke. SR elicited reaching and hand movements in individuals with stroke show improvements compared to voluntary in terms of muscle activity onset, amplitude, and coordination patterns (Honeycutt & Perreault, 2012; Honeycutt, Tresch & Perreault, 2015). Still, SR evokes functionally inappropriate flexion movements that increases with impairment (Honeycutt & Perreault, 2014). Furthermore, Choundhury et al., 2019 suggest

that SR may increase spasticity because stimulation of the reticulospinal tract.
Still, none of these concerns have been evaluated directly because to-date no laboratory has evaluated the impact of SR on voluntary reaching movements in individuals with stroke. The objective of this study was to evaluate the impact of a single session of SR on voluntary reaching in individuals with severe/moderate stroke. Optimistically, we hypothesized that a single session of training with SR would improve the voluntary movements in terms of final accuracy, total displacement, and max muscle activity.
Eleven individuals with severe/moderate impairment (UEFM: 8-41/66; Modified Ashworth: 0-4/4) resulting from a stroke participated. Subjects reached to 3 targets. A loud, startling stimulus was applied during 33% of trials. The first 10 voluntary (no startle) and the last 10 voluntary trials were compared. We found that voluntary reaching displacement, final accuracy, onset latency, and max muscle activity were all improved. Specifically, an increase in reaching displacement ($\Delta = 1.18$ cm, all: $P < 0.0003$) and decrease in final error ($\Delta = 0.83$ cm, all: $P < 0.013$). Faster muscle onsets in all muscles (average $\Delta = 77$ ms, all: $P < 0.017$) and larger max muscle activity in 73% of muscles (average $\Delta = 0.11$ mV, all: $P < 0.05$) was found.
In conclusion, a single session of reach training with SR enhanced voluntary movement in individuals with severe/moderate stroke. Moreover, the size of the improvement is notable. A recent review of task-specific training, shows a maximum of 11.1 % improvement in reaching distances, (Rensink, Schuurmans, Lindeman, & Hafsteinsdóttir, 2009) while we found a 15.8+/-4.5 %. While this study supports the further evaluation of SR as a therapeutic target, future studies should more carefully evaluate spasticity specifically as well as perform appropriate controls to ensure all effects are attributable to SR.

Disclosures: **M. Rahimi:** None. **C.F. Honeycutt:** None.

Poster

668. Sensorimotor Learning II

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Topic: E.04. Voluntary Movements

Support: Veterans Health Administration, Rehabilitation Research and Development Service - Award number 1I01RX001640-01A1
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National Institute of Health, Medical Scientist Training Program - Award number T32 GM007618

Title: Delineating the neural basis of flexible versus rigid skills

Authors: *S. KONDAPAVULUR, S. M. LEMKE, K. GANGULY;
Univ. of California, San Francisco, San Francisco, CA

Abstract: The rodent reach-to-grasp task of retrieving single pellets is often used to assess skilled upper limb movements. With motor skill acquisition and consolidation, execution becomes smooth, fast, and stereotyped - this is known to be paralleled by increased coordinated neural activity between primary motor cortex (M1) and dorsolateral striatum (DLS). We were interested in testing whether the motor skill typically achieved in this task is "flexible", i.e. can adapt to changes in task parameters, or is "rigid", i.e. a habitual action that may have to be unlearned in order to adapt to changes.
We specifically trained rats to reach to one location (Position A), until a fast, consistent, and accurate skill level was achieved. We then switched the pellet location to Position B, and observed whether the rats reached toward Position A (i.e. rigid skill state) or more toward Position B (i.e. flexible skill state). We then continued this training towards Position B over multiple days. We also recorded neural activity (both single unit activity and local field potential) from M1 and DLS over this period. Additionally, we inactivated DLS during the initial transition from Position A to Position B to assess if DLS may play a causal role in transitioning between positions.
We found that training rats to reach to a single location promoted rigid skill learning. When the pellet was initially switched to Position B, the rats primarily reached to Position A during the first session; with subsequent training to Position B, we observed more correct reaches to this location. Interestingly, M1 and DLS activity evolved during the transition from a rigid to flexible skill state. M1-DLS coordination was high during the rigid skill baseline of reaching towards Position A; however, this coordination was not present in the initial switch reach session with attempts towards Position B. With further training to Position B, M1-DLS coordination re-emerged. These results suggest that M1-DLS coordination reflects stereotypy of a learned movement and may reflect a rigid skilled state. Future work will determine how M1-DLS coordination can support multiple consolidated skilled states.

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Poster

668. Sensorimotor Learning II

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Topic: E.04. Voluntary Movements

Support: Australian Endeavour Research Fellowship awarded to HRM
CIHR Grant awarded to PLG

Title: Greater neural responses to others' errors is associated with motor learning by observing

Authors: *H. R. MCGREGOR[1], E.-M. REUTER[2], P. L. GRIBBLE[3], T. J. CARROLL[4];
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Abstract: While many of our motor skills are acquired through physical practice, we can also learn how to make movements by observing others. For example, individuals can learn how to reach in novel dynamic environments ('force fields', FF) by observing the movements of a tutor. Behavioural research suggests that observing a tutor's kinematic errors drives motor learning by observing. Here we used electroencephalograpy (EEG) to investigate if subjects' neural responses to observed errors relate to their observation-related gains in motor performance. Healthy subjects (n=40) held the handle of a vBot robotic manipulandum, and were instructed to perform straight reaching movements to visual targets in the horizontal plane. In a baseline condition, all subjects performed reaches in a 'null field' in which the robot did not apply forces to the hand. We then recorded EEG activity while subjects observed either a learning video (n=20) or a control video (n=20). The learning video showed a tutor adapting his reaches to a counterclockwise velocity-dependent force field (CCW FF). The control video showed a tutor performing reaches in an unlearnable FF environment in which the direction of the FF varied randomly from trial to trial. Subjects then performed reaches in a CCW FF as a behavioural assessment of learning achieved from observation. We found that subjects who had observed the learning video exhibited superior performance when they subsequently performed reaches in the CCW FF compared to subjects who did not observe learning in the control video. We used EEG data collected during observation to estimate subjects' neural responses to errors committed by the tutor. We extracted event-related potentials time-locked to the tutor's peak kinematic error on a trial by trial basis, and assessed the error-related negativity (ERN) component. For both groups, the amplitude of the ERN scaled with the magnitude of errors observed in the video. However, for the learning video group only, those subjects who exhibited greater neural responses when observing small errors were those who learned more from observation. This suggests that greater sensitivity to small errors committed by the tutor during learning was associated with increased observation-related gains in motor performance.

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Poster

668. Sensorimotor Learning II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 668.13/L27

Topic: E.04. Voluntary Movements

Support: CIHR
NSERC
Western Brainscan
CNPQ

Title: Generalizing movement patterns following shoulder fixation

Authors: *R. S. MAEDA[1], J. ZDYBAL[2], P. L. GRIBBLE[4], A. PRUSZYNSKI[3];
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Abstract: A common goal of motor learning is generalizing newly learned movement patterns beyond the training context. Here we tested whether learning a new physical property of the arm during self-initiated reaching generalizes to new arm configurations. Seventy human participants (38 females) performed a single-joint elbow reaching task and/or countered mechanical perturbations that created pure elbow motion using a robotic exoskeleton (KINARM, BKIN Tech). This robot permits shoulder and elbow rotation in the horizontal plane. Participants first performed single-joint elbow reaching with the shoulder joint either free to rotate or locked by the robotic manipulandum. With the shoulder free, we found activation of shoulder extensor muscles for pure elbow extension trials, as required to counter the interaction torques that arise at the shoulder due to forearm rotation. After locking the shoulder joint, we found a substantial reduction in shoulder muscle activity over many trials. This reduction is appropriate because locking the shoulder joint cancels the interaction torques and thus removes the need to activate shoulder muscles. In our first three experiments, we tested whether this reduction generalizes when reaching is self-initiated in (1) a different initial shoulder orientation, (2) a different initial elbow orientation and (3) for different reach distance/speed. If the nervous system attributes this learning as a novel an internal model of the arm's dynamics, then generalization should be broad regardless of joint orientation, and speed/distances. We found robust generalization across initial shoulder orientation and reach distance/speed but not for initial elbow orientation. In our fourth experiment, we tested whether generalization is also transferred to feedback control by applying mechanical perturbations and observing reflex responses in a distinct shoulder orientation. We found robust transfer to feedback control. Thus, the nervous system learns a coordination pattern following shoulder fixation rather than a general model of the altered limb dynamics.

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Poster

668. Sensorimotor Learning II

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Program #/Poster #: 668.14/L28

Topic: E.04. Voluntary Movements

Support: NIH 5T32NS091018-17
NIH 5T32NS091018-18

Title: Characterizing *de novo* learning of continuous motor skill

Authors: *C. S. YANG[1], N. J. COWAN[2], A. M. HAITH[3];
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Abstract: In order to perform new motor tasks, humans must learn to generate novel patterns of movement. It has been hypothesized that humans possess at least two motor learning mechanisms: 1) adaptation: adjustment of an existing motor skill, and 2) de novo learning: generating a new motor skill from scratch. Although both of these mechanisms are ethologically important, recent work has shown that the scope of behavioral change that can occur via adaptation is rather limited, and we believe many real-world skills, like riding a bike or playing the piano, must be learned de novo. However, we currently have a poor understanding of how real-world skills are learned because relatively few studies have examined de novo learning. To this end, we investigated the properties of motor controllers acquired through de novo learning. Healthy human participants learned to control a cursor under a challenging bimanual hand-to-cursor mapping, which we have previously established is learned de novo. We assessed how well participants learned the mapping by having them track a target moving in a sum-of-sinusoids trajectory, analyzing their behavior using a frequency-domain system identification approach. Participants reached asymptotic performance within 4 days of practice (as measured by the gain and phase of their frequency responses), reaching a plateau which was slightly poorer than that of baseline behavior. By measuring how the frequency responses of their tracking behavior improved, we could subsequently model how the control architecture of the sensorimotor system evolved with practice. We believe this work helps us to understand learning at the level of continuous control and is critical to deciphering how complex real-world skills are learned.

Disclosures: C.S. Yang: None. **N.J. Cowan:** None. **A.M. Haith:** None.

Poster

668. Sensorimotor Learning II

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Topic: E.04. Voluntary Movements

Support: NSERC (Canada)

Title: Time course of the long latency feedback response during short term motor adaptation

Authors: *S. K. COLTMAN, P. L. GRIBBLE;
Univ. of Western Ontario, London, ON, Canada

Abstract: The ability to adapt voluntary movements is essential for maintaining accurate performance. We can study motor adaptation in the laboratory by testing how human subjects adapt reaching movements of the arm to externally imposed force perturbations. It has been proposed that reaching toward a target uses a motor command generator, forward modelling that predicts the dynamics of the limb and updating of the initial commands using reliable feedback that is available during and after a movement. An underlying assumption of this framework is that feedback gains should depend on the dynamics of the task. Previous work has suggested that as participants learn to produce the appropriate motor commands to predictively compensate for a force field, they show an increase in the feedback gains associated with externally imposed force perturbations of the arm. Participants grasped the handle of a robotic manipulandum and performed reaches to a virtual visual target while the hand/arm were occluded. During reaching to a target 45° left of centre, we introduced an abrupt counter-clockwise velocity-dependent force field during a block of trials. As participants adapted their reaching movements to counter the force field we randomly interspersed mechanical probe trials designed to stretch the triceps muscle and elicit the long-latency feedback response. Short-term motor adaptation is believed to be supported by two separate processes, each with distinct timescales that operate simultaneously. Characteristically, the fast process learns quickly, but has poor retention; while the slow process has better retention but learns more slowly. We aimed to explore whether the feedback response changed in a parallel fashion to the voluntary system during the course of learning or whether it's time course was distinct. This will inform a deeper understanding of whether these two systems share the same underlying learning process(es) (i.e., fast and/or slow) or whether they rely on dissociable processes. Based on previous work suggesting that the feedback gains are greater in the early stages of learning a new task, and that with practice we learn to reduce our errors, improve our accuracy, become less variable, and develop smooth, effortless performance, we predicted that the time course of the long-latency feedback response will mirror the fast process.

Disclosures: S.K. Coltman: None. **P.L. Gribble:** None.

Poster

668. Sensorimotor Learning II

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Topic: E.04. Voluntary Movements

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NIHR Biomedical Research Centre, Oxford

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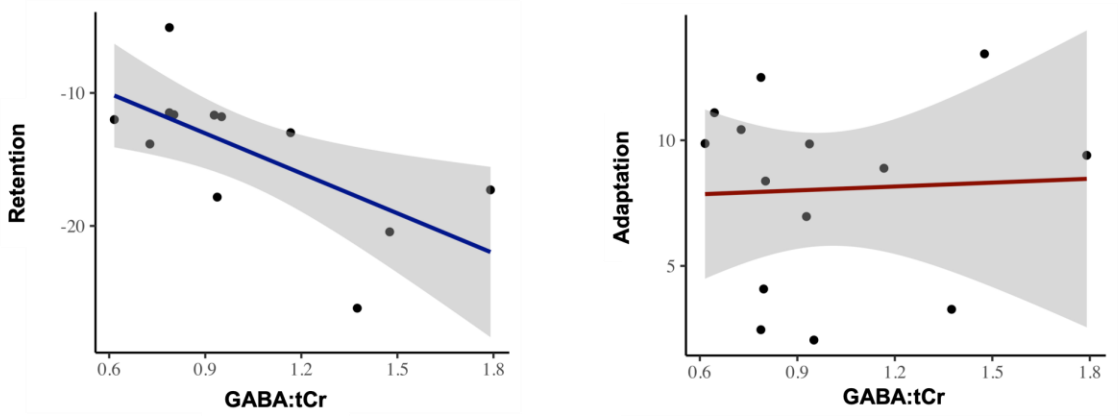
Title: Motor cortex neurotransmitters predict retention, but not adaptation

Authors: *C. R. NETTEKOVEN[1], S. BRADY[1], J. LEVENSTEIN[1], U. EMIR[2], N. JENKINSON[3], C. J. STAGG[1];
[1]Univ. of Oxford, Oxford, United Kingdom; [2]Purdue Univ., West Lafayette, IN; [3]Univ. of Birmingham, Birmingham, United Kingdom

Abstract: Neurotransmitter concentrations in human primary motor cortex (M1) relate to learning of motor skills. For example, decreases in M1 gamma-aminobutyric acid (GABA), as assessed by magnetic resonance spectroscopy (MRS) have been observed during learning of model-free tasks. However, it is not clear if similar changes are seen during learning of model-based tasks, where learning would be expected to occur outside M1, but retention is thought to be M1-dependent.
Methods:
Using a within-subject design (N=15 healthy participants) MRS data (7T) were acquired from the left M1 during the performance of a visuo-motor adaptation task using a hand-held joystick. During one session (adaptation session) visual feedback was rotated, and participants adapted their movements to the perturbed feedback. This was followed by a washout period (no offset), which allows to quantify the retention of the compensatory movement. During the other session (control session) no rotation was imposed.
Analysis:
Task performance was quantified using a model-free approach (mean error). To predict task performance (adaptation or retention) from metabolite concentrations, a regression analysis was performed.
Results:
As hypothesised, M1 GABA at baseline ($GABA_{Baseline}$) significantly predicted retention ($F_{1,11}$=-8.51, p=0.01), but not adaptation ($F_{1,12}$=0.03, p=0.87); participants with higher $GABA_{Baseline}$ retained more compensatory movement. M1 glutamate at baseline ($Glu_{Baseline}$) also predicted retention ($F_{1,11}$=10.47, p=0.01). Follow-up analysis showed that $GABA_{Baseline}$ and $Glu_{Baseline}$ were highly correlated (r_{14}=0.72, p=0.01) and suggested that the relationship with retention was driven by the shared variance of GABA and Glutamate. As expected, $GABA_{Baseline}$ did not correlate with retention (r_{11}=-0.25, p = 0.38) or adaptation (r_{11}=-0.22, p=0.51) in the control session.
In summary, we provide evidence that inter-individual differences in performance on a model-based motor task can be predicted from magnetic resonance spectroscopy-assessed neurochemical concentration levels in M1.



LEFT. Retention. GABA at baseline significantly predicts retention ($F(1,11) = 8.51$; $p = 0.01$).
RIGHT. Adaptation. GABA at baseline does not predict adaptation ($F(1,12) = 0.03$; $p = 0.87$).
As expected, GABA showed no relationship with retention ($r(11) = -0.25$, $p = 0.38$) or adaptation ($r(11) = -0.22$, $p = 0.51$) in the control session.

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Poster

668. Sensorimotor Learning II

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Topic: E.04. Voluntary Movements

Support: K01 AG047926
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ARCS Foundation

Title: Neuroanatomical correlates of motor learning and visuospatial processes in cognitively-intact older adults

Authors: *J. LINGO VANGILDER[1], M. C. FITZHUGH[2], C. ROGALSKY[2], S. Y. SCHAEFER[1];
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Abstract: We have recently shown that by testing older adults' visuospatial function, we can predict their motor learning capacity. In fact, our studies show that older adults with above-normal visuospatial scores retained up to four times as much skill as those with below-normal visuospatial scores, regardless of baseline upper extremity motor function, age, and other impairments in language, attention, or delayed memory. We hypothesize that visuospatial tests

have predictive value because they probe the health of critical neural structures for motor skill learning. Classic neuropsychological studies have long supported the role of parietal cortex in visuospatial function and more recent neuroimaging studies have shown that the structural integrity of white matter tracts between parietal and frontal cortices are related to various visuospatial abilities. More specifically, our preliminary data suggest that the right superior longitudinal fasciculus (SLF), a frontoparietal white matter tract, may be a candidate neural pathway for predicting visuospatial function in older adults and for explaining our previous behavioral findings. Thus, the purpose of this ongoing study is to address the gap in knowledge of the relationship between right SLF structure and motor learning ability. Cognitively-intact older adults (n=10, age>65) completed a baseline trial and 50 training trials on an upper extremity motor task using their nondominant hand, and were retested one week later to quantify the amount of motor skill learned and retained over a one-week period. Participants also underwent diffusion tensor magnetic resonance imaging to quantify right SLF fractional anisotropy (FA), a measure of white matter structural integrity. Results indicate that right SLF FA positively correlated with motor learning ability (R^2=0.34, p=0.079), where higher right SLF FA values predict better one-week motor learning. These preliminary data serve as proof-of-concept and support our hypothesis that motor learning processes may be integrated in the right SLF, and that SLF integrity may mediate the relationship between visuospatial test scores and motor learning outcomes. Moreover, results of this study suggest that paper-and-pencil visuospatial tests currently used in clinical settings could be used as a cost-effective proxy for neuroimaging, particularly in cases of contraindication or lack of imaging resources.

Disclosures: J. Lingo Vangilder: None. **M.C. Fitzhugh:** None. **C. Rogalsky:** None. **S.Y. Schaefer:** None.

Poster

668. Sensorimotor Learning II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 668.18/L32

Topic: E.04. Voluntary Movements

Support: BMBF (01GQ1424B)

Title: Computational analyses of chunking strategies in young and older adults to determine age-related differences

Authors: *P. MACEIRA-ELVIRA[1,2], J. E. TIMMERMANN[3], A.-C. SCHMID[1,2], M. J. WESSEL[1,2], M. ZIMERMAN[4], T. POPA[1,2], F. C. HUMMEL[1,2,5];
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Abstract: *Background and purpose:* Healthy aging entails changes in cognitive and motor function. Motor training can improve motor function in older adults, but learning is diminished in comparison to that observed in younger individuals. The origin of this impaired learning, e.g., speed, dexterity, brain plasticity or a combination of them remains to be singled out. The present study aims to detect differences in strategy in the execution of a motor task (i.e. chunking strategies) between young and older adults in order to identify underlying mechanisms and plausible targets for interventional strategies to improve motor learning in older adults.
Methods: 50 healthy participants from three different age groups (young [18-30 yo], middle-aged [50-65 yo] and old [>65 yo]) were trained in a finger sequence-tapping task over the course of five consecutive days. Data-driven computational methods were applied to detect motor deployment strategies (i.e. chunking) to determine whether there was a set of motor strategies characteristic to each age group.
Results: There were no differences in the execution error rates between groups. Still, mean classification accuracies of up-to 0.86 (F-score) were achieved when predicting young and old aged subjects from the chunking patterns generated on day 1. The middle-aged group could not be predicted effectively.
Conclusion: Young and old adults approach new tasks through markedly different motor strategies in the execution of sequential motor tasks, which might explain performance differences at a behavioral level. One of these different strategies is related to the evolution of chunking patterns of motor sequences during the learning process.

Disclosures: P. Maceira-Elvira: None. **J.E. Timmermann:** None. **A. Schmid:** None. **M.J. Wessel:** None. **M. Zimerman:** None. **T. Popa:** None. **F.C. Hummel:** None.

Poster

668. Sensorimotor Learning II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 668.19/L33

Topic: E.04. Voluntary Movements

Support: NSERC
OGS

Title: Conscious aiming strategies override implicit adaptation to opposing visuomotor perturbations

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Abstract: The ability to switch between different tools accurately and efficiently is a remarkable human feat afforded by a flexible and adaptive motor system. This is readily examined in dual adaptation paradigms, where the motor system is challenged to perform under switching, opposing visuomotor perturbations. Typically, dual adaptation doesn't proceed unless each mapping is trained in association with a predictive cue. In the first part of these experiments, we examined the efficacy of multiple cues in facilitating dual visuomotor adaptation including active follow-through movements, passive follow-through movements, active three-part lead-in movements, and a static visual control cue. In the final intervention, we gave participants a dual aiming strategy to dissociate the subcomponents of dual adaptation. This was motivated by recent advances revealing that adaptation can be characterized by at least two qualitatively different mechanisms: (1) an explicit process which arises due to the implementation of conscious aiming strategies, and (2) an implicit, unaware process, thought to reflect adaptation of internal models in the cerebellum. However, the extent by which dual adaptation is governed by a conscious, explicit process has yet to be investigated. To this end, we instructed an Explicit-Instruction group with a compensatory strategy about the perturbations (30° CW or 30° CCW rotations) and their relationships to each context (visual cues), and compared their performance to a No-Instruction group. Following perturbed training, participants were asked to either use or ignore the strategy as they reached without visual feedback. This Process Dissociation Procedure teased apart the implicit and explicit contributions to dual adaptation. First, we found that active movement sequences tend to facilitate dual learning but passive movement consequences do not. In the active movement experiments where dual learning was elicited, we found significant implicit and explicit reach aftereffects in the expected directions. Furthermore, static visual cues didn't elicit dual adaptation, but those in the Explicit-Instruction group were able to compensate by implementing aiming strategies. Critically, we found no implicit contributions, but an effect of instruction, suggesting that explicit aiming strategies inhibit implicit mechanisms in dual adaptation. Thus, by implementing conscious strategies, dual adaptation can be easily facilitated even when learning would not occur otherwise.

Disclosures: M.N. Ayala: None. **D.Y. Henriques:** None.

Poster

668. Sensorimotor Learning II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 668.20/L34

Topic: E.04. Voluntary Movements

Title: Distance control and proprioceptive localization of lower limb in patients with cerebellar disease

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Abstract: The accurate movement control and proprioceptive localization depends on our innate knowledge of limb state (i.e., proprioception, specifically limb position sense). The aim of this study was to investigate the effect of distance control and proprioceptive localization of lower limb in patients with cerebellar disease during different task conditions. Twelve patients with cerebellar disease (CD) and age- and sex-matched 12 normal controls participated in the study. Both groups practiced (i.e., 5 trial for each condition) reaching to the targets with their right lower limb presented at three distance conditions (5, 10, 15cm) while sitting. Kinematic data were measured to determine scaling of movement accuracy (i.e., error of distance and absolute distance error) from start to target position. The results demonstrated that error of distance and absolute distance error of CD patients were higher than normal controls. In particular, this difference was greater at 5cm than at 10cm and 15cm. Taken together, the results suggest that CD patients have deficit to distance control and proprioceptive localization during lower limb movement.

Disclosures: **Y. Song:** None. **S. Cheon:** None. **C. Lim:** None.

Poster

668. Sensorimotor Learning II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 668.21/L35

Topic: E.04. Voluntary Movements

Support: NIH Grant NS105839
NIH Grant NS092079

Title: Desensitization upon relearning for implicit sensorimotor adaptation

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Abstract: The motor system has an impressive ability to adapt to sudden environmental changes, and to quickly readjust when the changes are transient. If similar perturbations are re-

encountered, the learning is faster, a phenomenon known as savings. The lion's share of this effect is explained by the recall of an explicit aiming strategy (Haith *et al.*, 2015; Morehead *et al*., 2015), but it is possible that an implicit process also contributes to savings. We test this hypothesis using clamped visual feedback, in which a cursor follows an invariant path away from the target, independent of the hand path. This method was shown to induce implicit adaptation: Unaware reaching deviates to the opposite direction (Morehead *et al.*, 2017).
In Experiment 1, participants (n=16) reached to 8 targets located within a single quadrant. Exposure to 2° clamp offset over 80 cycles caused implicit adaptation. After a 10 cycles washout with veridical feedback, the clamp was re-introduced. Interestingly, early relearning was 49% faster, but the asymptote was 23% smaller, suggesting that the overall relearning decreased. The faster early relearning may reflect an implicit process that was not fully washed out by the short veridical feedback session. To address this possibility, in Experiment 2 (n=16) we introduced an extended veridical feedback washout of 30 cycles. Early relearning was now 33% slower, corroborating its dependency on the washout duration.
Due to adaptation, participants experience errors during the early veridical feedback washout, which may cause awareness of the clamp effect on reach direction. Therefore, the weaker relearning could result from an explicit strategy to compensate for the hand deviation. In Experiment 3, participants first adapted to either 2° or 15° clamp (n=32) for 60 cycles. We then used a reversed clamp (-2°/-15°), maintaining this feedback until the median reach direction was smaller than 3° for 3 consecutive cycles, and then presented veridical feedback (50 cycles overall). Thus, we washed out implicit adaptation while eliminating the experience of adaptation-driven errors. When repeating the original clamp, we again saw decrements in both early rate (30%) and asymptote (9%) of relearning. In Experiment 4 (n=32), we found that these effects did not generalize to the opposite side of the workspace.
In conclusion, instead of savings, we saw decreased implicit adaptation upon re-exposure that is workspace-specific. Similar effects in rodents were attributed to transient depletion of plasticity in cerebellar synapses (Nguyen-Vu *et al.,* 2017). The effect may also reflect a habituation-like response to a persistent error.

Disclosures: G. Avraham: None. **D.E. Parvin:** None. **H.E. Kim:** None. **J.R. Morehead:** None. **R.B. Ivry:** None.

Poster

668. Sensorimotor Learning II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 668.22/L36

Topic: E.04. Voluntary Movements

Support: R03AG056822

Title: Deficits in motor learning of older adults is correlated to delays in the reticulospinal system

Authors: J. J. SCHREIBER[1], K. ELLIOTT[1], S. Y. SCHAEFER[2], ***C. F. HONEYCUTT**[1]; [2]SBHSE, [1]Arizona State Univ., Tempe, AZ

Abstract: Motor skill acquisition, the process by which individuals practice and consolidate movement to become faster, more accurate and efficient, declines with age (Gunning-Dixon, Head, Raz, Acker, & Williamson, 2002; King, 2016; Roig, Ritterband-Rosenbaum, Lundbye-Jensen, & Nielsen, 2014; Seidler, 2007). Initial skill acquisition is dominated by cortical structures; however as learning proceeds, literature from rodents and songbirds suggests that there is a transition away from cortical execution (Kawai et. al. 2015; Andalman & Fee, 2009; Desmurget & Turner, 2010; Quaglino & Quaglino, 2007; Walter et al., 2019). Recent evidence indicates that the reticulospinal system may play an important role in integration and retention of learned motor skills. Specifically, reticulospinal contributions are shown to increase over the course of a 10-day training regimen (Kirkpatrick et. al. 2015).
The brainstem has known age-rated deficits including cell shrinkage and death in rodents (Sabel and Stein 1981) and volume loss in humans (Luft et al. 1999; Lambert et al. 2013). Given the role of the reticulospinal system in skill acquisition and older adult's poor capacity to learn, it begs the question: are delays in the reticulospinal system contributing to older adult's poor capacity to learn? Our objective was to evaluate if delays in the reticulospinal system (measured via the startle reflex) are correlated to impairment of motor learning in older adults. We hypothesized that individuals with fast startle responses would show the most learning and retention while individuals with delayed startle responses would show the least. We indeed found that individuals with fast and intact startle responses have larger % improvement and % retention compared to individuals with delayed startle responses. Further, linear regression analysis indicated that startle onset latency exists within a continuum of learning outcomes suggesting that startle onset latency may be a sensitive measure to predict learning deficits. There exists no method to determine an individual's relative learning capacity. Thus, this result opens the possibility of startle, which is an easy and inexpensive behavioral measure, being used to predict learning deficits in older adults to facilitate better dosing during rehabilitation therapy.

Disclosures: J.J. Schreiber: None. **K. Elliott:** None. **S.Y. Schaefer:** None. **C.F. Honeycutt:** None.

Poster

668. Sensorimotor Learning II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 668.23/L37

Topic: E.04. Voluntary Movements

Title: Comparing latencies of information processing supporting feedforward and feedback control of reaching

Authors: *K. KITA[1], C. YANG[2], Y. DU[1], A. M. HAITH[1];
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Abstract: Feedback responses to a mid-movement perturbation are initiated within around 100-150 ms. Preparation of feedforward movements has also been shown to occur within a similar time period. Furthermore, conflicting responses have been shown to emerge at different times for both feedforward and feedback. Feedforward and feedback control have, however, never been directly compared. Despite these compelling parallels, it remains unclear whether the time course for preparing a feedforward movement are the same, or whether preparation of feedforward movements might require additional processing stages. Here we directly compared the time course of information processing for feedforward and feedback responses both when acting under veridical feedback, and when acting under a mirror reversal. Human participants performed center-out reaching movements towards four equally-spaced targets at a distance of 10cm under two conditions: 1) a timed-response condition where participants were forced to respond at a range of preparation times (PTs) ranging from 100 to 600ms, 2) a target jump condition where participants initiated reaching to a target, but the target jumped 5cm orthogonally to the direction of movement. Condition 1 reveals the time course over which feedforward control is prepared, based on the minimum preparation time required to consistently generate accurate movements. Condition 2 reveals the latency at feedback responses are initiated to compensate for the target jump after participants were already moving. We found that target location was reflected in behavior at a similar latency in both conditions.Participants performed the same two conditions in an environment with mirror (up-down)-reversed visual feedback. When target processing required a movement orthogonal to the mirroring axis (i.e. up or down), both feedforward and feedback behavior exhibited two clear phases of behavior. In Condition 1, at low PTs, participants initiated movement towards the actual target location, but at longer PTs they were able to move their hand away from the target in order to bring the cursor to the target. In Condition 2, in response to target jumps upward or downward, participants initially pursued the target with their hand, but rapidly reversed their correction to move their hand away from the target, guiding the cursor to the target. The timescale of these events were broadly consistent across the two conditions. These results suggest that a single underlying process drives changes in feedforward and feedback control.

Disclosures: K. Kita: None. **C. Yang:** None. **Y. Du:** None. **A.M. Haith:** None.

Poster

668. Sensorimotor Learning II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 668.24/L38

Topic: E.04. Voluntary Movements

Title: Spiking neuron model of motor control with adaptation to visuomotor rotation

Authors: *N. VAIDYANATHAN, C. ELIASMITH;
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Abstract: There are numerous behavioral and physiological studies that show how the brain compensates for uncertainties and unexpected changes in the sensory environment while still successfully perform motor tasks. To date, there have been a variety of phenomenological models proposed for explaining this sensory motor adaptation. But in order to relate the suggested control algorithms with their neural realizations, it is important to have biologically plausible mechanisms that capture both neural activities and the higher order behaviors that they give rise to. Here we extend a previous model, the Recurrent Error-driven Adaptive Control Hierarchy (REACH), that accounts for dynamic and kinematic adaptation, to also capture visuomotor adaptations. To demonstrate this behavior, we consider the conventional task of 'visuomotor rotation' using a two link arm in a planar reaching task. The model consists of anatomically organized structures including M1, PMd and cerebellum to incorporate different aspects of the behavior. The extended model has a multimodal Kalman filter to accomodate an internal model for dynamic prediction of limb states and sensory integration of vision and proprioception. A spike based algorithm is implemented to learn the visuomotor transformation. Replicating experiments in humans and non-human primates, the model is made to reach when given either abrupt or fast implicit rotations. We also use the model to explore multirate adaptations to further demonstrate classical characteristics such as savings and interference. While the proposed model is consistent with the experimental data of rapid adaptations, the model also exhibits spiking activity comparable to empirical data. A plausible and anatomically organized neuron model describing the adaptation to visuomotor rotations, and eventually to other visuomotor transformations, can provide insights and significantly improve our understanding of the motor system organization and function.

Disclosures: N. Vaidyanathan: None. **C. Eliasmith:** None.

Poster

668. Sensorimotor Learning II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 668.25/L39

Topic: E.04. Voluntary Movements

Title: Punishment, but not reward, impairs retention and decreases cortical feedback related potentials during motor learning

Authors: *C. M. HILL[1,2], M. STRINGER[3], D. E. WADDELL[3], A. J. DEL ARCO[2];
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Abstract: Reward and punishment have demonstrated dissociable effects on motor learning, with punishment enhancing the learning rate and reward increasing retention of the motor task. However, these findings have been primarily demonstrated at the level of behavior, and no study has presented the neural correlates. The aim of this research is to determine whether reward and punishment feedback produces a different cortical neural response associated with motor learning and retention. Participants were randomly placed into one of three groups [Reward (n=14), Punishment (n=14), Control (n=14)] and performed 680 trials of a visuomotor rotation task under five testing conditions [Baseline (80 trials), Adaptation (200 trials), No Vision (200 trials), Washout (100 trials), and Readaptation (100 trials)] with a Wacom pen and tablet. Adaptation (learning phase), No Vision (retention phase), and Readaptation featured an incongruent position between the cursor and the target, with the cursor trajectory rotated 30-degrees counterclockwise to the target, requiring the participant to adapt their movement to hit the target. After each trial, feedback based on error magnitude was provided during the learning phase in the form of a positive number (Reward), negative number (Punishment) or two vertical lines (Control). Positive and negative numbers represented a monetary gain and loss, respectively. EEG was recorded throughout all task conditions from 28 electrodes placed according to the 10-20 system. Reach angle and event-related potentials (ERPs) time locked to feedback presentation (Reward, Punishment or Control) were calculated for each participant during the learning and retention phases of the task. We found that all feedback groups displayed similar changes in reach angles throughout the learning phase of the task, suggesting reinforcement feedback does not alter task adaptation and performance. However, the Punishment group did not maintain the learned reach angle during the retention phase (13.28 ±3.11°), while Reward (19.65 ±0.59°) and Control (19.34 ±1.59°) groups preserved their performance ($F(2,39)=4.157$, $p=0.023$, RMANOVA). Moreover, punishment significantly decreased the peak amplitude of the feedback ERPs during the retention phase compared to the learning phase ($F(2,35)=3.361$, $p=0.009$, RMANOVA). ERP changes were not found in the

Reward and Control groups. We propose that punishment feedback does not adequately update the internal representation of the adaptive behavior necessary to retain the motor task.

Disclosures: C.M. Hill: None. **M. Stringer:** None. **D.E. Waddell:** None. **A.J. Del arco:** None.

Poster

668. Sensorimotor Learning II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 668.26/L40

Topic: E.04. Voluntary Movements

Support: NSF CAREER Award 1555006

Title: Improved motor timing enhances time perception

Authors: *J. GUO[1], Z. ZHANG[3], D. STERNAD[4], J.-H. SONG[1,2];
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Abstract: Previous studies demonstrated that motor timing and time perception share common mechanisms and brain processes. For instance, participants who displayed larger timing variability in single-finger rhythmic tapping also demonstrated lower acuity in time perception (Keele et al., 1985). However, these studies examined simple movements, i.e. finger or foot tapping, performed in an explicitly rhythmic fashion. It is unclear whether the inherent timing of more complex movements without explicit periodicity also affected time perception. Here, we examined whether practicing a sequence of controlled throwing movements enhances the sensitivity of time-interval discrimination and, if so, whether this enhanced sensitivity is selectively linked to the timing of the trained movement. In the experiment, participants (n = 14) practiced throwing a ball to hit a target in a virtual environment for 4 daily sessions. Over 4 days of throwing practice, participants stabilized the release time between the onset of the throwing movements and the ball release to approximately 300 ms. Following each throwing session, participants also performed a time-interval discrimination task, in which they reported which of the first standard (t = 300, 600, 1000, or 3000 ms in each block) or the second comparison ($t \pm \alpha t$) time-interval both marked by two auditory beeps was longer. We found that with throwing practice, they enhanced the sensitivity of time discrimination selectively for the interval of 300 ms close to the release time, but not for others. In addition, within individuals, the magnitude of motor timing improvement predicts the enhancement of time-interval discrimination. These results demonstrated that improvement of motor timing enhances the sensitivity of time perception, even for timing patterns inherent to a more complex motor task. We interpret these

finding that there is a shared temporal mechanism between perception and movement regardless of rhythmicity or complexity of the motor tasks.

Disclosures: **J. Guo:** None. **Z. Zhang:** None. **D. Sternad:** None. **J. Song:** None.

Poster

668. Sensorimotor Learning II

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Topic: E.04. Voluntary Movements

Support: NSF-M3X-1825942
NIH-R01-HD087089
NSF-NRI-1637854
Fulbright-IIE-PS00261102

Title: Cracking a whip: Motor control beyond reach?

Authors: ***A. KROTOV**[1], Z. ZHANG[4], M. RUSSO[2], N. HOGAN[5], D. STERNAD[3];
[1]Bioengineering, [2]Biol., [3]Biology, Electrical and Computer Engin. and Physics, Northeastern Univ., Boston, MA; [4]Neurosci., Columbia Univ., New York, NY; [5]Mechanical Engin. and Brain and Cognitive Sci., MIT, Cambridge, MA

Abstract: Over the past decades, much of motor neuroscience research has focused on unconstrained reaching-like movements and summarized insights in descriptions of control and learning, including internal models and optimal feedback control strategies. However, this understanding of motor control is challenged when addressing more advanced tasks such as interacting with complex objects, i.e. objects that have internal dynamics. Using the extreme example of cracking a bullwhip, this study asked how humans manipulate the wave dynamics of the whip's infinite number of degrees of freedom. Prediction based on an internal model of this object would challenge even modern supercomputers. How do humans achieve their dexterity? To examine how humans learn to manipulate this complex object, the experimental study tested participants cracking a 1.8m-long bullwhip to hit a two-inch target at 2.2m distance with the tip of the whip. Two task variants were tested: hitting the target in a single-shot movement and hitting the target repeatedly using a rhythmic action to keep the whip in the air. We recruited one expert with 20 years of experience who performed one session of data collection. Fifteen novice participants practiced the task in 15 sessions over 5 weeks. The novices could view the expert performance as a model for their practice. Kinematics of subjects' torso, dominant arm, and the whip were measured with 3D motion capture. Ten markers attached to the whip were used to reconstruct this continuous object. Remarkably, analyses of the expert data revealed that variability over successive actions was smaller and the precision of hitting the target was higher

during continuous rhythmic movements. Principal component analysis of the seven markers on the whip revealed that variability decreased from the shoulder to the tip of the whip. Analysis of the novice participants' data showed that the error between the tip of the whip and the target decreased with practice, indicating skill learning. In addition, subjects were able to reduce the dimensionality of motions of their arm and torso and approach a reproducible near-planar motion of the whip. Maximum force and torque during each attempt decreased, leading to smoother whip movements. These trends were more pronounced when the task was performed rhythmically. Based on these first results, we suggest that subjects may represent this prodigiously complex dynamic object in terms of the primitive actions—rhythmic and discrete—they may use for interactive control. Faster learning with rhythmic performance may arise from the stability of the dynamic attractor that underlies rhythmic actions.

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Poster

669. Brain-Computer Interface: EMG

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 669.01/L42

Topic: E.05. Brain-Machine Interface

Support: DARPA BTO SPAWAR Pacific Grant/Contract No. N66001-15-C-4017
NSF Grant NSF/NCS-FO ECCS-1533649

Title: Portable control system enables dexterous home use of an advanced bionic arm

Authors: *M. R. BRINTON[1], E. L. BARCIKOWSKI[5], T. S. DAVIS[2], J. A. GEORGE[1], M. D. PASKETT[1], D. J. WARREN[1], C. C. DUNCAN[3], D. T. HUTCHINSON[4], G. A. CLARK[1]; [1]Biomed. Engin., [2]Neurosurg., [3]Physical Med. and Rehabil., [4]Orthopaedics, Univ. of Utah, Salt Lake City, UT; [5]Ripple Neuro, Salt Lake City, UT

Abstract: We present advances in developing and implementing a portable bionic-arm system with intuitive, dexterous control of several degrees-of-freedom (DOFs) using electromyographic (EMG) recordings and naturalistic, high-resolution sensory feedback. A portable processor (Nomad; Ripple, LLC) records and down-selects from 496 differential EMG channels (from 32 single-ended electrodes); predicts user intent using a modified Kalman filter (George et al., SfN 2019); and controls an advanced six-DOF bionic arm (DEKA "LUKE" Arm). To train the modified Kalman filter (MKF), users simply press a button and the portable processor records EMG signals while the users mimic preprogrammed movements of the bionic arm with their phantom limb and residual forearm muscles. The MKF is trained and the user has full control of the bionic arm in less than 15 minutes. Previously trained algorithms can also be loaded for

immediate use. The portable system stores the arm's 6 position and 13 force sensor values (sampled at 33 Hz) for post-hoc analysis. This rich dataset allows us to understand how amputees use prosthetic arms for daily tasks specific to their circumstance and of their own choosing—unlike predefined generic tasks often performed in controlled laboratory settings. For example, analyses of these data can provide information about preferred grasps and their frequency and strength. An upper-limb amputee performed a preliminary, supervised take-home trial of the portable system to complete activities of daily living (ADLs) of his own choosing and in his own home (e.g., donning shoes, opening/locking doors, turning on faucet, playing with dog, taking out trash, opening refrigerator). The participant repeatedly expressed his surprise and pleasure with the portable system. While opening and locking a door, he exclaimed "I couldn't do that with my [commercial prosthetic arm], for sure!"; while opening refrigerator and cabinet doors he remarked, "I would have never thought that would happen!" and "That [task] was a little more precise than I thought I could do." Ongoing developments include incorporating biomimetic stimulation (for closed-loop sensorimotor control) via implanted Utah Slanted Electrode Arrays; more advanced control algorithms (e.g., convolutional neural network); and a user-friendly tablet-based interface to train and adjust the motor control and sensory feedback algorithms via the portable processor's Wi-Fi network. When complete, this portable bionic-arm system will enable us to explore the functional and psychological benefits associated with long-term, at-home use of sensorized and dexterous bionic arms.

Disclosures: **M.R. Brinton:** None. **E.L. Barcikowski:** F. Consulting Fees (e.g., advisory boards); Ripple Neuro, Inc. **T.S. Davis:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent (WO2018026842A1). **J.A. George:** None. **M.D. Paskett:** None. **D.J. Warren:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent (WO2018026842A1; 8359083; 8639312). **G.A. Clark:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent (WO2018026842A1; WO2018023026A1; 8359083; 8639312). **C.C. Duncan:** None. **D.T. Hutchinson:** None.

Poster

669. Brain-Computer Interface: EMG

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 669.02/L43

Topic: E.05. Brain-Machine Interface

Support: NSF BRAIN Initiative Award No. 58502170
NSF Grant NSF/NCS-FO ECCS-1533649
DARPA BTO SPAWAR Pacific Grant/Contract No. N66001-15-C-4017

Title: Shared controllers improve control and performance of upper-limb prostheses

Authors: T. C. HANSEN[1], H. DANTAS[2], J. A. GEORGE[1], G. A. CLARK[1], *D. J. WARREN[1], V. MATHEWS[2];
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Abstract: This work explores approaches to provide intuitive and reliable control of bionic arms via a shared control system that uses multiple control algorithms in parallel, where a linear combination of their outputs is the control signal. Using multiple algorithms could provide the benefits of each algorithm while reducing the disadvantages of each alone. This system could allow for self-aware bionic arms that assist the user in efficiently performing everyday tasks.
We present a shared controller consisting of two control algorithms: a Kalman filter (KF) movement intent decoder and a classifier decoder employing a multilayer perceptron (MLP). The KF decoder allows for proportional real-time adjustments but is more prone to unintended movements than the MLP decoder. Each decoder was trained on 32 channels of surface electromyography (EMG) data obtained non-invasively from three intact-arm subjects (one subject was an author). During testing trials, the subjects performed a target touching task in a virtual environment where they moved digits of a virtual hand to specific targets and held them there for as long as possible. The percent time in the target region (PTTR) was calculated for each trial. Each subject's data were analyzed separately, treating each trial as a separate observation.
Experiments using the KF-only decoder or the MLP-only decoder had a median PTTR of 17% and 16%, respectively. The median PTTR for shared control ranged from 21% to 68% (Fig. 1). The shared controller PTTR was significantly higher than either the KF or MLP decoders alone across all subjects (Conover-Iman, $p < 0.001$ and $p < 0.001$, respectively, corrected for multiple comparisons). Given the limited sample size of this preliminary data, we intend to perform testing in additional subjects.
Following these results, we have begun investigating a shared control system using a bionic hand with sensors on the fingertips that detect proximity to a nearby object and contact pressure. We propose using shared control between EMG-based and proximity/pressure-based controllers to assist in reaching for and grasping objects.

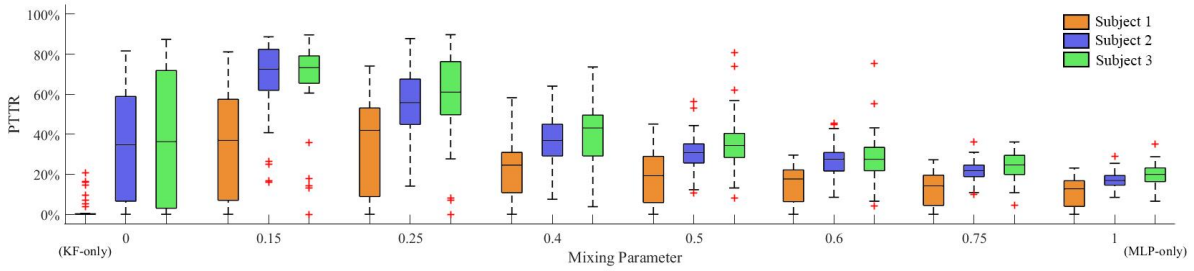

Fig. 1: Percentage Time in Target Region (PTTR) for a target touching task. Trials with KF-only control had a median PTTR of 17%, and trials with MLP-only control had a median PTTR of 16%. The shared controller with mixing parameter 0.15 (15% MLP and 85% KF) had the highest median PTTR at 68%, significantly outperforming the KF-only and MLP-only decoders across all subjects (Conover-Iman, $p < 0.001$ and $p < 0.001$, respectively for all subjects, corrected for multiple comparisions). Outliers outside upper or lower quartiles by ≥ 1.5 * IQR indicated with +

Disclosures: **D.J. Warren:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Blackrock

Microsystems. **T.C. Hansen:** None. **J.A. George:** None. **G.A. Clark:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Blackrock Microsystems. **H. Dantas:** None. **V. Mathews:** None.

Poster

669. Brain-Computer Interface: EMG

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 669.03/L44

Topic: E.05. Brain-Machine Interface

Support: SRC JUMP

Title: A wearable EMG-based hand gesture recognition system with real-time on-board incremental learning and classification

Authors: *A. MOIN[1], A. ZHOU[1], S. BENATTI[2], A. RAHIMI[3], A. MENON[1], G. ALEXANDROV[1], S. TAMAKLOE[1], J. K. TING[1], N. A. D. YAMAMOTO[1], Y. KHAN[1], F. L. BURGHARDT[1], A. C. ARIAS[1], L. BENINI[3], J. M. RABAEY[1];
[1]Dept. of Electrical Engin. and Computer Sci., Univ. of California, Berkeley, Berkeley, CA; [2]Univ. of Bologna, Bologna, Italy; [3]ETH Zurich, Zurich, Switzerland

Abstract: Hand gestures offer a natural way for humans to control, interact with, and engage with intelligent systems and devices. Applications of hand gesture recognition range from providing touchless user interfaces for consumer electronics to enabling natural, dexterous control of robotic arms and rehabilitative prostheses. Because many of these applications require long-term, continuous use of the device, it is crucial for hand gesture recognition systems to be contained within small, wearable form factors.
Here, we present a wearable, wireless system for EMG-based gesture recognition that enables high-density EMG acquisition and signal processing, as well as completely on-board and online training, inference, and incremental updates using a hyperdimensional (HD) computing machine learning model. The system consists of a custom-designed, screen-printed 64-channel flexible electrode array that minimizes wiring and enhances comfort without sacrificing signal quality. The electrode array interfaces with a device featuring a custom-designed low-power integrated circuit used to sample and digitize EMG for processing in an on-board FPGA, where we have implemented an HD computing classification algorithm.
Signal properties change with sweating, fatigue, muscle contraction effort, and electrode displacement due to changing situational contexts such as limb and body position or device doffing and donning. These variations can cause significant degradations in classification accuracy, usually because a new situational context was not considered during model training. Therefore, it is particularly important to be able to train or update the classification model on-the-fly, which is implemented efficiently on the hardwareby leveraging HD computing. We

achieve above 95% accuracy in classifying 21 common finger gestures, with little accuracy degradation between different arm positions and wear sessions.

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Poster

669. Brain-Computer Interface: EMG

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Program #/Poster #: 669.04/L45

Topic: E.05. Brain-Machine Interface

Support: VA Merit Review 1 I01 RX001077-01, R.F. Kirsch, PI
DARPA HAPTIX #N66001-15-C-4014
NIH Training Grant T32 EB004314

Title: A synergy-model-based regression for simultaneous, intuitive, proportional, high degree-of-freedom control in a prosthetic hand from chronically implanted EMG evaluated in virtual reality

Authors: *P. LUKYANENKO, H. DEWALD, J. LAMBRECHT, R. F. KIRSCH, D. J. TYLER, M. WILLIAMS;
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Abstract: With the development of high degree-of-freedom (DoF) prosthetic hands, patients' need for improved prosthetic hand control has become clear. One drawback of current feedforward controllers is their dependence on a high volume of user data needed for controller training and the frequent need for recalibration. We have previously demonstrated an intuitive, proportional, simultaneous and regression-based controller in 3 DoF using a K-nearest-neighbor decoder which remained stable over several months when using chronically implanted EMG. To create a similar controller with the added capability of scaling to higher DoF without requiring a prohibitive volume of user data, we leveraged a muscle synergy framework. The muscle activity in training data creates basis vectors in EMG feature space based on underlying muscle synergies. During operation, the algorithm decomposes EMG patterns into linear combinations of learned muscle patterns. This process allows training on simple, isolated DoF activities to be composed into several degrees of freedom simultaneously, arbitrarily, and with user controlled rates of motion. All clinical trials were performed under IRB, FDA, and DoN HAARP approval. Two trans-radial amputee subjects were implanted with bipolar EMG electrodes with percutaneous indwelling leads. At the time of the study, one subject (S8) had 8 functioning

bipolar electrodes, and the other subject (S6) had six. To gather training data, a VR system was used to guide users through sample movements in three and four degrees of freedom. To evaluate controller performance, subjects were asked to match a comprehensive set of targets in VR with 3 and 4 DoF controllers, as well as with their intact limb. 80 targets were presented in batches of 16, with user-defined rest periods between targets and 30 second time limits.
Targets were generated in a quasi-random manner to evenly sample gross movements in 3 and 4 Dof. Metrics include time-to-target and path efficiency. EMG controllers were re-evaluated over a 6-month period without retraining to evaluate stability over time. In 3 DoF, S8 and S6 performance remained consistent over 6 months post-training. Time-to-match was between 50 and 100% higher than corresponding intact limb match times. In 4 DoF over 6 months post-training S8 performance trended towards improvement whereas S6's match rate decreased substantially. This deterioration is likely due to an insufficient number of EMG channels being used to move in a higher dimension space. These results indicate that a synergy-model-based-regression is a promising method for high degree of freedom prosthetic hand control, provided sufficient EMG channels.

Disclosures: P. Lukyanenko: None. **H. Dewald:** None. **J. Lambrecht:** None. **R.F. Kirsch:** None. **D.J. Tyler:** None. **M. Williams:** None.

Poster

669. Brain-Computer Interface: EMG

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Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 669.05/L46

Topic: E.05. Brain-Machine Interface

Support: NSF-NRI #560172

Title: Combining data-driven and modeling-based approaches to improve myoelectric motor decoding

Authors: *R. M. HINSON, Jr[1], H. HUANG[2];
[1]Biomed. Engin., North Carolina State Univ., Raleigh, NC; [2]NCSU/UNC Joint Dept. of Biomed. Engin., North Carolina State Univ. and Univ. of North Carolina-Chapel Hill, Raleigh, NC

Abstract: The neural decoding of motor intent is a complex problem that is an active subject of research in rehabilitation fields. In particular, electromyography (EMG) is commonly used for the control of upper limb prosthetic devices by amputees because it is a readily accessible and rich source of neural information encoding motor commands. This technology has been widely applied using pattern recognition to map EMG activation patterns to multi-joint, physiologic motions for intuitive control. However, this approach only allows for a discrete set of motions to be generated by users. As a result, efforts to allow for continuous and simultaneous multi-joint

control have increased. These continuous mappings of EMG to motion have been implemented using machine learning-based techniques as well as musculoskeletal modeling-based approaches. In previous work, we implemented a generic (non-customized parameters) musculoskeletal model that multiple subjects used to control a virtual hand with no significant difference in performance compared to customized models. While transferable between users, this model was not optimized for each user. Therefore, in this study we aim to combine this generic musculoskeletal model with a data-driven model to improve performance while keeping the decoder transferable between users. We recorded motion capture data of 6 able-bodied subjects performing wrist flexion/extension and metacarpophalangeal (MCP) flexion/extension in cyclic and random motions in 9 different postures. This data was time-synced with surface EMG data from the extensor digitorum, flexor digitorum superficialis, extensor carpi radialis longus, and flexor carpi radialis muscles. An autoregressive kinematic model was trained using half the available data. The other half of the data were used for evaluation. This data-driven model was combined with the generic musculoskeletal model using an Unscented Kalman Filter. The data-driven model was used to predict the kinematics between timesteps while the musculoskeletal model used the EMG data for the update step. The results were compared to the musculoskeletal model alone. Preliminary results show no change in root mean square error (RMSE) or correlation (compared to kinematic data) for the wrist joint. However, significant ($p < 0.05$) decreases of 11.97%, 8.63%, and 6.81% in RMSE of MCP joint angle prediction were observed for isolated wrist, isolated MCP, and simultaneous joint motions, respectively. This demonstrates the potential benefits of this approach for motor decoding and prosthesis control, as it improves predictive accuracy while using generalizable approaches that don't require customization.

Disclosures: **R.M. Hinson:** None. **H. Huang:** None.

Poster

669. Brain-Computer Interface: EMG

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 669.06/M1

Topic: E.09. Motor Neurons and Muscle

Support: JSPS Overseas Research Fellowship

Title: Different motor unit recruitment pattern between peripheral nerve stimulation and motor point stimulation

Authors: *K. NAKAGAWA[1,2], K. L. FOK[1,3], K. MASANI[1,3];
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Abstract: Neuromuscular electrical stimulation is widely used to induce muscle contractions in many clinical settings. Neuromuscular electrical stimulation can be delivered via peripheral nerve stimulation (PNS) and motor point stimulation (MPS). Although MPS is often used in clinical settings such as upper and lower limb rehabilitation, its neural mechanism is not completely understood. Here we investigated the recruitment pattern of the motor unit during MPS compared to PNS. Ten able-bodied individuals participated. We measured electromyograms of plantarflexor muscles and the ankle joint torque. Twitch contractions were induced through tibial nerve stimulation for PNS and motor point of soleus muscle for MPS. When the stimulation intensity was gradually increased from the sub-threshold to the maximum, M-wave, H-reflex, F-wave and twitch torque were identified. We analyzed the duration from torque onset to peak torque (time-to-peak) to investigate the recruitment order of motor unit. H-reflex and M-wave were identified in PNS, while MPS did not evoke H-reflex but M-wave and F-wave. When we focused on the stimulation intensities with which only H-reflex was induced in PNS, we found that time-to-peak was longer in PNS than MPS, and that time-to-peak in MPS increased with increasing stimulation intensity while time-to-peak in PNS did not change depending on the stimulation intensity. Since time-to-peak reflects the balance of fast and slow muscle fibers recruited, shorter/longer time-to-peak indicates that fast muscle fibers were recruited more/less. Thus, these results suggested that the recruitment pattern of motor unit is reverse of the size principle in MPS, while random in PNS.

Disclosures: K. Nakagawa: None. **K.L. Fok:** None. **K. Masani:** None.

Poster

669. Brain-Computer Interface: EMG

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 669.07/M2

Topic: E.09. Motor Neurons and Muscle

Title: Compound muscles action potential (CMAP) as a new outcome measurement in SOD1 mouse model of ALS and oxaliplatin-induced polyneuropathy in mice

Authors: *R. O. PUSSINEN, T. BOLKVADZE, J. TOIVANEN, A.-M. KÄRKKÄINEN, M. DUDEK, D. MISZCZUK;
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Abstract: A motor neuron can activate hundreds of muscle fibers in synchrony with one single action potential, and the resulting electric signal is detectable from the muscle itself by electromyography (EMG). When the appropriate nerve is stimulated electrically, the evoked responses can be measured with surface or needle electrodes at a distal muscle level. Compound Muscle Action Potential (CMAP) is the measure of the evoked potential. CMAP is a clinically relevant measure frequently utilized in research studies such as oxaliplatin induced

polyneuropathy and in monitoring of patients with neuromuscular disorders such as amyotrophic lateral sclerosis (ALS). Also, CMAP measurements correlate well with age, severity and clinical measures of function. Furthermore, CMAP is minimally invasive and allow assessment of function longitudinally in the same individual.
In the present study, CMAP was measured in SOD1 mice and age-matched non-transgenic control littermates weekly on 8-18 weeks of age in parallel with clinical score assessment. In oxaliplatin model, male C57BL/6J mice were dosed with six injections of 4.5 mg/kg oxaliplatin i.p. (at days: 0, 4, 8, 12, 16, 20) and CMAP as well as cool allodynia acetone test was measured on days -4, 22, 29, 36 and 43. In all experiments, CMAP was recorded under isoflurane anesthesia. The stimulation was done close the sciatic nerve at the proximal hind limb using 26 G monopolar stimulation needle. Recording was performed on the skin overlying the proximal portion of the gastrocnemius muscle of the hindlimb. The sciatic CMAP responses were obtained by stimulating the sciatic nerve with square-wave pulses of 0.1 ms duration and intensity ranging from 1-10 mA.
Our electrophysiological investigations show that oxaliplatin challenge resulted in deficits in temporal summation in motor units and therefore evoke motor weakness and/or coordination. Furthermore, the progressive decrease of CMAP amplitudes was observed in SOD1 mice. Current data supports the use of this electrophysiological technique in the preclinical research of neuromuscular function in phenotyping as well as in future efficacy studies for drug development.

Disclosures: R.O. Pussinen: None. **T. Bolkvadze:** None. **J. Toivanen:** None. **A. Kärkkäinen:** None. **M. Dudek:** None. **D. Miszczuk:** None.

Poster

669. Brain-Computer Interface: EMG

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 669.08/M3

Topic: E.09. Motor Neurons and Muscle

Title: Electromyography device for effective communication in spastic cerebral disease

Authors: *G. LOPEZ-ARMAS, J. MARGAIN-MORENO, A. ARENAS-PEREZ, Y. NAVA-RAZO, D. GONZÁLEZ-MORALES;
Ctr. De Enseñanza Técnico Industrial, Guadalajara, Mexico

Abstract: Introduction: Spastic cerebral palsy is the most common type of cerebral palsy accompanied of cognitive impairment. Spasticity is a form of hypertonia, or increased muscle tone. This results in stiff muscles which can make movement difficult or even impossible. Therefore people may have difficulty moving from one position to another and controlling individual muscles or muscle groups needed for performing certain tasks like handling objects or

speaking due smaller muscles or muscle groups such as the tongue, facial muscles or vocal folds also are affected. In this work, we present a novel device that allow a direct communication that uses a signals from surface EMG to control a mobile application that allows the user with cerebral palsy to choose simple pictograms into a tablet through one muscle movement.
Methodology: The first stage consist an integrate instrument amplification and series of circuits that allow us to filter the signal in a range of 20 to 500 Hz, this stage is supplied by a 9 volt battery. In the stage of processing the signal, it an ADC included in a programed microcontroller. Each electrical pulse sends a command by serial communication to the mobile application. The application contains a bank of pictograms organized into the following categories: social, people, verbs, things, descriptive, places and micellanious. Each of the categories mentioned above is represented by basic colors that is used internationally. The developed application envioroment used is Ionic Framewok B4. This tool allows to create application on multiple plataforms (iOS, native Android, desktop and web as a progressive application) that can be updated and implemented with the server built into the cloud, focuses on the user experience with the interface and allows the user to navigate using the command received by serial communication, this system adapts to the cognitive abilities of the user, delimiting the number of words or phrases known by the user, as well as their mobility, since for its use It is only necessary to move a muscle voluntarily.
Results: We demonstrate the use of this device with 3 children with medical diagnostic of spastic cerebral palsy. We observe that users feels independence to communicate, which significantly improves their way of interacting with people and their quality of life.

Disclosures: G. Lopez-Armas: None. **J. Margain-Moreno:** None. **A. Arenas-Perez:** None. **Y. Nava-Razo:** None. **D. González-Morales:** None.

Poster

669. Brain-Computer Interface: EMG

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 669.09/M4

Topic: E.09. Motor Neurons and Muscle

Support: NIH R01 NS072342

Title: Development of a wearable sensor array for performing high-density electromyography in ambulatory subjects

Authors: *C. N. SCHOENEWALD[1], J. E. TING[2], D. SARMA[1], D. J. WEBER[3];
[1]Physical Med. and Rehabil., [2]Bioengineerng, [3]Bioengineering, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Peripheral neuropathy (PN) and diabetic polyneuropathy (DPN) are examples of neurological complications which cause sensory and motor fiber impairments, as well as pain, often localized in the lower-limbs. Diagnosing early stage muscle pathophysiology in conditions such as these is routinely completed through surface electromyography (sEMG). While traditional bipolar sEMG provides limited coverage of muscle activity, a high-density array of electrodes, specifically designed to align with muscle fibers, can measure and map myoelectric signals propagating throughout the entirety of a muscle. Furthermore, recording with a high-density array allows for decomposition of the composite activity into signals from individual motor units. Untethered, high-density arrays of sensors for measuring volitional and stimulation-evoked muscle activity across an entire leg have the potential to provide novel insights into the post-impairment functional recruitment of muscles during ambulation. As a step in the development of a wearable tool, preliminary studies were performed in able-bodied subjects during cued ankle movements with a prototype 32-channel high-density myoelectric array (HDMA), oriented over the medial and lateral gastrocnemius muscles. To obtain ideal interelectrode distances (IEDs), physiological features such as density and direction of muscle fibers, as well as surface area and depth of muscles were analyzed. Myoelectric features such as root-mean-square, an indicator of the amplitude of activity, and the power spectral density of the signal, a representation of the frequency content, were also considered. An assessment of the similarity in features across electrode pairs in the array showed a decrease in high correlation values at a horizontal IED of 40mm and a vertical IED of 15 mm. These were determined to be maximal spacing for collection over the subset of muscles in the calf region. Wearable HDMAs may offer new insights into the the myoelectric dynamics and spatiotemporal features of musculoskeletal control.

Disclosures: C.N. Schoenewald: None. **J.E. Ting:** None. **D. Sarma:** None. **D.J. Weber:** None.

Poster

669. Brain-Computer Interface: EMG

Location: Hall A

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Program #/Poster #: 669.10/M5

Topic: E.09. Motor Neurons and Muscle

Support: Undergraduate Research Fellowship, The University of Texas at Austin

Title: Neuromuscular fatigue and sex differences in patellofemoral joint control

Authors: *Z. WANG[1], A. CHEN[2], A. JOHNSON[3], L. GRIFFIN[1];
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Abstract: Patellofemoral pain (PFP) is one of the most common joint disorders, inflicting about one-quarter of Americans. The incidence of PFP is several times higher in females than in males. The vastus medialis oblique (VMO) and vastus lateralis (VL) are important medial and lateral patella stabilizers, while the VMO, vastus medialis longus (VML) and VL are synergists for leg extension. There are neuromuscular control imbalances among the VL, VML, and VMO in individuals with PFP. However, differences in neuromuscular control of the patella between the sexes have not been clearly elucidated. In addition, muscle fatigability can differ across muscles and sex. This, also, has not been investigated for control of the patella. The goal of this study is to investigate the impact of sex and neuromuscular fatigue on VL, VML and VMO activity during a sustained fatiguing 20% maximal voluntary isometric contraction (MVIC). All fatigue tasks were quarterly staged into 1^{st}, 2^{nd}, 3^{rd}, and 4^{th} fatigue phases. Surface EMG of the VL, VML, and VMO was recorded. Peaks of VMO-VL and VMO-VML EMG cross-correlation and peak EMG RMS amplitudes of each muscle (normalized to MVIC amplitudes) during the four phases were calculated. With sexes pooled, a repeated-measures ANOVA revealed that both VMO-VL and VMO-VML cross-correlation peaks increased with fatigue ($p<0.05$). Thus, fatigue causes an increase in common drives to all three muscles. When grouped by sex, the VMO-VML cross-correlation peaks increased to a greater degree with fatigue in males than in females (at 3^{rd} and 4^{th} fatigue phases, $p<0.05$). EMG RMS amplitudes of all three muscles also increased with fatigue ($p<0.05$). However, across all 4 fatigue phases, normalized VMO EMG RMS amplitudes were lower in females than in males (at 4^{th} phases, $p<0.05$), and VL EMG RMS amplitudes were higher in females than in males (at 1- 4^{th} phases, $p<0.05$). This demonstrates that healthy females may generate greater relative lateral pull on the patella than healthy males, which could cause patellar mal-tracking. Additionally, females displayed a lower correlation in VMO-VML medial synergistic activity during fatigue which could also lead to destabilization of the patella and PFP. This study was the first to reveal that sex-differences in neuromuscular control of the patella are exacerbated by neuromuscular fatigue.

Disclosures: Z. Wang: None. **A. Chen:** None. **A. Johnson:** None. **L. Griffin:** None.

Poster

669. Brain-Computer Interface: EMG

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Program #/Poster #: 669.11/M6

Topic: E.09. Motor Neurons and Muscle

Support: NIH Grant 1R01NS111982-01

Title: Spatio-temporal organization of mutual information between high-gamma neural envelope and muscle activity

Authors: *W. LIANG, V. PAPADOURAKIS, N. HATSOPOULOS;
Univ. of Chicago, Chicago, IL

Abstract: High gamma band amplitude of local field potential (LFP) in the primary motor cortex (M1) is known to modulate during movement [1], but it is unclear whether there is any spatio-temporal structuring in this modulation. This is an important issue because the relationship between physical layout on the cortical sheet and temporal organization of information could inform us about cortical information processing as well as provide mechanistic insights regarding energy saving with predominant local connections. To explore this question, we collected neural signals from 128 electrodes in M1 as well as electromyography (EMG) from 13 muscles of the shoulder, elbow, and hand, while a rhesus macaque performed 8-direction reaches constrained by a 2D exoskeletal robot. We computed the Hilbert envelope of the LFP between 100Hz and 200Hz; bandpass filtered EMG between 20 to 1000Hz followed by rectification and smoothing. Then we discretized the signals into (roughly) equal-occurrence bins for single variables, and computed mutual information between each EMG at a particular time point with each neural envelope independently at various leads and lags, spanning from -600 ms to 400ms relative to muscle activity. Finally we obtained a 3-way tensor (i.e. 3D array, electrodes*time lead/lag*muscles) of mutual information. To understand its potential low-dimensional structure, we performed CANDECOMP/PARAFAC (canonical decomposition/ parallel factors, CP) decomposition using alternating least squares [2], which approximates the tensor as a sum of outer products (i.e. factors) of 3 vectors (one for each dimension). We found that 3 factors could capture 77.8% of total variance. Information peaked with a short lead of 20ms for two major factors; and major hand muscles or wrist muscles each share spatio-temporal dynamics among themselves. We further rearranged the electrode vector into 2D cortical space and observed significant spatial gradients pointing towards the central sulcus. The lateral caudal M1 seems particularly informative, which is especially so for the extensor digitorum muscle we recorded from; coincidentally microstimulations at these locations caused hand movement in our previous somatotopic mapping. We will also explore short temporal trajectories and small groups of electrodes to expand the current single time/location analyses.

Disclosures: W. Liang: None. **V. Papadourakis:** None. **N. Hatsopoulos:** None.

Poster

669. Brain-Computer Interface: EMG

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 669.12/M7

Topic: E.09. Motor Neurons and Muscle

Title: Improving the repeatability of MUNIX using multi-channel surface electromyography

Authors: *Y. CAO[1], C. ZHANG[2], F. GAO[1], Y. ZHANG[2];
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Abstract: Motor Unit Number Index (MUNIX) is a neurological technique that provides a susceptive biomarker for monitoring innervation conditions in patients with neurodegenerative diseases. A satisfactory repeatability is essential for the clinical interpretation of MUNIX results. This study represents the first effort to evaluate the effect of channel number on the repeatability of MUNIX.
Five healthy subjects (27±2 years, one female) participated in this study. 128 channels of high-density surface electromyography (EMG) signals were recorded from the biceps brachii muscles of the dominate arms. Participants were instructed to perform isometric voluntary contractions at 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80% and 100% of maximal voluntary contraction. Multi-channel MUNIX is calculated by the weighted sum of single-channel MUNIX of all selected channels, with weight determined by the channel-specific CMAP amplitude. Trial-to-trial repeatability was estimated by the coefficient of variation (CV) of MUNIX from three experiment trials. A channel number of 1, 2, 4, 8, 16, 32, 64 and 128 were selected to assess its effect on the repeatability of MUNIX.
A significant lower trial-to-trial CV was observed when two or more EMG channels were included, compared to the CV of single-channel MUNIX. Concretely, CV of 2.9%, 2.6%, 2.3%, 2.3%, 2.3%, 2.1%, 2.0% and 1.8% was found for 1, 2, 4, 8, 16, 32, 64 and 128 channel MUNIX results, respectively.
Our results have demonstrated that increasing the number of channels can be an effective method to improve the repeatability of MUNIX. Additive myoelectric information is expected to provide a more comprehensive sampling of the motor unit information and further benefit MUNIX repeatability. However, the proposed multi-channel MUNIX method will complicate the experiment procedure and analysis when more channels are included, and it remains a trade-off between results consistency and evaluation complexity.

Disclosures: Y. Cao: None. **C. Zhang:** None. **F. Gao:** None. **Y. Zhang:** None.

Poster

669. Brain-Computer Interface: EMG

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 669.13/M8

Topic: E.09. Motor Neurons and Muscle

Support: JSPS KAKENHI 19K19827

Title: Facilitation from the anterior and middle parts of the deltoid to biceps brachii motoneurons in humans

Authors: *T. YOSHIMOTO, M. NITO, M. JIMENJI, W. HASHIZUME, A. NAITO;
Dept. of Anat. and Structural Sci., Yamagata Univ., Yamagata city, Japan

Abstract: Effects of low-threshold afferents from the anterior (DA), middle (DM) and posterior parts of the deltoid muscle (DP) to biceps brachii muscle (BB) motoneurons were studied in 7 healthy human subjects using a post-stimulus time-histogram (PSTH) and electromyogram-averaging (EMG-A) methods. As conditioning stimulation, electrical rectangular pulses (1.0 ms duration) were delivered to the axillary nerve branch innervating DA (DA nerve), DM (DM nerve) and DP (DP nerve) with the intensity below the motor threshold. In the PSTH study, motor unit firings of BB were recorded with a pair of needle electrodes. The stimulation to the DA and DM nerves induced a peak (facilitation) in 25/39 and 28/47 BB motor units, respectively. The remaining respective 14 and 19 received no effects by the stimulation. The central synaptic delay of the facilitation from the DA and DM nerves was 0.2±0.3 (mean ± S.D. ,n=8) and 0.1±0.1 (n=8) ms longer than that of the homonymous BB facilitation, respectively. In the EMG-A study, the stimulation to the DA and DM nerves induced a peak (facilitation) in rectified and averaged EMGs of BB recorded with bipolar surface electrodes. The facilitation from the DA and DM nerves diminished by tonic vibration stimuli (TVS) to the DA and DM muscle bellies, respectively, and recovered 30 to 40 minutes after removal of TVS. In both the PSTH and EMG-A studies, such facilitation was never provoked by cutaneous electrical stimulation. The conditioning stimulation to the DP nerve induced no effect. These findings suggest that facilitation from DA and DM to BB motoneurons exists in humans. The facilitation should be mediated by group Ia afferents though a monosynaptic path in the spinal cord.

Disclosures: T. Yoshimoto: None. **M. Nito:** None. **M. Jimenji:** None. **W. Hashizume:** None. **A. Naito:** None.

Poster

669. Brain-Computer Interface: EMG

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 669.14/M9

Topic: E.09. Motor Neurons and Muscle

Support: NIH R01 NS072342

Title: A wearable neural interface for detecting and decoding spared motor units in a person with tetraplegia

Authors: *J. TING[1], A. DEL VECCHIO[3], D. FRIEDENBERG[4], M. F. LIU[1], C. SCHOENEWALD[2], D. SARMA[2], J. L. COLLINGER[1,2,6], S. COLACHIS, IV[5], G. SHARMA[5], D. FARINA[3], D. J. WEBER[1,2];
[1]Bioengineering, [2]Physical Med. and Rehabil., Univ. of Pittsburgh, Pittsburgh, PA;

[3]Bioengineering, Imperial Col. London, London, United Kingdom; [4]Advanced Analytics Group, [5]Med. Devices and Neuromodulation Group, Battelle Mem. Inst., Columbus, OH; [6]VA Pittsburgh Hlth. Syst., Dept. of Veterans Affairs, Pittsburgh, PA

Abstract: We have found that discriminable myoelectric activity can be detected and decoded from the forearm of a person with chronic tetraplegia (C5 motor/C6 sensory American Spinal Injury Association Impairment Scale B spinal cord injury). Residual myoelectric activity after neurological injury may provide a robust control signal for neuroprosthetics and assistive devices. Electromyographic (EMG) activity was measured using a wearable sleeve containing 150 electrodes in a high-density EMG array covering the surface area of the forearm as the participant attempted voluntary movements, including flexion/extension of the fingers, hand open/close, flexion/extension and pronation/supination of the wrist, and flexion/extension of the elbow. The participant had normal strength of the elbow flexors and was able to extend his wrist fully with gravity removed but not against gravity with resistance. He had no visible movement of the elbow extensors, wrist and finger flexors, or finger abductors, despite producing low myoelectric activity. Individual finger flexion/extension movements were classified using multinomial logistic regression. The accuracy of each decoded movement was calculated as the proportion of samples classified correctly out of all samples. Thumb finger trials were classified with the highest accuracy (88%), followed by middle (76%), index (67%), pinky (65%), and, lastly, ring (33%). A one-sided T-test with alpha 0.05 was performed and showed that classification accuracies were significantly better than chance ($p=0.0037$). While accurate decoding of movement intent is essential for neuroprosthetic control, an analysis of signals generated by spared motor units can also provide a representation of the single unit spiking output of motor neurons in the spinal cord. Therefore, filtered EMG signals were decomposed into constituent trains of motor unit action potentials and waveforms were extracted for each channel. The activity of more than 30 motor neurons were identified, active specifically during pronation/supination of the wrist (4 units), flexion/extension of the elbow joint (7 units), and attempted movements of individual fingers (1-5 units). Additionally, a neural connectivity analysis was performed based on the power of the common oscillations of the identified motor neurons in the delta, alpha, and beta bands, showing clear common synaptic inputs. This neural interface technology has the potential to not only provide a non-invasive control strategy for neuroprosthetics but also may serve as a tool for studying the reorganization and recovery of spinal networks after neurological injury, such as stroke and spinal cord injury.

Disclosures: J. Ting: None. **A. Del Vecchio:** None. **D. Friedenberg:** None. **M.F. Liu:** None. **C. Schoenewald:** None. **D. Sarma:** None. **J.L. Collinger:** None. **S. Colachis:** None. **G. Sharma:** None. **D. Farina:** None. **D.J. Weber:** F. Consulting Fees (e.g., advisory boards); Battelle Memorial Institute.

Poster

669. Brain-Computer Interface: EMG

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 669.15/M10

Topic: E.09. Motor Neurons and Muscle

Title: Wavelet-based analysis of plantar flexor muscle recruitment strategies while hopping at different frequencies

Authors: *H. KIM, K. KIPP;
Physical Therapy, Marquette Univ., Milwaukee, WI

Abstract: Vertical hopping provides a simple model to study the function of plantar flexor muscles during dynamic activities, such as those encountered in sports. Given that chronic musculoskeletal injuries (e.g. Achilles tendinosis) are prevalent in sports that require repeated high-effort dynamic activities (e.g. basketball), knowledge about muscle activation strategies may provide insight into the neuromuscular demands and may inform injury prevention strategies. Using wavelet-based intensity analysis may help quantify muscle activation strategies and motor recruitment patterns. Therefore, the purpose of this study was to identify changes in recruitment strategies of plantar flexor muscles during double limb vertical hopping at different frequencies. We hypothesized that the intensity of soleus (SL) and medial gastrocnemius (MG) activation across all wavelets would increase as hopping frequency decreased (i.e., hopping height increased). Ten collegiate athletes (5 males, 5 females; Height: 177.5±8.4 m; Mass: 74.1±10.3 kg) performed double limb vertical hopping at three frequencies (slow: 2 Hz; medium: 2.2 Hz; fast: 2.4 Hz) in random order. Force plate and electromyography (EMG) were used to collect ground reaction force (GRF) and muscle activation data. The EMG data were analyzed during the ground contact phase. Wavelet intensity analysis was used to analyze intensity of muscle activation in the time-frequency domain. Thirteen non-linearly scaled wavelets with center frequencies (Fc) between 4-361 Hz were used. The total intensity of each wavelet was calculated by summing time-series intensity from each wavelet. The intensity of the wavelet with Fc of 4 Hz was excluded because of noise. The intensity of each wavelet at the different hopping frequencies were compared with Kruskal-Wallis and Dunn's post-hoc tests (alpha = 0.05). The Kruskal-Wallis test revealed that for the SL, wavelet intensities with low Fc (12, 23, 59 Hz) differed significantly across hopping frequencies, while none of the wavelet intensities from the MG differed. The post-hoc tests for the SL showed that the intensities of wavelets with Fc of 12, 23, 59 Hz increased by approximately 142% ($p<0.001$), 187% ($p<0.01$), and 163% ($p<0.05$), respectively. Inconsistent with our hypothesis, the results indicated that the intensity of SL activation did not increase across all wavelets. Moreover, the increase in SL recruitment occurred at lower wavelet frequencies, which may indicate that as the hopping speed decreased

(hopping height was increased) the activation of slow motor units increased, while GM recruitment did not differ between hopping frequencies.

Disclosures: H. Kim: None. **K. Kipp:** None.

Poster

669. Brain-Computer Interface: EMG

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 669.16/M11

Topic: E.09. Motor Neurons and Muscle

Title: Decoding of motor unit firing behavior across postures during isolated finger extension

Authors: *N. RUBIN[1], H. HUANG[1], X. HU[2], C. DAI[3], Y. ZHENG[2];
[1]NC State Univ., Raleigh, NC; [2]UNC Chapel Hill, Chapel Hill, NC; [3]Univ. of North Carolina at Chapel Hill, Chapel Hill, NC

Abstract: In recent decades decomposing surface EMG signals into individual motor unit firings has developed as a promising method to characterize firing patterns in a noninvasive manner. However, decompositions are often applied to signals acquired only in one postural configuration. The motor units recorded within a surface electrode's pickup range may be different due to the mechanical changes both electrodes and musculature would undergo across postures in a realistic setting. To investigate the robustness of decomposition's ability to identify the same motor units across postures, we recruited eight able-bodied subjects who performed isometric extensions of individual finger digits in three postural configurations of the wrist (pronated, neutral, supinated). Subjects followed a force trajectory varying between 0-50% of their maximum voluntary contraction while high-density EMG simultaneously recorded muscular activity of the extensor digitorum communis. Results indicate decompositions from EMG recorded in a neutral posture only identify a subset (mean < 40%) of units decomposed in recorded signals from other postures, indicating the method may not be robust to shifts in an electrode's pickup range. Of motor units identified in a given posture, we consistently observe a preference in firing rate between postures at the same force level. This coincides with prior work suggesting a coupling of a motor unit's firing to the mechanical effectiveness of innervated muscle fibers in order to maximize efficiency of an individual's overall neural drive.

Disclosures: N. Rubin: None. **H. Huang:** None. **X. Hu:** None. **C. Dai:** None. **Y. Zheng:** None.

Poster

669. Brain-Computer Interface: EMG

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 669.17/M12

Topic: E.05. Brain-Machine Interface

Title: Implantable multichannel wireless recording with support for custom electrode configurations

Authors: *J. C. LANDES, B. CROFTS, S. HIATT, D. MCDONNALL, A. M. WILDER; Ripple Neuro, Salt Lake City, UT

Abstract: Most electrophysiology experiments utilize neural recording devices that transmit data via percutaneous electronics. Percutaneous connections prevent the skin from healing fully and present a constant danger of infections that can track down the electrodes and be difficult to treat. Early failure of these experiments substantially limits the viability of long-term animal studies; thus, there is a need for an implantable recording device that eliminates percutaneous connections at an affordable cost. We have developed a low-cost inductively powered implantable device for recording multiple independent channels of EMG or LFP data. The recorded data is transmitted wirelessly to an external transceiver in real-time. The present design records up to 32 single referenced signals with 12-bit resolution at 2000 samples per second. Exposed solder pads allow for the attachment of custom electrodes through a resealable interface for multi-month animal electrophysiology experiments. The implant consists of a recording ASIC (application-specific integrated circuit) to amplify, filter, and digitize biopotential signals inside an electronics package that is inductively powered and transmits high-bandwidth data via infrared (IR) telemetry. The implant is potted in medical grade epoxy and can easily be attached to bipolar epimysial electrodes, ECoG grids, microwires, or custom electrodes. The implanted device has a footprint of 23 mm x 32 mm x 5 mm, which is comparable to other long-term recording devices implanted in non-human primates. Sensors are included for detecting system failures associated with water ingress or overheating. An external transceiver provides power and data transfer at distances up to 14 mm implant depth and alignment offsets of up to 10 mm and ±30°. The implant communicates with existing Ripple Grapevine Neural Interface systems through the external transceiver for data acquisition, and an additional magnetic coupling component allows for fast and robust alignment of the transceiver and implant in freely behaving animals. Three prototype implants with EMG electrodes consisting of stainless steel, helically-coiled leads in silicone tubes, have surpassed the 1-year mark in accelerated lifetime soak testing in an elevated temperature saline bath. Implants have been and continue to be tested on wireless communication and neural recording capability. Additional support for high frequency sampling (30,000 samples per second) will be implemented in future iterations of the implant making it

suitable for recording single-unit activity from microelectrodes in addition to EMG and field potentials.

Disclosures: **J.C. Landes:** A. Employment/Salary (full or part-time):; Ripple Neuro. **B. Crofts:** A. Employment/Salary (full or part-time):; Ripple Neuro. **A.M. Wilder:** A. Employment/Salary (full or part-time):; Ripple Neuro. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ripple Neuro. **S. Hiatt:** A. Employment/Salary (full or part-time):; Ripple Neuro. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ripple Neuro. **D. McDonnall:** A. Employment/Salary (full or part-time):; Ripple Neuro. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ripple Neuro.

Poster

669. Brain-Computer Interface: EMG

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 669.18/M13

Topic: E.05. Brain-Machine Interface

Support: NSF Grant CNS 1329829
USAMRAA W81XWH-16-1-0722

Title: Decoding hand motion intent using novel ultrasound imaging of the forearm muscles

Authors: B. MUKHERJEE[1], A. DHAWAN[1], S. PATWARDHAN[1], W. M. JOINER[2], ***S. SIKDAR**[1];
[1]Bioengineering, George Mason Univ., Fairfax, VA; [2]Dept. of Neurobiology, Physiol. and Behavior, Univ. of California, Davis, Davis, CA

Abstract: The vast majority of all trauma-related amputations in the United States involve the upper limbs. The development of multiarticulated myoelectric prosthetic hands in recent years have the potential to improve the quality of life and function of individuals with limb loss, but the ability to control these devices continues to be limited. A significant number of individuals who receive an upper extremity myoelectric prosthesis eventually abandon use of the system, primarily because of their limited functionality. Therefore, there continues to be an unmet need for an intuitive control approach that enable many different movements/abilities.We propose a paradigm shift in the field of prosthetic control using ultrasound imaging for sensing muscle deformation associated with volitional motor intent. This method is called sonomyography. We hypothesized that this method would enable more intuitive movement decoding, as ultrasound can resolve signals from deep within the tissue, and provides a rich signal source for decoding

intent. We investigated the use of sonomyography to decode volitional motor intent in 7 subjects (6 men and one woman) with upper limb loss (age range: 30-68 years, years since amputation: 1-50 years). Five subjects had unilateral traumatic amputation at a transradial level, one subject had a congenital transradial limb loss, while another subject had wrist disarticulation and transhumeral amputation. All subjects were tested in a virtual environment where they were asked to volitionally perform different imagined movements while their forearm muscles were imaged in cross section using a commercial ultrasound transducer. The image sequences were analyzed using a supervised learning algorithm to identify patterns of muscle deformation corresponding to the different performed movements. Our results show that subjects with traumatic limb loss achieved classification accuracies of 96.8-100% for for between 4 to 11 distinct movements within an hour of training. The subject with congenital limb loss had classification accuracy of 85% for 5 distinct movements. This is a significant improvement over myoelectric control methods, including state-of-the-art pattern recognition, which typically takes 10 weeks of intensive training to achieve similar motion discriminability. We attribute these improvements to the fact that sensing mechanical muscle deformation enables the control signal to be congruent to the user's innate residual proprioception and phantom limb schema, making our paradigm intuitive and adaptable.

Disclosures: **S. Sikdar:** A. Employment/Salary (full or part-time):; George Mason University. **B. Mukherjee:** A. Employment/Salary (full or part-time):; George Mason University. **A. Dhawan:** A. Employment/Salary (full or part-time):; George Mason University. **S. Patwardhan:** A. Employment/Salary (full or part-time):; George Mason University. **W.M. Joiner:** None.

Poster

669. Brain-Computer Interface: EMG

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 669.19/M14

Topic: E.05. Brain-Machine Interface

Support: NSF Grant 1329829
United States Department of Defense, Award Number: W81XWH-16-1-0722

Title: Using novel imaging techniques to examine selective control of the residual musculature of upper-extremity amputees

Authors: *S. PATWARDHAN[1], A. DHAWAN[2], B. MUKHERJEE[1], W. M. JOINER[4], S. SIKDAR[3];
[1]Bioengineering Dept., [2]Computer Sci. Dept., [3]Bioengineering, George Mason Univ., Fairfax, VA; [4]Dept. of Neurobiology, Physiol. and Behavior, Univ. of California, Davis, Davis, CA

Abstract: Amputees often cite difficulty of use as a key factor for abandoning their prosthesis, creating a pressing need for an improved control methodology. A major challenge of using traditional surface electromyography electrodes has been the difficulty in achieving intuitive and robust proportional control of multiple degrees of freedom. To address this problem, we used a control method (sonomyography) that overcomes several limitations of myoelectric control. In sonomyography, muscle mechanical deformations are sensed using ultrasound, as compared to electrical activation, and therefore the resulting control signals can directly control the position of the end effector, making it more congruent with the remaining proprioception within the residual limb. Ultrasound imaging can non-invasively resolve individual muscles and detect dynamic activity within different functional compartments. We tested sonomyography with 5 upper-extremity amputees (4 traumatic and 1 congenital) and 5 able-bodied subjects. In the task, dynamic ultrasound images measured contracting muscle deformations during actual motions of the limb, or approximated motions in the residuum. This signal was used to move a screen cursor to a series of targets, and hold the cursor at that location within a quantization bound. Performance metrics consisted of position error (the mean error between the cursor and the target position), stability error (the standard deviation of the cursor position from the target position), task completion rate and movement time. Both traumatic and congenital amputee subjects with no prior experience of using a sonomyography-based interface were able to demonstrate fine graded control of an end-effector controlled by muscle activation patterns in the remaining forearm with position and stability errors being below 3.5% and 12.1%, respectively. Consistent with Fitts's law, movement time was significantly correlated and increased with task difficulty for all participants ($R > 0.85$). Finally, the average task completion rate was higher than 94%. Our results demonstrate the potential of using sonomyographic signals for intuitive dexterous control of multiarticulated prostheses with potential clinical applications in fundamental investigations of motor control and biomechanics.

Disclosures: S. Patwardhan: None. **A. Dhawan:** None. **B. Mukherjee:** None. **W.M. Joiner:** None. **S. Sikdar:** None.

Poster

670. Sensorimotor Control, Movements, and Motor Cortex

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 670.01/M15

Topic: E.05. Brain-Machine Interface

Support: NIH Grant R01 NS053603

Title: Probing the relationship between motor cortex and upper limb muscles during spontaneous natural movements

Authors: *X. MA[1], K. L. BODKIN[1], A. FARSHCHIAN[1], E. ALTAN[1], M. E. FRACOL[2], L. E. JANES[2], F. A. MUSSA-IVALDI[1,3,4], L. E. MILLER[1,3,4];
[1]Dept. of Physiol., [2]Dept. of Surgery, [3]Dept. of Biomed. Engin., [4]Dept. of Physical Med. and Rehabil., Northwestern Univ., Chicago, IL

Abstract: Primary motor cortex (M1) needs to generate control signals to synergistically activate many combinations of muscles in order to perform the diverse movements of daily living. Most existing sensorimotor studies have investigated the mapping from M1 activity to muscles by training monkeys to perform a few instructed movements in highly restricted conditions. Motivated by the demand of extending those in-lab studies to a wider realm, here we propose to explore the interaction between M1 and muscles during more natural movements of unrestrained monkeys. We implanted an electrode array in hand M1 and intramuscular electromyographic (EMG) leads in the arm and hand of one monkey. We simultaneously recorded these signals wirelessly while the monkey was in a plastic telemetry cage in which it could perform various free-form hand movements. We performed temporal clustering of the EMG signals to categorize the monkey's various movements. We divided the entire dataset into short time bins and projected the EMG from selected muscles within each time bin to a low dimensional space using nonlinear methods. We found that low-dimensional projections of time bins with similar EMG patterns were adjacent. This allowed us to use conventional clustering algorithms to sort hours of continuous recordings into identified categories of movements that had similar muscle activity patterns. We then investigated the consistency of the relationship between M1 and muscle activity across these movement categories. We built a variety of linear and nonlinear decoders to predict EMG from M1 recordings. We found that recurrent neural network (RNN) based decoders could achieve EMG predictions as good as those for in-lab tasks when training and testing with data from the same category of movements. RNNs consistently outperformed linear Wiener filter-based decoders. However, such single-category decoders, whether linear or nonlinear, could not make accurate EMG predictions across categories. We also trained the decoders with samples from a combination of categories, which allowed RNN decoders to yield accurate EMG predictions for all categories included in the training set, but still not on held-out categories. Linear decoders remained inaccurate even with robust training data. From these results we posit that there could be a number of nonlinear components involved in the interaction between M1 and muscles for natural movements, for which the motor system needs to produce a diversity of muscle activity patterns. Categorizing these unstructured movements has enabled us to compare different M1 and EMG activity patterns in an organized way, and therefore probe those components quantitatively.

Disclosures: X. Ma: None. **K.L. Bodkin:** None. **A. Farshchian:** None. **E. Altan:** None. **M.E. Fracol:** None. **L.E. Janes:** None. **F.A. Mussa-Ivaldi:** None. **L.E. Miller:** None.

Poster

670. Sensorimotor Control, Movements, and Motor Cortex

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 670.02/M16

Topic: E.05. Brain-Machine Interface

Support: NIH Grant Grant 5R01NS053603-12

Title: Development of a comprehensive brain-computer interface decoder of natural movements

Authors: *A. FARSHCHIAN, X. MA, E. ALTAN, K. BODKIN, M. E. FRACOL, L. E. JANES, E. PERREAULT, S. SOLLA, F. MUSSA-IVALDI, L. MILLER;
Northwestern Univ., Chicago, IL

Abstract: Brain-computer interfaces (BCIs) have emerged as a clinically viable solution to help survivors of spinal cord injury operate assistive devices or to restore movement after paralysis. A central component of a BCI is a decoder that predicts movement to provide kinematic control of a computer cursor or a robotic arm, or to produce artificially generated muscle activity to restore movement of a paralyzed arm through functional electrical stimulation. Most existing BCI decoders are built for simple, stereotyped tasks performed in laboratory settings, and fail to operate across the wide range of activities of daily living. To build a more general decoder, we have developed a wireless BCI that simultaneously records motor cortical neural activity and the activity of multiple arm muscles throughout a range of natural, unconstrained behaviors (foraging, feeding, and grooming) while the monkey is in its cage. We show that current decoding techniques fall short of generalizing across these tasks and of providing reliable muscle activity predictions, probably due to 1) the performance of multiple tasks with higher variability in each execution, 2) periods of time when substantial cortical activity is present with no muscle activity, and 3) inherently noisier wireless recordings in a cage. To compensate for these shortfalls, we are beginning to pursue recent techniques in the field of Natural Language Processing and Machine Translation to build a comprehensive decoder that works by mapping short sequences of neural activity onto similar sequences of muscle activity. In brief, we project each neural activity sequence onto multiple low-dimensional subspaces. In each subspace, we create shorter sequences (subsequences) through linear combinations of the projected sequences. Finally, we concatenate the subsequences to get a transformed sequence of neural activity that has the same length as the original sequence. We use this transformed sequence of neural activity as the input to an autoregressive network that predicts a sequence of muscle activity. This work is part of an ongoing effort to adapt Machine Learning (ML) techniques to characterize and decode neural activity. We have recently demonstrated that ML techniques for domain adaptation can be extended to successfully unveil the stable statistics of neural activity during stereotyped laboratory tasks. Here we propose an ML-based decoder designed to account for

short term features of neural dynamics. Accurate muscle predictions across the rich variety of observed cage behaviors would lead to a general BCI capable of sustained performance across a wide range of activities of daily living.

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Poster

670. Sensorimotor Control, Movements, and Motor Cortex

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 670.03/M17

Topic: E.05. Brain-Machine Interface

Support: NIH Grant R01 NS095251

Title: Reaction times in response to multi-electrode intracortical microstimulation are faster than to limb perturbations

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Abstract: Tetraplegic patients using brain-machine interfaces (BMIs) can now make visually-guided reaches with robotic arms. However, in addition to vision, restoring proprioceptive feedback to these patients will be critical, as evidenced by the movement deficiencies in patients with proprioceptive loss. Proprioception is critical in large part because it provides much faster feedback than vision. Intracortical microstimulation (ICMS), which can be used to elicit conscious percepts in monkeys and humans, is a promising approach. The reaction time (RT) in response to single-electrode stimulation, though, is typically slower than that to tactile and often even visual cues, implying that ICMS cannot provide fast enough feedback, making it unsuitable for restoring proprioception. Fortunately, for most sensory modalities, the RT decreases with increased stimulus intensity. Thus, it may be that stimulation intensities beyond what has previously been used will result in faster RTs. To test this, we compared the RT to ICMS applied through multi-electrode arrays in area 2 of somatosensory cortex to that of limb perturbations and visual cues in a simple RT paradigm. We found that the RT to single-electrode ICMS decreased with increased amplitude, frequency, and train length. For the highest single-electrode stimulation we tested routinely, 100μA at 330Hz, 78% of electrodes resulted in slower RTs than limb perturbations, with latencies similar to that of a visual cue. While increasing the stimulation amplitude beyond 100μA resulted in faster RTs, sustained stimulation at this level may cause damage to tissue surrounding the electrodes. Alternatively, by stimulating through multiple

electrodes (mICMS), a large amount of current can be injected while keeping that through each electrode at a safe level. We found that stimulation with greater than 480μA equally distributed over 16 electrodes produced RTs about 20ms faster than limb perturbations, roughly the conduction delay to cortex from the periphery. At constant total current, increasing the number of electrodes resulted in slower RTs, possibly because the current on some electrodes fell below an activation threshold. To determine if the distance between electrodes influences the mICMS RT, we stimulated through small groups of adjacent and non-adjacent electrodes. Adjacent electrodes resulted in slightly, but not significantly, slower RTs than non-adjacent electrodes. Together, these results suggest that it may be possible to use mICMS to provide fast feedback. Spatial-temporally patterned mICMS may be needed in future neuroprosthetics to convey useful somatosensory information.

Disclosures: J. Sombeck: None. **L.E. Miller:** None.

Poster

670. Sensorimotor Control, Movements, and Motor Cortex

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 670.04/M18

Topic: E.05. Brain-Machine Interface

Support: NIH Grant R01 NS053603

Title: Dimensionality of neural subspaces for the control of natural and stereotyped movements

Authors: *E. ALTAN[1], K. L. BODKIN[1], J. A. GALLEGO[2], A. FARSHCHIANSADEGH[1], X. MA[1], F. A. MUSSA-IVALDI[1], S. A. SOLLA[1], E. J. PERREAULT[1], L. E. MILLER[1]; [1]Northwestern Univ., Chicago, IL; [2]Ctr. De Automatica Y Robotica, Arganda Del Rey, Spain

Abstract: Activity of primary motor (M1) cortical neurons likely reflects the coordination observed in muscles across motor tasks, from simple movements to highly dexterous ones. Like synergistic muscle activity, population activity in M1 appears to be constrained to a low-dimensional subspace within the space of all possible patterns. This neural coordination can be quantified through the intrinsic dimensionality (ID) and covariance patterns of neural population activity. Here, we focused on the ID. Previous laboratory studies have shown that the ID was not only much smaller than the number of recorded neurons, but even smaller than the number of involved muscles. However, the relation between M1 activity during natural tasks that might be more relevant to the activities of daily living and that of the more common repetitive laboratory tasks remains unknown. Is the low ID of M1 a byproduct of constrained laboratory behaviors? If so, is the ID of M1 activity during unconstrained behaviors such as grooming, foraging, or feeding, higher than that of laboratory tasks? A reasonable expectation is that some natural behaviors, such as grabbing a bar with a power grasp, are simple and low-dimensional, whereas

others, like playing with toys, may be complex and high-dimensional. Here, we used a two-step approach to estimate the ID of recordings from the hand area of M1 as monkeys performed different motor tasks in the laboratory and while engaged in natural behaviors in their home cage. We first denoised the neural signals using a deep learning method that identifies common signals in two random, non-overlapping samples of the electrode channels recorded in each session. We then estimated the ID of the denoised neural signals using Fisher Separability Analysis. Surprisingly, we found that the IDs of neural recordings during natural behaviors ranged between 2 and 5 for randomly selected, one-minute lengths of data, comparable to those of laboratory tasks. The IDs associated with natural behaviors were smaller than those of some laboratory tasks (visually guided wrist flexion/extension movements) but larger than those of others (power grasp). An interpretation of this finding is that ID alone may not suffice to describe differences in neural population activity across behaviors, and that additional measures, such as covariance, may be necessary. Importantly, the low ID we observed across natural and laboratory tasks suggests that neural decoders for individual behaviors can operate on a low-dimensional subspace of the neural signals. It remains to be seen if it is possible to construct a general decoder that can operate across a range of subspaces, each associated with a specific behavior.

Disclosures: **E. Altan:** None. **K.L. Bodkin:** None. **J.A. Gallego:** None. **A. Farshchiansadegh:** None. **X. Ma:** None. **F.A. Mussa-Ivaldi:** None. **S.A. Solla:** None. **E.J. Perreault:** None. **L.E. Miller:** None.

Poster

670. Sensorimotor Control, Movements, and Motor Cortex

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Title: Uncovering de-noised EMG representations using deep learning models of muscle population dynamics

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Abstract: Coordinating the activity of groups of muscles is critical for motor function, and underlies diverse movements such as respiration, walking, reaching, and grasping. However, a major barrier to understanding how the brain coordinates muscle activation is that electromyographic (EMG) activity is noisy, making it difficult to interpret on a moment-to-moment basis. Furthermore, the standard approach to processing EMG (i.e., rectification and smoothing) treats temporal complexity in EMG signals as noise. Here, we developed a new method to "de-noise" EMG signals that are recorded simultaneously from multiple muscles. Our working model is that the coordinated activity of muscles during movement is the output of a dynamical system. Thus, by accurately modeling these underlying dynamics we might substantially de-noise EMG. To test this we used Latent Factor Analysis via Dynamical Systems (LFADS), a deep learning technique we previously developed to model the dynamics of neuronal population activity. LFADS uses artificial recurrent neural networks to uncover nonlinear dynamics from high-dimensional data in an unsupervised manner. Notably, the statistics of EMG are substantially different from neuronal population spiking activity, necessitating key modifications to the LFADS modeling architecture. We tested our model on intramuscular EMG recorded from 12-14 muscles from two paradigms: (1) rat hindlimb during locomotion and (2) monkey forearm during an isometric center-out wrist force task. When applied to the rat locomotion data, the model produced single-trial representations of muscle activity that improved joint angle and joint velocity decoding for eight different joints. Similarly, when applied to the monkey data, the single-trial representations from LFADS produced more accurate predictions of the force applied by the monkey to the manipulandum. Interestingly, the EMG was also substantially more predictable from simultaneously-recorded M1 population activity. Ultimately, our results suggest that modeling the dynamics of EMG recorded from multiple muscles uncovers more informative representations of muscle activation than traditional approaches, and may open new avenues to studying temporal coordination of individual muscles and their precise control through inputs from motor cortex.

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Poster

670. Sensorimotor Control, Movements, and Motor Cortex

Location: Hall A

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Program #/Poster #: 670.06/M20

Topic: E.05. Brain-Machine Interface

Support: 5 F31 NS106833-02
R01 NS095162

Title: Modeled muscle spindle primary afferents predict firing rates of cuneate nucleus neurons in the awake monkey

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Abstract: The cuneate nucleus (CN) is the first potential site for somatosensory transformations in the CNS. For simplicity, we previously modeled the activity of these neurons during reaching movements using the position and velocity of the hand, as is typically done for somatosensory cortical neurons. However, given their location only one or two synapses from the sensory afferents, models based on afferent receptor signals might be more appropriate. Muscle spindle responses to length change have a complex nonlinear relation to motion, including history dependence, which may significantly affect modeled CN activity. In this study, we predict the firing of CN neurons during reaching using simulated muscle spindle activity. We implanted three monkeys with Utah microelectrode arrays (MEA) in CN. We captured the kinematics of the arm using a custom motion tracking system while the monkeys performed a center-out reaching task with the ipsilateral limb. We did sensory mappings of the receptive fields (RFs) of CN neurons, tentatively identifying those that received muscle spindle inputs by a combination of passive arm movements, muscle palpation, vibration, and light brushing to reveal cutaneous fields. We used a previously published musculoskeletal model to compute the lengths of 39 muscles of the arm. We ran these muscle kinematics through existing models of the muscle spindle primary and secondary afferents to compute simulated firing rates of one representative muscle spindle per muscle. We fit Poisson generalized linear models (GLMs) relating the simulated spindle firing rates to the firing rate of individual CN neurons. These models performed better than extrinsic kinematic encoding models (including only the position, velocity, and acceleration of the hand). Furthermore by changing simulated gamma drive, we tested various hypotheses about its control, including fusimotor set and alpha-gamma coactivation hypotheses. Because movements included both actively generated and passively imposed conditions, we could test how these gamma-drive hypotheses generalized across conditions. This approach will not however, allow us to disentangle the effects of altered gamma drive from those due to descending input from sensorimotor cortex. In order to understand how proprioceptive information changes as it moves centrally, it is important to understand the behavior of the sensors in the periphery. By modeling muscle spindle afferents, we show that the firing at the level of CN is related more closely to the peripheral receptor signals than to muscle length change or hand movement.

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Poster

670. Sensorimotor Control, Movements, and Motor Cortex

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Topic: E.05. Brain-Machine Interface

Support: NIH Grant R01 NS095251

Title: Lateral connectivity may underlie cortical organization of proprioception

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Abstract: As in the visual system, proprioceptive signals must be projected from a high-dimensional peripheral representation - from skeletal muscles, tendons, joints, and skin receptors -- to a two-dimensional cortical sheet. However, despite the critical role of proprioception in movement, we know relatively little about this process compared to its analog in the visual system. To understand the neural principles by which peripheral proprioceptive afferent signals undergo this transformation from high- to low-dimensional spaces, we used a neural-network model of the proprioceptive afferent system based on variational auto encoders. The final latent layer of this network was designated as the simulated “cortical” layer, with Poisson neurons organized in a two-dimensional grid. The overall goal of the network was to reconstruct the simulated proprioceptive inputs to the network from the latent cortical layer which was subjected to lateral inhibition and Poisson-sampled spiking. We trained this network using simulated proprioceptive afferent signals generate from data collected from a monkey performing a planar reaching task. The network weights were found through several training epochs to find the optimal representation of the peripheral inputs. We found several emergent properties within this self-organizing map that reflect classical properties of S1 neurons. First, the modeled neurons exhibited cosine tuning to movement direction. The preferred directions (PDs) of the neurons were distributed across all directions, despite a more nonuniform distribution of PDs for the peripheral inputs themselves. As for actual S1 neurons, these PDs were biased toward and away from the body. At a less localized level, we found small “neighborhoods” of simulated neurons with similar PDs. This finding also reflects our earlier observation that neurons recorded from a given electrode are more likely to have similar PDs that those recorded on different electrodes. In all, these results demonstrate principles by which the proprioceptive system may represent

peripheral inputs in cortex. Local clustering of similarly tuned proprioceptive neurons could be advantageous for coordination of multi-joint feedback and postural control. In the brain, these local clusters may carry additional functional relevance, such as task-level feedback for different movement contexts. Beyond these questions of basic science, these findings may be important for efforts to restore somatosensory function through intracortical microstimulation, as the topography of proprioceptive cortex could greatly affect the ability to elicit naturalistic sensations.

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Poster

670. Sensorimotor Control, Movements, and Motor Cortex

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Center for Neurotechnology at the Univ. of Washington
Tianqiao and Chrissy Chen Brain-machine Interface Center at Caltech
NSF 1533589

Title: Closed-loop interface for inducing cortical plasticity in humans

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Abstract: Spike-timing-dependent plasticity promotion has been shown previously in *in vivo* experiments in animal studies. For example, spike-triggered stimulation of one brain site triggered from spikes recorded in another site can modify synaptic connections between the sites in monkeys. Here we present evidence of changes in neural activity that could reflect spike-timing-dependent plasticity promotion in human recordings. We stimulated primary somatosensory cortex (S1) at a fixed lag (20 ms) from spikes recorded from supramarginal gyrus (SMG) of a 35-year-old tetraplegic patient with Neuroport microelectrode arrays (Blackrock Microsystems). In a stimulation condition, with the patient at rest, stimulation was delivered over 15 minutes to eight channels in S1, selected to include the electrode with highest spike-spike correlation with SMG, and spacing the remaining seven to limit charge per phase per area. Pre-

and post-stimulation recordings (200 s) were compared to quantify changes in functional connectivity assessed by correlation measures. In a control condition, the same set of stimulation channels was used, but stimulation pulses were delivered randomly, at an average rate equal to that of the stimulation condition.
On average, 71.5 of 96 channels in S1 showed a significant decrease in firing rate correlation (Kruskal-Wallis test, $p<0.05$, corrected for false discovery rate) with the selected recording channel after stimulation (n=2), versus 3.3 channels for the control condition (n=3), showing significant difference between the two conditions (t-test, $p<0.05$). The number of channels with significant increase in spike correlation was not significantly different between two conditions (1.5 versus 8.7 channels). Furthermore, there was no significant difference in firing rate between control and stimulation conditions (t-test, $p<0.05$), including the selected recording channel. These results demonstrate the possibility of using spike-triggered stimulation for inducing cortical plasticity in humans. Future data collection will allow us to explore this effect in more detail with different parameters, such as the lag between spike and stimulation, and the channel pairs for stimulation and recording. For instance, we will examine if there are lags that produce increased activity rather than decrease in activity. In addition, different methods for quantifying connectivity will be examined.

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Poster

670. Sensorimotor Control, Movements, and Motor Cortex

Location: Hall A

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Topic: E.05. Brain-Machine Interface

Support: NIH BRAIN U01
T&C Chen Institute at Caltech
Kavli Nanoscience Institute at Caltech
DARPA HAPTIX

Title: Quantitative scanning electron microscopy analysis of intracortical microelectrode arrays after five years in human neocortex

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Abstract: Stable, sensitive electrodes are fundamental to the robust operation of brain-machine interfaces (BMI), devices which read out brain activity to control assistive devices and write feedback information back into the brain. The purpose of this work is to quantify failure modes of long-term implantation in the human cortex by using SEM to observe defects in the electrode metallization and insulation. We examined two microelectrode arrays, implanted in the cortex of a human tetraplegic research participant for five years, in a scanning electron microscope (SEM). These "Utah" microelectrode arrays (NeuroPort, Blackrock Microsystems, Salt Lake City, UT) were implanted in anterior intraparietal area (AIP) and Brodmann's area 5 (BA5). While implanted, both arrays showed similar recording trends, with initially high impedances, but then gradually decaying over the implant lifetime. Action potentials recorded from the two arrays could be variable across sessions and between arrays but the number of units was consistent on average over time. Five years after implant, the arrays were explanted intact and examined under SEM. We scored each electrode on a scale from 0 (poor quality) to 5 (high quality) for the condition of the platinum metallization at the electrode tip and the insulation along the electrode shaft. The AIP array scored 2.3 ± 1.0 (a.u., metallization) and 4.6 ± 0.7 (a.u., insulation) whereas the BA5 array scored 1.5 ± 1.3 (metallization) and 2.8 ± 1.3 (insulation), indicating that the BA5 array electrodes were in generally worse condition both in terms of the metallization and insulation. Perhaps due to this difference in conditions, metallization quality was a good predictor of electrode impedance (measured *in vivo* two months prior to explant) for the AIP array (linear regression; $p<0.05$) but not for the BA5 array. Insulation quality was not strongly predictive of impedance in either array. These findings begin to quantify the relationship between the physical condition of microelectrodes implanted in cortex and their capacity to record electrical activity. The data presented here are especially important as multi-year clinical trials of BMIs in human are becoming more common and could lead to improved manufacturing practices or novel electrode designs to improve long-term performance of BMIs.

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Poster

670. Sensorimotor Control, Movements, and Motor Cortex

Location: Hall A

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Program #/Poster #: 670.10/M24

Topic: E.05. Brain-Machine Interface

Support: DARPA HAPTIX N66001-15C-4017
NSF 1533649

NSF 0903715

Title: Improvement and quantitative analysis of tip metal stability for Utah slanted arrays in long-term clinical studies with a sensorimotor prosthesis

Authors: *L. RIETH[1], B. BAKER[2], R. SHARMA[2], R. B. CALDWELL[6], D. T. KLUGER[7], J. A. GEORGE[3], A. HARDING[4], D. J. WARREN[5];
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Abstract: Translation of penetrating multielectrode array (MEA) technologies into clinical use has been hampered by the difficulty in achieving long-term stable recording and stimulation performance. Performance degradation has been attributed to abiotic and biotic processes. This study quantitatively assesses degradation of Utah Slanted Electrode Arrays (USEAs) implanted in the peripheral nerves of human subjects for up to 17 months. The purpose of this work is to determine the abiotic failure mechanisms for these MEAs and the associated impact on impedance and performance, so that this knowledge can be leveraged to mitigate the degradation mechanisms. One such mitigation is electrode material innovation, and we show that recent advancements in this direction are promising based on accelerated stimulation stability test results.

A total of 7 USEAs were implanted in 3 subjects: HS1, HS2, and HS3; for 3, 14, and 17 months, respectively. After explantation, electrode condition was analyzed by SEM and scored based on evident damage: 1 (little), 2 (modest), 3 (significant), and 4 (severe). Mean and median damage values ranged 2.04 to 2.77, and 2 to 3 respectively, and statistically significant differences were observed between the electrode arrays for different subjects, and thus the associated differing indwelling times ($p=0.004$ between HS1 and HS2 arrays). HS3 arrays received much less stimulation that HS1 and HS2 arrays, but the degradation values (2.77, 2.63. 2.52) indicated worse degradation was observed. Prior results have also indicated there is not a correlation between stimulation doses up to 19 mC and the tip degradation. Statistical analysis of this data is in process, and is expected to further support that in-dwelling time best correlates with electrode degradation for the 7 USEAs studied here, as opposed to stimulation dose, electrode impedance, or location on array. Additional spatial statistical comparisons will be executed to identify patterns or associations between these electrode characteristics.

In addition, we used the stimulation-stability method developed within the lab to compare the stability of the current practice Blackrock metallization, which has already benefited from technology transfer from the HAPTIX program, to the current optimized Utah tip metallization. Preliminary results have suggested that the Utah metallization can more reliably tolerate a dose of 1 million biphasic pulses using 2.1 mA of stimulation current, representing 840 mC of injected charge.

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Poster

670. Sensorimotor Control, Movements, and Motor Cortex

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 670.11/M25

Topic: E.05. Brain-Machine Interface

Title: Neuroprosthetic control via cortical sequence generation

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Abstract: Several neuroprosthetic learning studies have shown that after an initial phase of exploration, spatiotemporal activity patterns that lead to desired outcomes are selected and consolidated. It is known that 'indirect' neurons, that do not directly control a neuroprosthetic effector, show a suppression of modulation depth across learning but can also demonstrate task related tuning. It is possible that these cells become incorporated into functional neuronal assemblies that help coordinate neurons that directly drive an effector- but it is not clear why this particular subset of neurons becomes involved, and how they may act to stabilize and reinforce output. Using chronic single and multi-photon calcium imaging, we created a Brain-Machine Interface (BMI) paradigm in which mice learned to perform a neuroprosthetic task using the coordinated activity of a small ensemble of neurons in sensorimotor cortex (L2/3), guided by auditory feedback (Clancy, 2014). This approach provides long-term access to hundreds of neurons, referenced to an easily quantified output layer of a few neuron's activity. We find that a subset of the local cortical population gradually converges to form highly reproducible, spatiotemporally organized sequences that precede and follow the activity of output neurons. Similar time-locked, repeatable sequences of neural activity are known to underlie many forms of memory and sensory guided behavior, from the tracking of behaviorally relevant variables to the planning and coordination of movements. Neuroprosthetic tasks may provide key insights as to how these patterns self-organize and refine in a case where the link between behavior and individual neuron activity is well defined. In this poster we examine the formation, structure and stability of these emergent, spatially organized network patterns.

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Poster

670. Sensorimotor Control, Movements, and Motor Cortex

Location: Hall A

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Program #/Poster #: 670.12/M26

Topic: E.05. Brain-Machine Interface

Support: U19 NS104649

Title: Isolating cell-type specific subpopulations of motor cortex neurons during neuroprosthetic learning

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Abstract: Projections from cortex to the striatum are governed by two different types of neurons, pyramidal tract (PT) and intratelencephalic (IT). These subpopulations of neurons differ in electrical properties, belong to different functional circuits and may be diversely involved in cognitive processes. However, it is still unclear how PTs and ITs may contribute to learning due to the immense complexity of cortical interconnections and the innate variability of natural behavior. In order to investigate the functional roles of these projecting neurons during learning, we labeled the different cortical subpopulations using retrograde labeling via viral infection and took advantage of a neuroprosthetic task that links directly the activity of neurons with the behavior of the animal. Mice learned to modulate the activity of either PT or IT labeled neurons to control a one-dimensional auditory cursor linked to a sucrose water reward. Here, we investigate PT and IT functional role during learning while monitoring large-scale neural dynamics surrounding the two distinct cortical cell types across multiple cortical layers.

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Poster

670. Sensorimotor Control, Movements, and Motor Cortex

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Topic: E.05. Brain-Machine Interface

Support: NESD Program (DARPA-BAA-16-09-NESD-FP-001)

Title: The sheep (Ovis aries) as a clinical translational model for intracortical microelectrodes

Authors: *I. N. MCNAMARA[1], M. STRAKA[2], M. HANNA[2], K. SAHASRABUDDHE[2], K. BOERGENS[2], R. J. EDGINGTON[2], Y. KONG[2], H. S. SOHAL[2], M. R. ANGLE[2];
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Abstract: Successful clinical translation of a medical device depends on the appropriate selection of the animal model used for preclinical testing. For intracortical electrodes used inapplications including brain machine interfaces, the choice has historically been non human primates (NHPs). These safety studies are often performed with concurrent testing of basic science experimental hypotheses and thus require extensive animal training on specific sensory or motor tasks before device implantation. For a device-oriented translational model that does not require training-based task performance, other preclinical models with similar structure and function to the human brain should be considered. Here we show the benefits of using sheep as an animal model for clinical translation.

The sheep brain is similar in anatomy to the human brain, especially in terms of sulci and gyri formation. Interestingly, the sheep brain is the neurosurgery model of choice for practicing procedures before deploying surgical techniques on human patients. Sheep have been used as a preclinical model for deep brain stimulation (Lentz L), a therapy for treating various neurological disorders. To date, sheep have been used for chronic cortical recordings for stentrode technology (Opie et al. 2018), as well as Electrocorticographram (ECoG) recordings for mapping areas of the sensory areas of the cortex (Gkogkidis et al. 2017). However, sheep have not been used for intracortical electrode studies in part because detailed studies are lacking for comprehensive structure and function of sensory areas.

Here we characterize structural and functional cortical sensory areas in the sheep cortex. We show histological analysis to delineate the cortical layers in various sensory areas, such as visual, auditory and motor cortices. Immunofluorescent imaging was performed to confirm the gross morphology (Nissl), presence of neurons (NeuN), and meningeal structure (IgG). In addition, we performed electrophysiological characterization through both functional ECoG mapping and intracortical recording of various sensory areas. We are able to obtain high fidelity spikes and ECoG recordings to enable the formation of sensory maps.

The sheep brain is a good translational model for intracortical microelectrodes. Their brains are similar to humans and from a device standpoint, any technological innovations (e.g. novel device insertion strategies) in this model will translate well to the human cortex. Further, neural activity can be used to form sensory maps in a similar way as primates, with a faster turnaround time than common NHP experiments and therefore streamlining the device testing pathway.

Disclosures: **I.N. McNamara:** A. Employment/Salary (full or part-time):; Paradromics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Paradromics. **M. Straka:** None. **M. Hanna:**

None. **K. Sahasrabuddhe:** None. **K. Boergens:** None. **R.J. Edgington:** None. **Y. Kong:** None. **H.S. Sohal:** None. **M.R. Angle:** None.

Poster

670. Sensorimotor Control, Movements, and Motor Cortex

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 670.14/M28

Topic: E.05. Brain-Machine Interface

Support: DARPA NESD Grant N66001-17-C-4005

Title: The Argo: A 65,536 channel preclinical neural recording system by Paradromics, Inc

Authors: *H. SOHAL, M. STRAKA, M. HANNA, K. SAHASRABUDDHE, I. MCNAMARA, K. BOERGENS, R. J. EDGINGTON, A. KHAN, Y. KONG, M. R. ANGLE;
Paradromics, Inc, Austin, TX

Abstract: Microwire electrode arrays provide a scalable means of recording from large ensembles of neurons *in vivo*, particularly when these arrays are bonded to high density complementary metal-oxide semiconductor (CMOS) readout circuits [1,2]. Here we describe a custom neural recording system that can be bonded to microwire electrode arrays for large scale extracellular recording in a head-fixed *in vivo* preparation. The system supports up to 65,536 channels, read out simultaneously at up to 39,000 samples per second and 12 bits of resolution. The total system bandwidth is 30 gbps, which can be streamed directly to disk or viewed in real-time through a digital oscilloscope running on a web browser. This system represents a significant improvement over existing CMOS microelectrode arrays in terms of data throughput and overall usability. We report our first demonstration of the system in rat cortex, recording in a head-fixed in-vivo preparation from arrays of <2,000 wires. We will also report on early work adapting the system for use in a large animal preparation [3] for arrays >10,000 wires. This system paves the way for future, implantable devices based on large scale microwire-CMOS arrays.
References:1. Obaid A, Hanna M-E, Wu Y-W, Kollo M, Racz R, Angle MR, et al. Massively Parallel Microwire Arrays Integrated with CMOS chips for Neural Recording. doi:10.1101/5732952. Kollo M, Racz RR, Hanna M-ES, Obaid AM, Angle MR, Wray W, et al. CHIME: CMOS-hosted in-vivo microelectrodes for massively scalable neuronal recordings. doi:10.1101/5700693.McNamara I, Straka M, Hanna M, Sahasrabuddhe K, Boergens, el al. The Sheep (Ovis Aries) as a Clinical Translational Model for Intracortical Microelectrodes. Society for Neuroscience, Chicago, 2019

Disclosures: H. Sohal: A. Employment/Salary (full or part-time):; paradromics inc. **M. Straka:** A. Employment/Salary (full or part-time):; paradromics inc. **M. Hanna:** A.

Employment/Salary (full or part-time):; paradromics inc. **K. Sahasrabuddhe:** A. Employment/Salary (full or part-time):; paradromics inc. **I. McNamara:** A. Employment/Salary (full or part-time):; paradromics inc. **K. Boergens:** A. Employment/Salary (full or part-time):; paradromics inc. **R.J. Edgington:** A. Employment/Salary (full or part-time):; paradromics inc. **A. Khan:** A. Employment/Salary (full or part-time):; paradromics inc. **Y. Kong:** A. Employment/Salary (full or part-time):; paradromics inc. **M.R. Angle:** A. Employment/Salary (full or part-time):; paradromics inc.

Poster

670. Sensorimotor Control, Movements, and Motor Cortex

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 670.15/M29

Topic: E.05. Brain-Machine Interface

Title: Histological confirmation of contents of neurotrophic electrode after recording for a decade

Authors: *P. R. KENNEDY[1], **M. GEARING**[2];
[1]Neural Signals Inc, Duluth, GA; [2]Emory Univ., Atlanta, GA

Abstract: The Neurotrophic Electrode (NE) is designed to record longitudinally the same identifiable neural signals over years. Prior recordings endured 1.4 years in rats and 1.3 years in monkeys and up to four years in humans. In the one human (MR) in whom histology was available, it was not satisfactory due to technical problems with the autopsy. The present histological result was obtained from subject ER, 13 years after implantation with final recordings at year ten. He was too ill to function and perform conditioning studies at that time, but at year nine conditioning studies were satisfactorily performed (3) indicating that the recorded signals were not noise. Instead, they were functional single units. Autopsy was performed at the time of death, and histological findings are presented here.
Histological analysis: The neural tissue inside the NE was processed in the Neuropathology/Histochemistry Core laboratory at Emory University. H&E stain demonstrated basic neuropil with no neurons. Immunohistochemistry for neurofilaments revealed ingrown neurites. Myelination of the axons has been demonstrated with LFB-PAS stain. In addition, GFAP immunostain demonstrated no significant gliosis.
These results suggest that the neural activity is associated with neurofilament-containing neuronal processes.

Disclosures: **P.R. Kennedy:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 98%. **M. Gearing:** None.

Poster

670. Sensorimotor Control, Movements, and Motor Cortex

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 670.16/M30

Topic: E.05. Brain-Machine Interface

Support: ERC-2012-AdG 320708-iCONNECT

Title: Grasp force task reveals onset-offset response in ECoG high-frequency band

Authors: *M. P. BRANCO, S. GEUKES, E. J. AARNOUTSE, M. J. VANSTEENSEL, Z. V. FREUDENBURG, N. F. RAMSEY;
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Abstract: One emerging goal of research using Brain-Computer Interfaces (BCIs) is movement restoration. Using electrocorticogram (ECoG) signals, multiple hand movement features have been successfully decoded from the surface of the somatosensory cortex (SMC), both in a discrete (e.g. hand gestures) and a continuous (e.g. fingertip trajectories) manner. In order to design a BCI system that can accurately manipulate objects, continuous decoding of grasp force is necessary. This has been done in previous studies, where the high-frequency band (HFB; >70Hz) power changes provided discriminative information for an accurate decoding of grasping force. However, as the models used in previous studies contained information from multiple features over multiple areas in the brain, it remains unclear what parameters are encoded by the HFB signals and how these are represented temporally. To investigate this, and to gain insight in the temporal dynamics of the HFB during grasping movements, we continuously modeled the ECoG HFB response recorded from 9 subjects with intractable epilepsy while performing three different grasp force tasks: namely, fast impulse-like responses, continuous dynamic force and isometric force contractions. Using these three tasks, we investigated how the HFB follows the force profile. We compared two models, one based on the exerted force magnitude and another based on the derivative of the exerted force (i.e., movement onset-offset), with the mean HFB signal over electrodes in four different cortical regions-of-interest: all electrodes, electrodes covering the primary motor cortex, the central sulcus and the primary somatosensory cortex. We show that a model based on the force onset and offset consistently shows a better fit to the HFB when compared with a model based on the force profile, especially for the subjects implanted with high-resolution ECoG grids, and that the best fit was irrespective of the electrode location. This suggests that HFB power, although useful for continuous decoding, is not continuously related to force but rather to the changes in movement. This information can be taken into consideration in understanding and decoding neural signals, in particular for BCI.

Disclosures: **M.P. Branco:** None. **S. Geukes:** None. **E.J. Aarnoutse:** None. **M.J. Vansteensel:** None. **Z.V. Freudenburg:** None. **N.F. Ramsey:** None.

Poster

670. Sensorimotor Control, Movements, and Motor Cortex

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 670.17/M31

Topic: E.05. Brain-Machine Interface

Support: NIH Grant K12HD073945
NIH Grant P51 OD010425
NSF Grant EEC- 1028725

Title: Demonstration of an optimized, large-scale optogenetic interface for non-human primates

Authors: *D. J. GRIGGS[1], W. K. S. OJEMANN[2], K. KHATEEB[2], M. CHU[1], A. YAZDAN-SHAHMORAD[3];
[1]Electrical and Computer Engin., [2]Bioengineering, [3]Bioengineering and Electrical Engin., Univ. of Washington, Seattle, WA

Abstract: High spatial and temporal precision and cell type specificity make optogenetics a powerful tool for studying fundamental neural mechanisms and developing neurorehabilitation techniques. To these ends, we recently introduced an optimized large-scale optogenetic interface for non-human primates (NHPs) [1].
Briefly, this interface consists of a flexible recording and stimulating micro-electrocorticography (μECoG) array which we have integrated into a transparent silicone artificial dura to make a "μECoG-dura". Surgical implantation of the μECoG-dura provides both optical access to about 5 cm^2 of the brain and μECoG recording capability which collectively enable large-scale cortical optogenetic experimentation. This interface improves upon the stability and scale of our previous interface iterations [2]. Previously, optical access to the brain was limited to 2-3 weeks due to opaque tissue growth across the optical window, μECoG recording hardware was prone to corrosion, and the setup was limited to 2-3 simultaneous optical stimulation channels. Here, we will validate that our optimized design allows for months of optical access, is corrosion resistant, and supports up to 16 LEDs for simultaneous optical stimulation, thus improving the stability and scale of the interface.
We will genetically modify cortical neurons of the NHP with convection enhanced delivery (CED), a pressure based injection approach, to efficiently obtain uniform, widespread viral vector delivery [2]. After transduction and interface implantation, various optical and electrical stimulation protocols will be employed to modulate neural activity and the results will be recorded by the μECoG-dura.
If successful, our experiments will validate the stability and scale of the interface design by (1) increasing the length of time of optical access to neural tissue from a few weeks to several months, (2) demonstrating no significant corrosion to electrical recording hardware, and (3)

demonstrating neural modulation via various optogenetic and electrical stimulation protocols as measured by μECoG recordings.
This work will set the stage for the development of stable, large-scale, multi-modal neural modulation protocols. Such protocols may be designed to help answer fundamental questions of cortical organization and plasticity and develop neurorehabilitation techniques.
References:
[1] DJ Griggs et. al., "Optimized large-scale optogenetic interface for non-human primates," *SPIE*, 2019.
[2] A Yazdan-Shahmorad et. al., "A Large-Scale Interface for Optogenetic Stimulation and Recording in Nonhuman Primates," *Neuron*, 2016.

Disclosures: D.J. Griggs: None. **W.K.S. Ojemann:** None. **K. Khateeb:** None. **M. Chu:** None. **A. Yazdan-Shahmorad:** None.

Poster

670. Sensorimotor Control, Movements, and Motor Cortex

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 670.18/M32

Topic: E.05. Brain-Machine Interface

Support: Office of the Assistant Secretary of Defense for Health Affairs through the Peer Reviewed Medical Research Program [grant number W81XWH-15-1-0607]
The University of Texas at Dallas

Title: Laminar decoding of the rat forelimb during a knob supination task

Authors: *J. O. USORO[1], C. KUNG[1], W. E. VOIT[2], S. A. HAYS[1], J. J. PANCRAZIO[1];
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Abstract: Introduction: Brain-machine interfaces enable the decoding, i.e. the translation, of neuronal activity into movement kinematics that can be used to control neuroprostheses[1]. To date, most motor decoding applications use the standard Utah electrode array, which is limited to recording neuronal activity in a single depth within the cortex. Evidence suggests however, that there may be laminar differences in sensory- and movement-encoding neurons[2], particularly for complex behaviors. In this study, we investigate the feasibility of using laminar arrays to decode a novel, wrist-supination task, and characterize layer-specific contributions of neuronal activity involved in this movement in a rodent model.
Methods: All procedures were approved by the Institutional Animal Care and Use Committee at the University of Texas at Dallas. Female Sprague Dawley rats were trained to perform a knob supination task[3]. Afterwards, rats were surgically implanted with either shape memory polymer (SMP, IC-5-16E, Qualia Labs, Inc., USA) or NeuroNexus (A1x16-3mm-100-177-CM16LP,

NeuroNexus Technologies Inc., USA) probes in the forelimb representation of the left motor cortex. Neuronal activity was recorded while the rats performed the task, and both the neural and supination data were fed into a decoding algorithm. The algorithm was first trained on test data before making predictions on new data sets. Accuracy of the algorithm was assessed by its ability to predict successful supination trials.
Results: Neural activity was recorded during all sessions, with one session recording from 20 single units across 16 channels. Visual inspection of the raster plot from this trial revealed fairly consistent activity from electrodes that were deeper in the cortex, whereas the activity at shallower electrode sites were temporally modulated by the task, indicating that these movement-evoked potentials may be a result of directionally- or kinematically-tuned neurons. From this activity, preliminary analysis indicated that the algorithm was approximately 70% accurate in predicting successful supination trials in the test data.
Conclusions: Based on preliminary results, we were able to successfully decode wrist supination using laminar probes. Data collection and analysis is ongoing however, and will allow us to refine the algorithm for more accurate predictions, further characterize laminar contributions to the supination task, and investigate the efficacy of using SMP probes for chronic motor decoding.
References: [1]Patil, P. et al., *Neurotherapeutics 5,* 137-146. 2008. [2]Allitt, B. J. et al., *J. Physiol. 595,* 7223-7247. 2017. [3]Butensky, S. D. *et al., J. Vis. Exp. (127).* 2017.

Disclosures: **J.O. Usoro:** None. **C. Kung:** None. **W.E. Voit:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Qualia Labs, Inc.. **S.A. Hays:** None. **J.J. Pancrazio:** None.

Poster

670. Sensorimotor Control, Movements, and Motor Cortex

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 670.19/M33

Topic: E.05. Brain-Machine Interface

Support: ERC-2012-AdG 320708-iCONNECT

Title: The effects of frontal cortex lesions on sensorimotor BCI control features

Authors: ***Z. V. FREUDENBURG**[1], M. J. VANSTEENSEL[2], E. J. AARNOUTSE[3], K. J. MILLER[4], N. F. RAMSEY[2];
[1]Dept. of Neurol. and Neurosurg., [3]Neurol. and Neurosurg., [4]Neurosurg., [2]Univ. Med. Ctr. Utrecht, Utrecht, Netherlands

Abstract: The sensorimotor cortex is a frequently targeted brain area for the development of Brain-Computer Interfaces (BCIs) for communication in people with severe paralysis and

communication problems. It is widely acknowledged that this area displays an increase in high-frequency band (HFB) power and Event Related Desynchronization (ERD) in the lower frequency band (LFB) during movement, as well as low-frequency Event Related Synchronization (ERS) upon cessation of movement. The ability to modulate the neural signal in the sensorimotor cortex by imagining or attempting to move is crucial for the implementation of sensorimotor BCI in people who are unable to execute movements. However, most common causes of loss of motor function, such as stroke, are themselves associated with significant damage to the brain, potentially affecting the functional modulation of HFB, LFB ERD, and LFB ERS control features. While BCIs aim to target non-compromised brain regions, LFB functional features are often driven by remote brain regions and thus may be affected even when HFB control features are present. Here we analyzed HFB and LFB features of 24 subjects implanted with ECoG electrode grids for epilepsy monitoring who were evaluated to be MRI negative (no indications of cortical or sub-cortical lesions; 9 subjects) or who had MRI abnormalities (15 subjects). We used HFB power as a selection criterion for electrodes over the primary motor cortex (M1), central sulcus (CS) or primary somatosensory cortex (S1) that responded to hand movements, and compared the LFB features of these electrodes between lesion and non-lesion subjects. We show that the mere presence of MRI abnormalities is not always associated with deviant LFB features. Yet, when lesions are located in the frontal cortex (6 subjects), both ERD and ERS LFB features in M1 and CS are significantly different from those of MRI negative subjects. Interestingly this was not the case for S1. These results indicate that damage to the frontal cortex can affect the sensorimotor rhythms even in the absence of direct damage to the motor cortex. Since altered sensorimotor features may affect BCI control, and may require dedicated decoding algorithms, our findings call for a careful evaluation of individuals intending to use a sensorimotor BCI.

Disclosures: Z.V. Freudenburg: None. **M.J. Vansteensel:** None. **E.J. Aarnoutse:** None. **K.J. Miller:** None. **N.F. Ramsey:** None.

Poster

670. Sensorimotor Control, Movements, and Motor Cortex

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 670.20/M34

Topic: E.05. Brain-Machine Interface

Support: DARPA BTO SPAWAR Pacific Grant/Contract No. N66001-15-C-4017

Title: Performance of wireless Utah slanted electrode arrays in cat: The SARA-USEA

Authors: *D. R. HILGART[1], D. J. WARREN[1], S. J. BARRUS[2], G. A. CLARK[1];
[1]Biomed. Engin., Univ. of Utah, Salt Lake City, UT; [2]Ripple LLC, Salt Lake City, UT

Abstract: Here we describe the first successful use of a chronically implanted, wireless, 64-channel stimulation system (Stimulating and Recording Array, SARA; Ripple, LLC) attached to a Utah Slanted Electrode Array (USEA; Blackrock Microsystems). USEAs have been shown to interface effectively with peripheral nerves in both animal models and humans (Brinton et al., George et al., and Hansen et al., SfN 2019). Localized peripheral nerve stimulation is potentially advantageous for restoration of function for both spinal cord injury and limb loss. To date, access to chronically implanted USEAs has been through percutaneous wire connections that are prone to infection and wire breakage. The SARA is designed to be fully implanted under the skin, and interfaces with an external wireless transceiver through infrared telemetry, radio frequency telemetry, and inductive power. We implanted one SARA-USEA device in the sciatic nerve of 5 felines. Devices were tested under anesthesia at 1, 4, 13, and 26 weeks post-implantation, with tissue samples acquired at the last test date. At the time of implant and at all subsequent tested time points, the SARA-USEA device successfully demonstrated the ability to be powered by and communicate with external hardware wirelessly through the skin. Devices were tested by stimulating groups of 1 to 4 electrodes and measuring the resulting muscle compound action potential (mCAP) in 4 lower leg muscles, as well as measuring the impedance of each electrode. At the time of abstract submission, 2 animals have reached the 26-week time point, 2 have reached the 13-week time point, and 1 animal provided only impedance data for the 13-week time point for reasons unrelated to the device. At the latest time point available for each animal, between 54 and 64 electrodes remained functionally connected (impedance < 300 kΩ), and 46-64 electrode groups per animal evoked suprathreshold muscle responses (mCAP > 0.5 mV). Responses were often highly selective among muscles, demonstrating precise control over nerve fiber activation. Such precision is important in clinical settings for providing selective activation of paralyzed muscles after spinal cord injury or stroke, or precise sensory feedback in an individual with amputation. This work has been performed in compliance with current Good Laboratory Practice regulations to demonstrate safety and efficacy. Its results will support and Investigational Device Exemption submission to the FDA prior to clinical study.

Disclosures: D.R. Hilgart: None. **D.J. Warren:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent: WO2018026842A1, Patent: 8359083, Patent: 8639312. **S.J. Barrus:** None. **G.A. Clark:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent: WO2018026842A1, Patent: 8359083, Patent: 8639312, Patent: WO2018023026A1.

Poster

670. Sensorimotor Control, Movements, and Motor Cortex

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 670.21/M35

Topic: E.05. Brain-Machine Interface

Support: NCATS of NIH Grant KL2TR001854

Title: Sub-cortical human brain modulation during response conflicts in a modified Stroop task

Authors: *K.-H. CHEN[1], R. MARTIN DEL CAMPO-VERA[1], R. SEBASTIAN[1], D. R. KRAMER[1,2], S. KELLIS[1,2,3,4], B. LEE[1,2];
[1]Dept. of Neurosurg., Univ. of Southern California, Keck Sch. of Med., Los Angeles, CA; [2]Neurorestoration Ctr., USC, Los Angeles, CA; [3]Biol. and Biol. Engin., [4]T&C Chen BMI Ctr., Caltech, Pasadena, CA

Abstract: Human brain modulation during response conflict (e.g. the modified Stroop task) has been studied primarily using functional magnetic resonance imaging (fMRI) due to its non-invasive nature. Few studies have examined modulation with intracranial electroencephalography (iEEG); however, one recent study found theta oscillations (3-8 Hz) in hippocampus relevant to successful task response. Neural activity during these tasks in other regions of the limbic system and in other frequency bands such as in beta band (13-30 Hz) of iEEG have been less well documented. In this study, five epilepsy patients (20-50 years; three females) were implanted with intracranial depth electrodes (AD-TECH, Oak Creek, WI). Participants gave informed consent to participate in an IRB-approved study in which they performed the modified Stroop Task with four variations: (A) naming a color block; (B) reading color words in white font; and naming the font color when the word is congruent (C) or incongruent (D) with that color. Neural signals were recorded (NeuroPort, Blackrock Microsystems, Salt Lake City, UT) and spectral power during the response phase was normalized to the rest phase. Consistent with previous work, we observed significant change in beta band in hippocampus head and tail (n=3 patients; Kruskal-Wallis ANOVA, Multiple Comparison Test, $p < 0.05$) between variants A and D. We also found significant change in beta band in amygdala (n=3; $p < 0.05$) and orbital frontal cortex (n=3; $p < 0.01$) between these two variants. When comparing task variations B and D, amygdala again showed significant change in the beta band (n=3; $p < 0.05$). Based on these results, we observe that, in addition to hippocampus as shown in prior studies, the amygdala and orbitofrontal cortex are also recruited during response conflict tasks. This finding suggests roles for these two brain areas beyond emotional processing.

Disclosures: K. Chen: None. **R. Martin del campo-vera:** None. **R. Sebastian:** None. **D.R. Kramer:** None. **S. Kellis:** None. **B. Lee:** None.

Poster

670. Sensorimotor Control, Movements, and Motor Cortex

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 670.22/M36

Topic: E.05. Brain-Machine Interface

Support: National Center for Advancing Translational Science (NCATS) of the U.S. National Institutes of Health (KL2TR001854)

Title: Neuromodulatory assessment of depth-EEG oscillations in reaching arm movements

Authors: *R. MARTIN DEL CAMPO VERA[1], K.-H. CHEN[1], R. SEBASTIAN[1], D. R. KRAMER[1,2], S. KELLIS[1,2,3,4], B. LEE[1,2];
[1]Neurosurg., [2]Neurorestoration Ctr., USC, Los Angeles, CA; [3]Biol. and Biol. Engin., [4]T&C Chen BMI Ctr., Caltech, Pasadena, CA

Abstract: With many human intracranial studies of motor neurophysiology focusing on cortical areas, the role of subcortical brain areas in movement has not been as well investigated. An increase in the use of stereotactic electroencephalography (sEEG) for clinical treatment of epilepsy has led to more opportunities to record from deeper brain structures. This study examines spectral power across multiple subcortical structures during reaching movements. Five people (four female) aged between 20 and 50 years old, had AD-TECH depth electrodes implanted as part of their epilepsy monitoring, targeting orbitofrontal, frontal, insula, amygdala, hippocampus, temporal, precentral, parietal, and occipital brain areas. They gave informed consent to participate in an IRB-approved study of reaching movements while in the epilepsy monitoring unit. The participants performed a reaching task during which, after a brief period with no visual stimulus, they pointed to a dot displayed in the center of the screen (fixation), then reached to one of eight targets, equidistantly spaced around the unit circle, illuminated on the screen (response). Broadband neural activity was recorded at 2,000 samples per second (NeuroPort, Blackrock Microsystems, Salt Lake City, UT), and spectral power was computed in alpha (8-13 Hz), beta (13-30 Hz), low gamma (30-80 Hz), and high gamma (80-150 Hz) frequency bands. In each of these bands, we tested whether power increased or decreased during movement. We found that the hippocampus was the most common area among participants (four out of five) to exhibit a significant change between fixation and response (two-sample bootstrap hypothesis test for difference of means; $p<0.05$), followed by the amygdala in three participants. Significant changes in spectral power in other brain structures were also observed but only in two or fewer participants. In keeping with prior literature, spectral power significantly decreased in the beta band in 71% of targeted brain structures and increased in the high gamma band in 75%. In contrast, we observed mixed changes in alpha and low gamma. These results suggest that neural circuits in hippocampus and amygdala modulate during motor control. If robust across persons, such modulation could be incorporated into a brain-machine interface system to allow those with limited physical movement to operate a neuroprosthesis through their neural activity.

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Poster

670. Sensorimotor Control, Movements, and Motor Cortex

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 670.23/M37

Topic: E.05. Brain-Machine Interface

Title: Calcium signals from layer 2/3 of motor cortex encode lever movement

Authors: *J. HAN[1], S. ZHANG[2], R. WANG[2], Y. REN[2];
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Abstract: Previous motor brain-machine interfaces (BMIs) studies mainly harnessed spike activity from pyramidal neurons in layer 5 with electrophysiological recordings. But the activity of neuron population in layer 2/3 was seldom studied because of the difficulty in electrophysiological recording technique. Here we used a miniature fluorescent microscope (Miniscope) systems to collect calcium signals of neurons in layer 2/3 in primary motor cortex (M1) of C57BL/6J mice (male, aged 8-12 weeks) during a lever-pressing task. We tried to exam whether the movement of lever could be decoded with calcium signals obtained from layer 2/3 in M1. We firstly trained mice to press a lever to get water as rewards. Virus was then injected into the M1 cortex to express GCaMP6f. The calcium signals from the layer2/3 of M1 were collected when mice were performing lever-pressing task. Meanwhile, a pressure sensor was used to record the pressure values on the lever. We found that less than half (about 40%) of the calcium signals from layer 2/3 showed a significant increase when the mouse was pressing the bar. However, in this group of press-related calcium signals, only a few (less than 5%) of them are pressure value-related, that is, with the increase of pressure, the calcium transients of neurons also increases correspondingly, and vice versa. The neuronal activity in layer 2/3 also showed a positive correlation with the pressure value, that is, the higher the pressure value, the stronger calcium signal of the neuronal population. And furthermore, this correlation was held continuously during the task period. These results indicates that a subset of calcium signals in layer 2/3 are highly correlated with the lever-pressing task in mice, and the pressure values maybe encoded only by several neurons in a pattern similar to "sparse coding". Or we can interpret it as information about pressure values stored primarily in several individual neurons. Moreover, the pressure value could be continuously decoded by the calcium signals of neuronal activity in layer 2/3. It undoubtedly provides a new idea for motion decoding. In the future, scientists may decode the motion information of rodents or even higher primates through the interneurons in the superficial layer.

Disclosures: **J. Han:** None. **S. Zhang:** None. **R. Wang:** None. **Y. Ren:** None.

Poster

670. Sensorimotor Control, Movements, and Motor Cortex

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 670.24/DP08/M38

ControlExtraData.DynamicPosterDisplay:
Dynamic Poster
Topic: E.05. Brain-Machine Interface

Support: NSF ECCS Grant 1763350

Title: Recording neural activity with a battery-free wireless neurosensor

Authors: *C. MONCION[1], J. BORGES[2], D. BORREGO[3], L. BALACHANDAR[1], S. BOJJA-VENKATAKRISHNAN[4], J. L. VOLAKIS[4], J. RIERA DIAZ[1];
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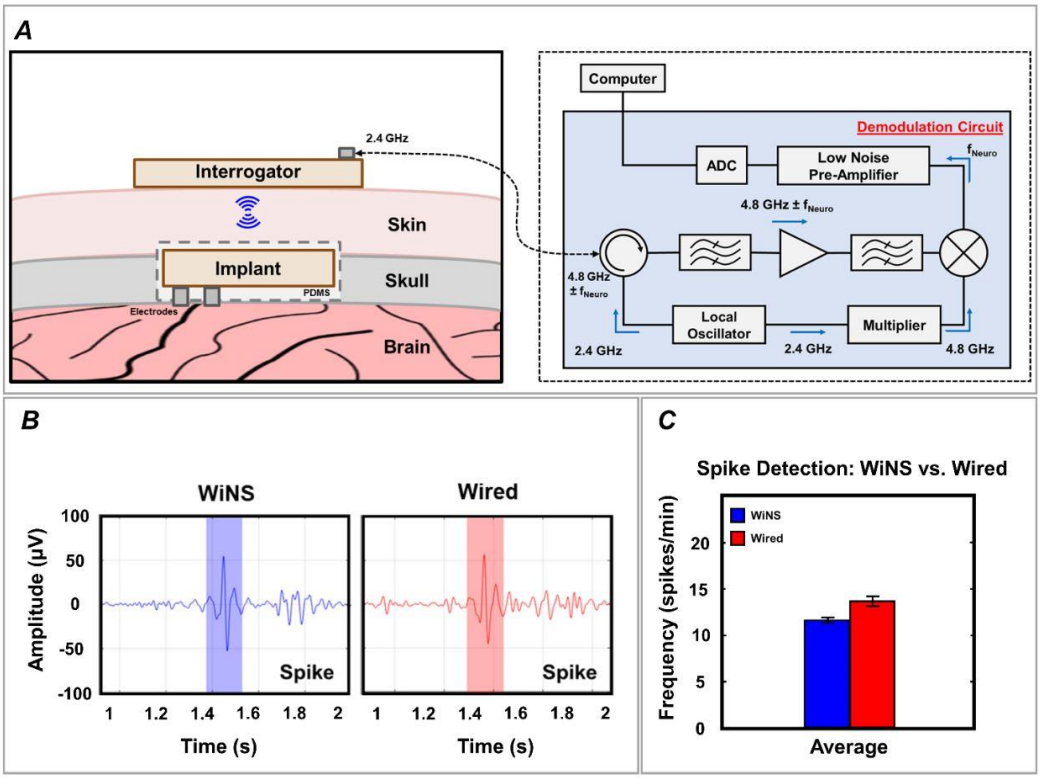
Abstract: Surgical outcome in patients with drug-resistant epilepsy relies on accurate localization of epileptogenic foci, a step achievable using ECoG recording while patients are implanted for several days. The use of FDA approved wired amplifiers for ECoG data acquisition poses risks for these patients due to wires left protruding from the scalp, including infection and severe discomfort. Current wireless solutions (Neuropace RNS System) require the use of a power source, which can generate tissue-damaging heat. We have proposed a battery-free wireless neurosensing system (WiNS), consisting of an implant, an external interrogator antenna and a demodulation circuit (Fig. 1A). The implant is designed to be placed directly on top of the cortex through a craniotomy (Fig. 1A). Wireless communication is achieved using a RF carrier signal (2.4 GHz) supplied with the interrogator, that mixes, via an anti-parallel diode pair (APDP) in the implant, with the neuronal electric potential difference across a pair of electrodes, and then transmitted back to the interrogator (Lee, Kiourti, and Volakis 2017). In Moncion et al. (2019), we demonstrated that this ground-breaking technology can record electrophysiological signals of a variety of amplitudes, ranging from a few mV (ECG) down to μV (somatosensory evoked potentials). As we aim to apply this technology to epilepsy clinical practice, it is critical to evaluate signal distortion and detectability of interictal epileptiform discharges (IEDs), a hallmark of epilepsy. To this end, we implanted the WiNS in 5 rats with pilocarpine model-induced chronic temporal lobe epilepsy (TLE). To quantify signal distortion, IEDs were simultaneously recorded using a commercially-available wired system (AD Instrument Animal BioAmp) while the rats were under sedation and fixed to a stereotaxic. Results indicate that negligible distortion of the smaller type of IED, specifically spikes (Fig. 1B). Furthermore, we compared spike detection between WiNS and the wired system also indicating an inconsequential difference (Fig. 1C).



Disclosures: **C. Moncion:** None. **J. Borges:** None. **L. Balachandar:** None. **S. Bojja-Venkatakrishnan:** None. **J.L. Volakis:** None. **J. Riera Diaz:** None.

Poster

670. Sensorimotor Control, Movements, and Motor Cortex

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 670.25/M39

Topic: E.05. Brain-Machine Interface

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NSF NCS BCS 1533672
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Title: Evidence of a memory trace in motor cortex after short term learning

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Abstract: Many different neural activity patterns can lead to the same behavior. Does learning a new task change what neural activity patterns the brain uses to perform a previously learned task? We hypothesized that learning a new task might leave a memory trace, such that after learning a new task, the neural activity patterns used to perform the original task have changed. In particular, the original task might be performed using neural activity patterns that exhibit a "trace" of the newly-learned task. That is, the neural activity patterns after learning might remain somewhat appropriate for the newly-learned task while the subject is performing the original task. A difficulty in addressing this hypothesis is that in most tasks, the causal relationship between neural activity and behavior is unknown. To overcome this, we leveraged a brain-computer interface (BCI). In a BCI, the mapping between neural activity and behavior is specified by the experimenters. Multielectrode arrays were implanted in the primary motor cortex of rhesus monkeys, so that monkeys could control the movement of a computer cursor by volitionally modulating the activity of ~90 neural units. Monkeys proficiently used an intuitive “original” mapping in a baseline period, and then the mapping was switched to a perturbed “new” mapping that had to be learned through trial and error. After several hundred trials, we returned to the original mapping in a washout period. A major benefit of this experimental paradigm is that it allows us to quantify how appropriate neural activity is for a given mapping, even when that mapping is not currently being used. To evaluate whether learning a new mapping leaves a memory trace in motor cortex, we quantified the extent to which neural activity patterns produced by the animal during the washout period would be useful for driving the cursor using the perturbed mapping, and compared this to neural activity patterns produced during the baseline period. We found evidence of a memory trace, in that neural activity during the late portion of the washout period was more appropriate for the perturbed mapping than neural activity during the baseline period. This result held when we controlled for behavioral differences between the baseline and washout periods. Overall, our findings suggest that learning a new task brings neural activity to a novel solution for the original task that also provides benefit for the new task. This phenomenon may be a mechanism by which the brain could more rapidly learn when re-exposed to the same perturbation, a phenomenon known as “savings”.

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Poster

671. Reflexes

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 671.01/M40

Topic: E.06. Posture and Gait

Support: Canadian Institutes of Health Research
Spinal Cord Injury Treatment Centre Society
Alberta Paraplegic Foundation
Rick Hansen Institute
Canada Foundation for Innovation

Title: Transcutaneous spinal cord stimulation of the cervical cord modulates lumbar locomotor networks

Authors: T. S. BARSS, B. PARHIZI, *V. K. MUSHAHWAR;
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Abstract: The overall goal of this project is to investigate the contribution of the cervical networks of the spinal cord to the improvement of walking capacity after spinal cord injury (SCI). We recently demonstrated that active engagement of the arms coordinately with the legs in an arm and leg (A&L) cycling paradigm significantly improves walking speed in people with incomplete SCI compared to their baseline levels (Zhou et al, 2018a). Importantly, these increases were significantly larger than those obtained by legs-only cycling. Moreover, while legs-only cycling resulted in increases in walking speed that were similar to those reported using gait-specific interventions such as bodyweight-supported treadmill training, A&L cycling training resulted in twice larger increases in walking speed (Zhou et al, 2018a). These larger increases were partly the result of improvements in corticospinal drive and modulation of cervico-lumbar connectivity (Zhou et al, 2017, 2018b).
In this study, we examined the effect of transcutaneous spinal cord stimulation (tSCS) on the modulation of cervico-lumbar connectivity, in an effort to determine its use in combination with A&L cycling to further enhance the gains in walking capacity. Thirteen neurologically-intact adults participated in the study. The excitability of the H-reflex elicited in the soleus muscle was examined under 6 different conditions: 1) arms held in a static position (‘arms static’) without tSCS; 2) arms static with tSCS applied to the lumbar region of the spinal cord; 3) arms static with tSCS applied to the cervical cord; 4) arms cycling without tSCS; 5) arms cycling with tSCS applied to the lumbar cord; and 6) arms cycling with tSCS applied to the cervical cord.
The amplitude of the soleus H-reflex was significantly suppressed by ~25% when the arms were cycling (without tSCS) relative to arms static (without tSCS). Very interestingly, tSCS applied to the cervical cord with arms static also significantly suppressed the soleus H-reflex by ~25%.

However, arms static with tSCS applied to the lumbar cord did not suppress the soleus H-reflex. The combination of arms cycling with cervical tSCS or lumbar tSCS did not result in additional suppression of the soleus H-reflex beyond that obtained with arms cycling alone.
The results suggest that both rhythmic activation of the cervical spinal cord through voluntary arm cycling or tonic activation of the cervical spinal cord through tSCS significantly modulate the activity of the lumbar locomotor networks. This further demonstrates the importance of engaging the cervical networks actively along with the legs in rehabilitation interventions for improving walking capacity after SCI.

Disclosures: T.S. Barss: None. **B. Parhizi:** None. **V.K. Mushahwar:** None.

Poster

671. Reflexes

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 671.02/M41

Topic: E.06. Posture and Gait

Support: Netherlands Organisation for Scientific Research (NWO), domain Applied and Engineering Sciences [Project 14903]

Title: Duration dependence of the medium-latency M2 stretch reflex in the ankle plantarflexors

Authors: *R. C. VAN 'T VELD[1], E. H. F. VAN ASSELDONK[1], A. C. SCHOUTEN[1,2]; [1]Biomechanical Engin., Univ. of Twente, Enschede, Netherlands; [2]Biomechanical Engin., Delft Univ. of Technol., Delft, Netherlands

Abstract: Motorized assessments of the short-latency M1 and medium-latency M2 stretch reflex are performed to understand the physiological origins of these responses and for spasticity assessment. For ramp-and-hold assessments, M1 magnitude increases with stretch velocity in both upper and lower limb, while the dependence of M2 on stretch duration has only been shown in the upper limb. This M2 dependence includes a minimum stretch duration required to elicit M2 and a maximum duration at which M2 plateaus. The M2 duration dependence has not been shown in the lower limb and, if it exists, minimum and maximum threshold durations may differ. The goal of this study is to systematically explore M2 duration dependence in the ankle plantarflexors.
Eight healthy volunteers (4 men, 19-29y) participated in this study. 30 different dorsiflexing perturbations were applied to the right ankle joint with varying durations (36-137 ms) and velocities (1.3-3.4 rad/s). All perturbations used ramp-and-hold profiles with a fixed parabolic acceleration curve (max. 140 rad/s^2). Participants were seated and instructed to generate a 3 Nm plantarflexing background torque. The experiment consisted of 12 blocks with 2 min. of rest in between, and with all 30 perturbations used once, in randomized order, in every block. Soleus

(SOL) electromyography (EMG) was 5Hz high-pass filtered, rectified and sorted per condition, removing all stretches outside the background torque criterion (3±0.2 Nm). M2 magnitudes were taken as average of the logarithm of the area under the curve of a 30 ms window, which started 25 ms after M1 onset. Linear mixed models (LMM) with subjects as random factor were used to test velocity and duration as predictor (N=240).
For perturbations with a 36-60 ms duration, SOL M2 depended on duration, not velocity (duration p=0.009, velocity p=0.183). The LMM with duration predictor explained 89% of the total variance and M2 magnitude increased with duration. For perturbations with a 60-137 ms duration, M2 depended on velocity, not duration (duration p=0.777, velocity p<0.001). The LMM with velocity predictor explained 91% of the total variance. For these longer durations, M2 magnitude reached a plateau value and this plateau value increased with velocity.
Similar to the upper limb, M2 in the SOL muscle was found to depend on stretch duration. For short durations (<60 ms) M2 increased with duration, while M2 plateaus for long durations (>60 ms). This M2 plateau magnitude depended on stretch velocity, which has not been reported in the upper limb. Our results highlight the importance of reporting and accounting for stretch duration and velocity for motorized M2 assessments in the lower limb.

Disclosures: **R.C. van 't Veld:** None. **E.H.F. van Asseldonk:** None. **A.C. Schouten:** None.

Poster

671. Reflexes

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Topic: E.06. Posture and Gait

Support: Centre National de la Recherche Scientifique (CNRS)
Centra National d'Etudes Spatiales (CNES)
Fondation pour la Recherche Médicale (FRM)

Title: Development of dual vestibulospinal pathways responsible for trunk postural control in Xenopus

Authors: ***D. LE RAY**, A. OLECHOWSKI-BESSAGUET, F. M. LAMBERT, R. GRANDEMANGE, L. CARDOIT, G. BARRIOS, E. COURTY;
Univ. Bordeaux CNRS Umr5287 - INCIA, Bordeaux, France

Abstract: Vestibular information is critical for the control of locomotion and posture. In quadruped vertebrates, the control of posture was demonstrated to rely mainly on vestibulospinal pathways acting directly on both body axial and limb extensor muscle systems. However, several studies in the last decade also suggested a substantial modulation of spinal axial networks by central commands arising from lumbar segments during active locomotion. Especially, we have

previously shown that an ascending lumbar drive overwhelms the descending control of thoracic postural circuitry to adjust body posture during limb-based swimming in the aquatic frog Xenopus laevis. We therefore undertook the investigation of the central pathways and effectors responsible for the control of posture in Xenopus and their developmental adaptation to metamorphosis-induced changes in biomechanical apparatus. We show that most axial motoneurons (MNs) in tadpole rostral spinal segments 6-8 undergo dramatic morphological modifications during metamorphosis, which results in juvenile thoracic postural MNs exhibiting particular dendritic arborization allowing them to gather information from both sides of the cord. Such juvenile MNs respond to vestibular natural stimulation with early position- and delayed velocity-related discharges, the latter occurring simultaneously with ipsilateral hindlimb extensor bursts. Furthermore, thoracic MNs monosynaptically respond to electrical stimulation of the two brainstem vestibulospinal nuclei and to stimulation of ascending interneurons located in the rostral lumbar cord. Finally, we show that vestibulospinal fibers activate rostral lumbar interneurons projecting into thoracic segments. Altogether, our results complete the scheme of the vestibulospinal control of posture by clearly demonstrating the existence of a novel pathway, which implicates a lumbar relay, conveys specific vestibular velocity-related inputs to thoracic MNs, and participates in trunk postural stabilization in the absence of active locomotion.

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Poster

671. Reflexes

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 671.04/M43

Topic: E.06. Posture and Gait

Support: Gatsby Charitable Foundation
Wellcome Trust

Title: Alteration of sensory-motor reflex gain in different environmental contexts

Authors: E. WITTS, M. MATHEWS, S. THOMPSON, *A. J. MURRAY;
Sainsbury Wellcome Ctr., Univ. Col. London, London, United Kingdom

Abstract: The generation of coordinated movement relies on sensory input being correctly interpreted in order to produce appropriate motor output. Even relatively simple sensory-motor reflexes, such as the motor corrective response generated after a postural perturbation must be tuned to salient features of the environment. One example of this sensory-motor gain control is the increase in motor response to vestibular stimulation during threatening conditions. In this context the same sensory stimulus produces an altered motor response dependent on the

environmental context, however, the neural circuit mechanisms for this modulation of sensory-motor gain are not well understood.
Here, we have developed a novel behavioural paradigm where mice in an enclosure must generate a postural correction in response to a lateral balance perturbation. We altered the environmental context by varying the height of the walls of the enclosure, and recorded hindlimb EMG responses under two environmental conditions one with a high-walled (less-threatening) enclosure and one with a low-walled (more threatening) enclosure. This task therefore allowed us to measure vestibulo-motor responses to a stereotyped stimulus while varying the spatial context.
We found that identical magnitudes of postural perturbation produced different motor responses in different environmental contexts. In particular, a more threatening context produced larger peak EMG responses than a less threatening environment. To investigate the neural circuits responsible for this alteration of sensory-motor gain we probed the function of the lateral vestibular nucleus (LVN), an area of the brainstem that gives rise to the lateral vestibulospinal tract and is known to be required for generating postural corrective responses. Transient inhibition of the LVN via the expression of archaerhodopsin and implantation of an optical fibre resulted in a greatly reduced EMG response in both threatening and non-threatening conditions, suggesting the LVN is required for the generation of this postural correction. To probe the neural circuits that influence LVN activity we performed monosynaptic rabies tracing selectively from lateral vestibulospinal tract (LVST)-neurons. We found that LVST neurons receive a diverse array of inputs, particularly from multiple cortical and cerebellar regions as well as areas involved in providing sensory feedback. Our current investigations are focussed on functionally probing the inputs to the LVN in order to understand the circuits that alter sensory-motor reflex gain.

Disclosures: **A.J. Murray:** None. **E. Witts:** None. **M. Mathews:** None. **S. Thompson:** None.

Poster

671. Reflexes

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 671.05/M44

Topic: E.06. Posture and Gait

Title: Comparison of femoral nerve and quadriceps muscle stimulation onto soleus motor output: Potential role for Golgi tendon organ feedback

Authors: *M. A. LYLE, E. JOHNSON, F. KIRKLAND, D. LUO, C. VARAN;
Emory Univ., Atlanta, GA

Abstract: Force feedback from Golgi tendon organs (GTOs) has widespread intermuscular projections implying a role in motor coordination, but the functional implications have been

difficult to determine. This is because methods to study GTO circuits use nerve stimulation or muscle stretch, which also activate muscle spindle afferents. Muscle contraction naturally activates GTOs and reduces spindle firing due to fascicle shortening. Thus, muscle stimulation-evoked twitches provide an opportunity to bias GTO activity and thus study their intermuscular actions more selectively than nerve stimulation; we have recently demonstrated strong support for this premise in the cat. Here, we tested the hypothesis that stimulation-evoked twitches can be used to bias GTO feedback in humans. The hypothesis was evaluated by comparing the effects of femoral nerve and quadriceps (Q) muscle stimulation onto soleus motor output. Femoral nerve stimulation evokes short latency excitatory spindle feedback and long duration inhibition onto soleus currently attributed to recurrent inhibition. Thus, we hypothesize femoral n stimulation, but not Q stimulation, will elicit excitatory feedback onto the soleus; Stimulation-evoked twitch force magnitude will relate to the magnitude of inhibition; Acute muscle fatigue will reduce GTO input (i.e. twitch force) and thus the magnitude and duration of soleus inhibition. Participants are seated on a HUMAC dynamometer. EMG was recorded from the soleus and stimulation electrodes applied to vastus medialis and lateralis motor points, and the femoral n in the femoral triangle. Stimulation/twitch force relations were identified for the femoral n and Q by stimulating at 1-3x motor threshold while recording knee torque. Stimulation-evoked interactions were evaluated by stimulating the femoral n or Q while subjects held 20% soleus MVIC with visual feedback. Two to three stimulation intensities for femoral n and Q, matched for twitch-evoked forces were completed. A Q stimulation fatigue protocol was used until twitch torques reduced by ~50%, followed by a conditioning trial with the same prefatigue current. To date, short latency excitation has been observed with femoral n but not with Q stim. In all individuals, increased soleus inhibition with increased stimulation intensity was found. Preliminary results suggest acute Q fatigue may be a way to distinguish recurrent inhibition from GTO feedback. Our data suggest muscle twitches naturally bias GTO feedback (i.e. lack excitatory feedback onto the soleus; relation of twitch force and soleus inhibition). Evaluating GTO feedback with muscle stimulation is anticipated to help advance the role of GTOs.

Disclosures: **M.A. Lyle:** None. **E. Johnson:** None. **F. Kirkland:** None. **D. Luo:** None. **C. Varan:** None.

Poster

671. Reflexes

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KSCHIRT

Title: Evidence for non-linear summation of inhibitory inputs from the length and force-dependent feedback sources onto feline ankle extensor muscle

Authors: *E. KAJTAZ[1], S. F. MCMURTRY[1], A. M. DE BOEF[1], L. R. MONTGOMERY[2], D. R. HOWLAND[3,4], T. NICHOLS[1];
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Abstract: Specific and unique roles can be assigned to two main muscle mechanoreceptors: muscle spindles have been, almost universally, described as sensors of muscle length and change in its length, whereas the activity of Golgi tendon organs (GTO's) is a function of muscle active force. The respective connectivity of these two pathways, length and force-dependent feedback, forms a neural network of widely distributed sensory inputs in the spinal cord: each motoneuronal pool receives an excitatory length feedback from its homonymous muscle, inhibitory length feedback from its antagonistic muscles, and inhibitory force-dependent feedback from its close synergists and/or distant heteronomous muscles. The question emerges how the two sources of inhibition converge onto recipient motoneuronal pools. The experiments described in this abstract tested the hypothesis that two sources of inhibition, Ia reciprocal inhibition originating from antagonistic muscle spindles and Ib inhibition originating from heteronomous and synergistic GTO's, converge linearly onto recipient extensor motoneurons. If they do, that would mean that interneuronal pools mediating length-dependent reciprocal inhibition and force-dependent inhibition are separate and independent. If, however, the magnitude of inhibition from both sources concurrently is smaller than the summation of magnitudes from individual sources, that may suggest that, at least partially, Ia and Ib inhibitory interneuronal pools are shared resources across these two inhibitory pathways. We utilized the decerebrate cat and measured the magnitude of inhibitory feedback between extensor and flexor muscles spanning the ankle joint of the feline hind limb. Following the recovery from lateral T9-T10 thoracic hemisection, decerebration and removal of anesthesia, three paired muscles, denoted as recipient and two donors of inhibition, were stretched in different combinations, and intermuscular interaction assessed as a change in the stretch reflex magnitude of the recipient muscle due to the stretch of each donor and both of them together. Detailed analysis is underway. Preliminarily, we observed that the magnitude of inhibition from combined sources is smaller than the sum of inhibition magnitudes from each source individually. These observations suggest that stiffness of each muscle, and therefore a joint, is determined globally by non-linear convergence of feedback from many external sources throughout the limb and body. Funding: DVA, RR&D B2316R, B7165R & B9249S, NINDS NS097781, NICHD HD32571, NIH 8-P30GM103507, KSCHIRT & Rebecca Hammond Chair.

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Poster

671. Reflexes

Location: Hall A

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Program #/Poster #: 671.07/N2

Topic: E.06. Posture and Gait

Title: Effects of age' vestibular and visual systems on the soleus H reflex

Authors: ***A. CELIK**, F. J. ROJAS, M. CEPERO GONZALEZ, D. M. KOCEJA, K. KITANO; Indiana Univ., Bloomington, IN

Abstract: The vestibular system, visual and proprioceptive pathways provide information about control of posture, movement and balance. Loss of postural control directly leads to a greater incidence of falling in the elderly population causing serious health problems. One important neuromuscular mechanism instrumental in the control of posture and balance is the reflex system. However, the age-related changes of vestibular and visual systems and their relationship with the reflex system are not clear. The purpose of this study was to investigate the effects of age, the vestibular and the visual systems on the modulation pattern of the soleus H reflex. Seventeen neurologically healthy volunteers were categorized by age in two groups: young (n = 8, mean age = 22.1±5.0 yr) and elderly (n = 9, mean age = 59.3±12.8 yr). Maximal soleus H-reflex (H-max) and motor response (M-max) amplitudes were determined prior to testing at each condition while subjects were lying supine on a tilt table for standardization. Stimulation intensity was set to evoke a 5-10% M-wave on each trial. Participants received 5 test H-reflex stimuli in two conditions, static 60º and dynamic 60º on a tilt table. Both tilt conditions were performed with vision and no vision. A 3-way repeated-measures analysis of variance (ANOVA) 2 (groups: young/old) x 2 (condition: static/dynamic) x 2(vision: vision/no vision) was used to assess changes in H-reflexes. All data were expressed relative to the H-reflex amplitude at 0º static on the tilt table. The results showed a significant 3-way interaction (p= 0.038). The old group showed greater H-reflex amplitude in the no vision condition at static 60º (vision: 0.97; no vision: 1.23) whereas in the young group less modulation was demonstrated in the same condition (vision: 1.15; no vision: 1.12). These results suggest in young subjects the vestibular system produced a suppression of the H-reflex with or without visual input; however in the old group vision was necessary for this suppression. The interaction between the visual and vestibular systems as we age needs to be further explored.

Disclosures: **A. Celik:** None. **F.J. Rojas:** None. **M. Cepero Gonzalez:** None. **D.M. Koceja:** None. **K. Kitano:** None.

Poster

671. Reflexes

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Program #/Poster #: 671.08/N3

Topic: E.06. Posture and Gait

Support: EU FP7 Grant #ICT-2011.5.2
STW Grant #10733
STW Grant #14903

Title: Treadmill perturbations to evoke stretch reflexes during gait in children with cerebral palsy

Authors: *E. FLUX[1], L. SLOOT[1,2], J. HARLAAR[3,1], A. I. BUIZER[1], M. M. VAN DER KROGT[1];
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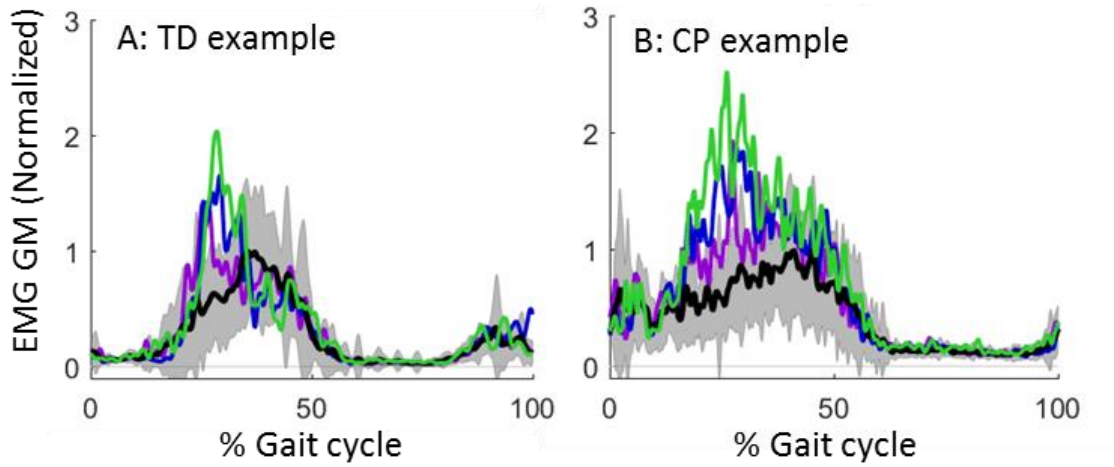
Abstract: Introduction Spasticity, i.e. exaggerated velocity-dependent stretch reflexes, is one of the key impairments in neurological diseases, but its effect on gait is unclear. Treadmill accelerations can be used to quantify calf muscle reflexes during gait in healthy adults [1]. This study examined the applicability of this method for children, both typically developing (TD) and with cerebral palsy (CP). **Methods** 15 TD and 20 CP children walked 6 minutes on a split-belt instrumented treadmill at comfortable speed. Backward treadmill accelerations were unexpectedly applied at three intensities to the most affected (CP) or right leg (TD) just after initial contact. 3D kinematics were collected and EMG was recorded for soleus and gastrocnemius and normalized to peak in unperturbed walking. Muscle-tendon lengths and velocities were calculated using OpenSim. Effect of perturbations was evaluated on knee and ankle angles, muscle-tendon velocity and RMS EMG [2]. Spasticity was classified as low (N=12) or high (N=8) using physical examination. **Results** Perturbations with increasing intensity resulted in increased ankle dorsiflexion, up to 5.7±1.5° (TD) and 3.8±2.1° (CP), without changes in knee angle. This caused increased stretch velocity of calf muscles, resulting in increasing bursts of muscle activity up to 3 (TD) and 3.5 (CP) times the unperturbed value. Reactions in CP were much more variable than in TD. Children with high spasticity showed 0.6 and 0.8 times less muscle lengthening, but 1.3 and 1.4 times higher increases in RMS EMG than TD children and CP children with low spasticity respectively. **Discussion** The results indicate that stretch reflexes can be evoked using treadmill perturbations in both TD and CP children. The lower and more variable changes in joint angles and muscle-tendon lengthening in CP are likely due to altered posture in early stance, but does not interfere with the reflex evoking ability. The

enhanced muscle response in children with high spasticity indicates that treadmill perturbations are a promising method to assess spasticity during gait. [1] Sloot, PLoS One 2015



Disclosures: **E. Flux:** None. **L. Sloot:** None. **J. Harlaar:** None. **A.I. Buizer:** None. **M.M. van der Krogt:** None.

Poster

671. Reflexes

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 671.09/N4

Topic: E.06. Posture and Gait

Title: Modulation of human soleus H-reflex induced by visual perturbation

Authors: *K. KITANO, A. M. PHIPPS, D. M. KOCEJA;
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Abstract: An H-reflex and related techniques have been widely used to evaluate postural control mechanisms at the spinal level in humans. Previous studies have demonstrated that human posture is controlled by tactile sensory, proprioceptive, vestibular, and visual systems. Additionally, it has been known that soleus H-reflex is modulated through changes in ankle angle (proprioception), body orientation (vestibular system), and aging. The purpose of the study was to evaluate whether visual perturbation has an effect on human soleus H-reflex modulation. Four young adult subjects participated. Each subject had no history of neuromuscular disease and were of a normal fitness level. An EMG signal was collected from the right soleus at 2 kHz

sampling rate and stimulating electrodes were placed at the right popliteal fossa. Control H-reflex amplitudes were set at 20% of M-max. Subjects stood on a force plate that was enclosed within a motorized, moveable wall. The size of wall enclosure was approximately 70 cm (W) x 70 cm (D) X 230 cm (H) and the color was white. Subject's vision was limited in front and both side aspects in the enclosure box. In order to administer visual perturbation, the walls were moved for 2.2 sec at 9.3 cm/sec. Direction of the wall movement was set away from a subject and initial distance between the wall and subjects was approximately 40 cm. Test stimulation was delivered at 0 msec, 100 msec, 200 msec, 400 msec, 800 msec, and 1600 msec after wall movement. Alpha-level was set at 0.05. The results showed a significant difference between the amplitudes at 400 msec and at 1600 msec (88.8% vs. 105% of a control value, respectively). Results suggest that spinal mechanisms are modulated by visual information.

Disclosures: K. Kitano: None. **A.M. Phipps:** None. **D.M. Koceja:** None.

Poster

671. Reflexes

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 671.10/N5

Topic: E.06. Posture and Gait

Support: ERC Grant Agreement n. 291339, project 4DEEG
NIH National Center for Advancing Translational Sciences (UL1TR001422),
NIH grant R01HD039343
NIH grant R01NS058667.
ImPACT Program of the Council for Science, Technology and Innovation (Cabinet Office, Government of Japan

Title: 4d-EEG: Signal propagation through the brain based on EEG and diffusion MRI

Authors: *F. C. T. VAN DER HELM[1], O. G. FILATOVA[2], Y. YANG[2], P. MACEIRA-ELVIRA[2], R. TIAN[2], G. KWAKKEL[3], Y. TAKEDA[4], O. YAMASHITA[4], J. P. DEWALD[5]; [1]Biomechanical Engin., [2]BIomechanical Engin., Delft Univ. of Technol., Delft, Netherlands; [3]Rehabil. Med., Vrije Univ. Med. Ctr., Amsterdam, Netherlands; [4]Neural Information Analysis Laboratories,, ATR, Kyoto, Japan; [5]Physical Therapy and Human Movement Sci., Northwestern Univ., Chicago, IL

Abstract: Neuroimaging techniques, such as fMRI and dMRI, have a high spatial resolution. However, low temporal resolution of fMRI provides less insight of dynamic changes of brain activity. In contrast, electro-neurophysiological techniques, such as electroencephalography (EEG), have an excellent temporal resolution to measure such transient events, however are hindered by its low spatial resolution. The goal of this study is to enhance the spatial (3D)

resolution of EEG with dMRI, and combine this with the fast dynamic changes in EEG over time (1D) resulting in signal propagation through the brain (4D-EEG).
This proof-of-principle study used a novel multimodal brain imaging technique namely Variational Bayesian Multimodal Encephalography (VBMEG), which aims to improve the spatial resolution of EEG for tracking the information flow inside the brain, using constraints derived from anatomical MRI and diffusion MRI. EEG data were acquired from two individuals suffering from a stroke as well as two able-bodied participants. Electrical stimuli were delivered sequentially at their index finger in the left and right hand, respectively. A source localization method (sLORETA) was used to estimate EEG sources at each time instant, resulting in high Variance Accounted For (VAF above 80%). EEG sources were combined with the tracts obtained with dMRI. A Multivariate Auto-Regressive (MAR) model was used to estimate the causal relationship between the EEG sources in time, which is effectively the signal propagation through the brain.The MAR model between sources resulted in a high VAF (above 90%) in the cross-validation test.
The estimated dynamic information flow was compared between chronic hemiparetic stroke and able-bodied individuals. The results demonstrate that stroke patients had considerable activity in the contralesional hemisphere, through the corpus callosum. This methodology may lead to the development of a quantitative tool for monitoring functional changes of the cortical neural networks after a unilateral brain injury. This will facilitate the research into neuroplasticity and the diagnosis and treatment of stroke rehabilitation.

Disclosures: F.C.T. Van Der Helm: None. **O.G. Filatova:** None. **Y. Yang:** None. **P. Maceira-Elvira:** None. **R. Tian:** None. **G. Kwakkel:** None. **Y. Takeda:** None. **O. Yamashita:** None. **J.P. Dewald:** None.

Poster

671. Reflexes

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 671.11/N6

Topic: E.06. Posture and Gait

Title: Contributions of extrinsic tail muscles to the rat tail nociceptive withdrawal response through reconstruction: Role of non-linearity

Authors: *A. M. BRAZELL, J. Q. NGUYEN, C. L. CLELAND;
James Madison Univ., Harrisonburg, VA

Abstract: Neural control of movement is complex. Synergies have the potential to lessen computational complexity, especially in the rat tail, which is controlled by over 300 muscles or muscle fascicles. Currently, we are using EMG to identify muscle activation and synergies. In addition, we have developed a “reconstruction” approach to characterize the patterns of muscle

activity associated with the nociceptive withdrawal response (NWR). In this approach, we first recorded the tail movement in response to a noxious heat stimulus using high-speed video. Second, we recorded the tail movements ("movement primitives") produced by manual stretch of the tendons originating from individual extrinsic muscles in anesthetized rats. Third, we mathematically reconstructed the observed movement by *linearly* adding the movement primitives to determine the pattern of muscles activation that could have created the movement. However, one potential limitation of this approach is that movement primitives are unlikely to add linearly. The specific aim of our current experiment seeks to test linearity by determining to what extent the movement primitives sum linearly, and if they don't, how we can more accurately model their nonlinear summation. In anesthetized, adult Sprague-Dawley rats, we pulled on one tendon, a second tendon, and then both tendons simultaneously to create movement which we quantified via video tracking. We then compared linear summation of the individual movements to the combined movement. Our results demonstrate that for small movements the movement primitives sum linearly, however the summation is up to 30% sublinear for large movements. We will use these results to devise a mathematical model for adding muscle primitives that accounts for the size of the movement primitive, so that our calculated sum in the previous experiments more accurately matches the observed NWR movement.

Disclosures: A.M. Brazell: None. **J.Q. Nguyen:** None. **C.L. Cleland:** None.

Poster

671. Reflexes

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 671.12/N7

Topic: E.06. Posture and Gait

Title: Patterns of activity of intrinsic tail muscles during the heat evoked nociceptive withdrawal response in the rat

Authors: *A. B. PEROE, S. M. EVANS, H. IZADPANAH, C. L. CLELAND;
James Madison Univ., Harrisonburg, VA

Abstract: Motor control is complicated by muscular redundancy. Synergies provide one potential solution to simplify computational complexity. The rat tail, which is controlled by over 300 extrinsic and intrinsic muscles or muscle fascicles, is an ideal model system to use electromyography (EMG) to explore the role of muscular synergies in a hyper-redundant limb or appendage. Previous studies in our laboratory recorded muscle activity from intrinsic tail muscles; however their approach did not allow for selective recording from intrinsic tail muscles. Our goal was to develop a method for selectively recording muscle activity from the six intrinsic tail muscles and to use the method to explore synergies within these muscles. Rats (Sprague-

Dawley) were briefly anesthetized to insert into the tail bipolar fine wire electrodes, each of which consisted of 36g, multi-stranded stainless-steel wires, de-insulated by a distal diagonal cut. The de-insulated portions were positioned as close as possible to reduce cross-talk. Electrodes were placed into dorsolateral, lateral and ventral muscles that span coccygeal vertebrae. Either six electrodes were placed in each of the six muscles at the same level to evaluate cross-talk, or within one muscle type at seven locations to evaluate the pattern of muscle activity. Under isometric conditions, heat stimuli (980nm laser) were delivered to the lateral surface at multiple locations along the tail and single unit EMG was discriminated. Our results demonstrated the intrinsic muscles of the tail be recorded with minimal cross talk between adjacent muscles at the same level. The left and right dorsolateral muscles, which are in close contact with each other, showed only <20% crosstalk for motor unit potentials >50mV. No cross-talk was observed between the other pairs of muscles.

Disclosures: **A.B. Peroe:** None. **S.M. Evans:** None. **H. Izadpanah:** None. **C.L. Cleland:** None.

Poster

671. Reflexes

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 671.13/N8

Topic: E.06. Posture and Gait

Title: Dependence of the nociceptive withdrawal response on stimulus location in the intact, unanesthetized rat

Authors: *B. SIMPSON, M. FERLAZZO, M. RUGGERI, C. EVANS, C. L. CLELAND; James Madison Univ., Harrisonburg, VA

Abstract: The nociceptive withdrawal response (NWR) is characterized by withdrawal of the limb to avoid noxious stimuli. Although the NWR has been studied in humans and spinalized animals, it is unclear whether there is a dependence on stimulus location in intact, unanesthetized, non-human animals. The aim of our research was to use high speed video of the intact, unanesthetized rat's limb to determine if there is an effect of stimulus location on the NWR evoked by heat and electrical stimuli. Rats (n=7) were stimulated at five locations on the plantar surface of the hind foot and two opposing locations (anterior, posterior) on the lower leg using either heat (980nm laser) or electrical current (3xT, 5 pulses). The resulting movement associated with the NWR was quantified in the sagittal plane with high speed video (500 fps) to determine the time course of joint angle (ankle, knee, hip) and conventional video underneath to determine the initial and final location of the foot in the frontal plane. Preliminary results demonstrate that the heat-evoked NWR consisted of three sequential phases: 1) slow rostral/dorsal "lean" that included slight extension at the ankle, 2) rapid flexion around the ankle,

knee and hip, and 3) rapid replacement of the foot on the surface in the rostral or caudal direction. Unexpectedly, the rapid flexion around the ankle, knee, and hip did not depend on plantar stimulus location ($p>0.05$, Linear Mixed Effects). Similarly, stimuli delivered to the anterior and posterior aspects of the lower leg resulted in similar movements. In contrast, the early, slow ankle extension was significantly greater for caudal stimuli delivered to the foot ($P<0.00001$, LME). Electrical stimuli resulted in a vastly different movement. The upward movement was greater, the foot was always replaced in the caudal direction, and the contralateral hind leg was often lifted. For both stimuli, the magnitude of response greatly exceeded similar responses in humans. In summary, the NWR appears more complex than previously appreciated, including at least three different components which vary in their dependence on stimulus location. The disparate results of electrical stimulation were especially intriguing, since electrical stimulus is commonly used in human studies of the NWR.

Disclosures: B. Simpson: None. **C.L. Cleland:** None. **M. Ferlazzo:** None. **M. Ruggeri:** None. **C. Evans:** None.

Poster

671. Reflexes

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 671.14/N9

Topic: E.06. Posture and Gait

Support: University of Miami Provost's Research Award

Title: Neural excitability during single-limb balance following a lateral ankle sprain

Authors: *K.-M. KIM[1], J. KIM[1], O. DAHMAN[1], Y. AN[2], K. KIM[3];
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Abstract: There is clear evidence that single-limb balance (SLB) impairs following lateral ankle sprain (LAS) and poorer SLB is associated with a higher risk of LAS. However, the underlying neurophysiological mechanism remains unclear. Previous research suggested that proprioceptive deficits that arise from damaged mechanoreceptors within the injured ligaments following LAS. However, there is emerging evidence, suggesting that efferent motor control of SLB such as neural excitability of lower leg muscles may change following LAS. Thus, the purpose of the study was to investigate the neural excitability of soleus muscle during SLB following LAS. The present study utilized a case-control study design with two groups: LAS and healthy control. A total of 16 subjects participated in the study: 8 subjects with LAS within two weeks of the injury onset (5 females; age=20±2.2yrs, height=172.2±7.6cm, mass=70.6±10.1kg) and eight healthy

controls without any history of ankle sprain (4 females; age=21±3.0yrs, height=174.7±10.4cm, mass=67.3±14.4kg). All participants have completed two separate tests of neural excitability in random order while balancing with injured limbs in the LAS group or side-matched limbs in the healthy control group. The tests were for eliciting (1) Hoffmann reflex (H-reflex) to estimate spinal excitability and (2) motor evoked potential (MEP) to quantify corticospinal excitability. For H-reflex peripheral electrical stimulations to the tibial nerve were utilized to elicit not only H-reflex but also motor responses. We recorded five trials of maximum H-reflexes (H-max) and motor responses (M-max). For MEP transcranial magnetic stimulation (TMS) was used to excite a cortical area innervating the soleus muscle. We collected ten trials of MEP at a TMS intensity of 120% of active motor threshold. Both averages of H-max and MEP responses were normalized to the M-max average to allow for between-group comparisons. We performed two independent t-tests with the alpha level was set at <0.05. There were no significant group differences for Hmax/Mmax ratio (LAS: 0.57±0.23 and healthy control: 0.61±0.10, p=0.62) and for MEP/Mmax ratio (LAS: 0.11±0.07 and healthy control: 0.14±0.09, p=0.39). These preliminary results indicate that spinal and corticospinal excitability may not change following LAS, and suggest that other neurophysiological mechanisms may contribute to single-limb balance deficits following LAS.

Disclosures: K. Kim: None. **J. Kim:** None. **O. Dahman:** None. **Y. An:** None. **K. Kim:** None.

Poster

672. Neural and Contextual Modulation of Sexual Behavior

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 672.01/N10

Topic: F.02. Behavioral Neuroendocrinology

Title: Exposure to genistein in male and female Long-Evans rats affects reproductive physiology and behavior

Authors: *F. A. GUARRACI, M. ALI, M. BROYLES, L. K. DAVIS, C. M. GONZALEZ, D. LUCERO, L. STARY;
Southwestern Univ., Georgetown, TX

Abstract: The present study was designed to examine the effects of neonatal genistein exposure on measures of reproductive physiology and behavior. Approximately 24 hours after birth, male and female Long-Evans rat pups were injected daily with genistein (0.15 mg/kg, s.c.; n=23) or olive oil (n = 22) for 5 days, beginning on postnatal day (PD) 1. After weaning at PD 23, preputial separation in males and vaginal opening in females were examined daily until all subjects reached puberty. For all female subjects, we examined vaginal cytology daily for 28 days starting ~ PD 55. Two months after monitoring estrous cyclicity, the female subjects were given the opportunity to interact with a gonadally intact male or a sexually receptive female rat

on the day of behavioral estrus to assess sexual motivation (i.e., partner-preference test with and without physical contact). For all male subjects, we assessed the development of male copulatory behavior once weekly for 3 weeks beginning ~ PD 55. On week 4, sexual motivation was assessed using the partner-preference test (without physical contact). We found that neonatal exposure to genistein had no effect on puberty onset in male or female rats. However, female subjects exposed to genistein displayed more irregular estrous cycles than controls. Neonatal genistein exposure also altered the development of male copulatory behavior, as indicated by increased mount frequency and increased intromission frequency. In contrast, neither female nor male sexual motivation was affected by genistein. The results of the present study have important implications for the development of reproductive physiology and behavior in human neonates exposed to genistein in soy-based baby-formula.

Disclosures: F.A. Guarraci: None. **M. Ali:** None. **M. Broyles:** None. **L.K. Davis:** None. **C.M. Gonzalez:** None. **D. Lucero:** None. **L. Stary:** None.

Poster

672. Neural and Contextual Modulation of Sexual Behavior

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 672.02/N11

Topic: F.02. Behavioral Neuroendocrinology

Support: PFP1295-16

Title: Perinatal SSRI exposure and rat sexual behavior

Authors: *E. M. S. SNOEREN[1], J. HEGSTAD[2], D. J. HOUWING[3], J. D. OLIVIER[4], R. HEIJKOOP[2];
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Abstract: Perinatal exposure to SSRIs might have long-lasting effects on the developing child. Regarding sexual behavior, the time of SSRI exposure appears to be crucial: previous studies showed that prenatal exposure did not affect male copulatory behavior, while postnatal exposure decreased the number of mounts, intromissions and ejaculations. In females, on the other hand, it was shown that postnatal SSRI exposure increased proceptive and receptive behavior. To date, little is known about sexual behavior of rats under more naturalistic circumstances, where sexual competition and partner choice might play a role. Our study aims to investigate perinatal fluoxetine exposure in rats and the effects on male and female sexual behavior during the complete behavioral estrous cycle in a seminatural environment.

Dams received a daily dose of 10 mg/kg fluoxetine (FLX) per day or vehicle (CTR) from gestational day 0 until weaning on postnatal day 21. In 5 cohorts of 8 rats (4 males, 4 females), the offspring (n=10) were tested in a seminatural environment during 8 consecutive days. To induce sexual receptivity (without which copulation will not take place), females were hormonally primed on day 7. All male and female copulatory behaviors were scored and categorized in "copulatory bouts", defined as the time between the initial mount or intromission (males) or lordosis (females) and the beginning of a period of sexual inactivity lasting for more than 60 min. We studied the timing and content of the bouts, as well as which conspecifics were engaged in the behavior. Furthermore, we studied the display of other social and conflict behaviors over the course of the copulatory bouts.

Disclosures: E.M.S. Snoeren: None. **J. Hegstad:** None. **D.J. Houwing:** None. **J.D. Olivier:** None. **R. Heijkoop:** None.

Poster

672. Neural and Contextual Modulation of Sexual Behavior

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 672.03/N12

Topic: F.02. Behavioral Neuroendocrinology

Title: A novel function of fibroblast growth factor 5 (FGF5)—The critical role in central regulation of mouse sociosexual behavior

Authors: *K. MATSUDA[1], K. NAKAMURA[2], A. MUNETOMO[3], T. HAMADA[4], J. IMAKI[5], Y. KONDO[1];
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Abstract: Fibroblast Growth factor 5 (FGF5) broadly expresses in the central nervous system. However, our knowledge of the function is limited except for the blood brain barrier, and little has been known especially on the behavioral regulation. In this study, we first demonstrated behavioral characteristic of FGF5 null mutant male mice, compared to that of wild-type (WT) males. When exposing to odors of sexually mature males and receptive females simultaneously, WT males explored female odor significantly longer than male odor, while FGF5 null males displayed significantly shorter investigation for either odors than WT males, frequently resulting in no preference. In sexual behavior tests, FGF5 null males showed significantly lower sexual activities and longer latency in ejaculation than WT males. Furthermore, FGF5 null males showed higher anxiety-like behavior in the elevated plus maze, spent longer time in the closed

arms that WT males did. In the tube dominance test, FGF5 null males frequently lost to WT males.
Since we found severe dysfunction in sociosexual behavior of FGF5 null mice, we reexamined FGF5 mRNA expression in the mouse forebrain, indicating that FGF5 gene expresses broadly such as in the olfactory bulb (OB), the amygdala, the hippocampus, and the hypothalamus. Immunohistochemistry (IHC) and in situ hybridization (ISH) studies detected the signals in common in the hippocampus, the cerebral cortices, and the thalamic reticular nucleus. However, the signals were generally weak and able to confirm the PCR results only partly. Furthermore, the inconsistency was found between IHC and ISH. Intense signals in the granular layer of CA2, CA3 and dentate gyrus, but weak in CA1, of the hippocampus were observed by ISH, while immunoreactive patchy particle (not cellular form) were found in the hippocampus including CA1 by IHC. ISH detected weak signals in the OB, but IHC failed. The current study demonstrates that secretory FGF5 in the central nervous system is involved in neural regulation of sociosexual behavior, suggesting to concern some psychiatric disease in human, similar to FGF2, through binding FGF receptor 1 (FGFR1).

Disclosures: **K. Matsuda:** None. **K. Nakamura:** None. **A. Munetomo:** None. **T. Hamada:** None. **J. Imaki:** None. **Y. Kondo:** None.

Poster

672. Neural and Contextual Modulation of Sexual Behavior

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 672.04/N13

Topic: F.02. Behavioral Neuroendocrinology

Support: CONACyT: AMM 595375 and VSZ 595360

Title: Effect of sexual behavior and denervation on the expression of adrenergic, cholinergic, androgens and prolactin receptors in major pelvic ganglion

Authors: *A. MATEOS-MORENO[1], V. SÁNCHEZ-ZAVALETA[1], F. ROJAS-DURÁN[2], G. ARANDA-ABREU[2], D. HERRERA-COVARRUBIAS[2], J. MANZO[2], M. HERNÁNDEZ-AGUILAR[2];
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Abstract: The Major Pelvic Ganglion (GPM) of male rat is an autonomic structure responsible for modulating pelvic organs, including the prostate gland. This, is regulated by hormones such as prolactin (PRL) and testosterone (T) and is also controlled by the GPM, which receives preganglionic fibers from the Pelvic (PvN) and Hypogastric (HgN) nerves. MPG controls the function of prostate gland by the release of noradrenaline and acetylcholine. It is know, that

performance of sexual behavior induces an increase in the serum levels of prolactin (PRL) and testosterone (T), as well as its receptors in the prostate and increase in the neuronal activity of the GPM, but it has not been reported if this sexual behavior also increases the expression of receptors for acetylcholine (M3), noradrenaline (α1a), androgens (AR) and prolactin (PRLR) in MPG. On the other hand, there is evidence that PvN and HgN axotomy promotes alterations in prostatic cytoarchitecture. Therefore, another objective of the present study was to evaluate the effect of suspension of the nervous control by bilateral section of pelvic and hypogastric nerves, on the expression of the mentioned receptors, in order to correlate them with the observed histological changes. Methods: Wistar male rats of 3 months of age were used to form the following groups: intact (INT), sexually expert (S.E), false surgery (SHAM), and denervated of PvN, HgN and PvN+HgN. GPM was extracted 15 days post-surgery and levels of expression of receptors were analyzed: adrenergic (α1a), muscarinic (M3), androgens (AR) and prolactin (RPRL). Results: Sexual behavior did not alter the expression of any of the receptors analyzed. Axotomy of both nerves induced a significant increase in the expression of the AR and M3 receptor, however it did not alter the expression of PRL nor adrenergic (α1a) receptors. Conclussion: The sexual behavior does not alter expression of analyzed receptors, but damage in preganglionar neurotransmission induced by the denervation produced an increase of the RA and M3 receptor. This suggests that histological alterations observed in prostate of denervated animals may be a consequence of alteration in expression of at least these two receptors.

Disclosures: **A. Mateos-Moreno:** None. **V. Sánchez-Zavaleta:** None. **F. Rojas-Durán:** None. **G. Aranda-Abreu:** None. **D. Herrera-Covarrubias:** None. **J. Manzo:** None. **M. Hernández-Aguilar:** None.

Poster

672. Neural and Contextual Modulation of Sexual Behavior

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 672.05/N14

Topic: F.02. Behavioral Neuroendocrinology

Support: CONACyT: VSZ 595360, AMM 595375; UV-CA-304

Title: Sexual behavior induces morphometric changes in major pelvic ganglion and prostate

Authors: *V. SÁNCHEZ-ZAVALETA[1], A. MATEOS-MORENO[1], G. E. ARANDA-ABREU[2], D. HERRERA-COVARRUBIAS[2], J. MANZO[2], R. TOLEDO-CÁRDENAS[2], J. SUÁREZ-MEDELLIN[2], M. E. HERNÁNDEZ-AGUILAR[2];
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Abstract: Background: The prostate is an important sexual gland for reproductive success, since it contributes 30 percent of whole content of semen, so it plays a fundamental role for male fertility. This gland is regulated by hormones such as androgens, estrogens and prolactin, but it also receives innervation from postganglionic fibers that emerge from the major pelvic ganglion (MPG), which in turn contains preganglionic fibers from the pelvic and hypogastric nerves. On the other hand, the prostate responds to sexual behavior, since it induces an increase in prostatic fluid synthesis. However, to date there are no studies that indicate how this physiological stimulus impacts on this gland. Therefore, the aim of this study was to evaluate the effect of the execution of sexual behavior on the histological characteristics not only of the prostate but also of the GPM. **Methodology:** Twelve male Wistar rats three months old were used for the experiment, distributed in two groups: without sexual experience (Naive) and sexually experienced (SE) subjects. **Results**: Sexual behavior promoted a significant increase in whole MPG area ($p < 0.05$), number of SIF cells ($p < 0.05$), as well as in neural soma ($p < 0.001$); while in the ventral and dorsolateral prostates increased the alveolar area ($p < 0.001$), epithelial height ($p < 0.001$) and nucleus area of epithelial cells ($p < 0.001$). **Conclusions:** Sexual experience induces beneficial histological changes in both, MPG and prostate, which suggests that this behavior is an important factor that favors maturation processes in both structures. It should be noted that this work is the first to show the effect of sexual behavior on the histology of an autonomic ganglion such as MPG.

Disclosures: V. Sánchez-Zavaleta: None. **A. Mateos-Moreno:** None. **G.E. Aranda-Abreu:** None. **D. Herrera-Covarrubias:** None. **J. Manzo:** None. **R. Toledo-Cárdenas:** None. **J. Suárez-Medellin:** None. **M.E. Hernández-Aguilar:** None.

Poster

672. Neural and Contextual Modulation of Sexual Behavior

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 672.06/N15

Topic: F.02. Behavioral Neuroendocrinology

Title: Sex-specific regulation of central vasopressin in mouse sociosexual behavior

Authors: *K. SHIMIZU[1,2], K. NAKAMURA[3], Y. KONDO[2];
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Abstract: Arginine Vasopressin (AVP) has been known as not only a hormone regulating blood pressure and water metabolism in the kidney but also a central peptide regulating various behaviors including social behavior. Two types of AVP receptors, v1a and v1b, are expressed in the brain, and many studies has been investigating the function of each of them. However, it

remains unclear how central AVP regulates sexual behavior in male and female mice. In this study, we examined the effect of double-KO (dKO) of v1a and v1b on sociosexual behaviors in male and female mice, comparing to those of wild-type (WT) mice. Male subjects were intact and female subjects were ovariectomized and primed with estrogen and progesterone. In the weekly sexual preference tests exposing to airborne odors of mature males and receptive females, both WT and dKO mice showed clear preference for the opposite-sex odor to the same-sex odor. Sexual behaviors were tested in enriched large cage equipped with several objects which prompted social interactions (In the female tests, the area accessible to stimulus males was restricted a half of the cage by tethering to measure female pacing behavior). The dKO males showed significantly increased numbers of pursuing and approaching behaviors than WT males did, resulting in significantly larger number of mounts in dKO males. In contrast, dKO females had decreased number of approaching behaviors to stimulus males than WT females did, resulting significantly smaller number of mounts received. In WT and dKO females, we additionally tested for the preference of soiled beddings collected from home cages of intact males and receptive females. WT females showed significantly longer time spent for nose-contact investigation to the male soiled beddings than female one, while no difference was found in investigation time of dKO females for male and female soiled beddings. Our current data demonstrate that central AVP regulates male and female mouse sexual behavior in completely opposite way, inhibitory in males and facilitatory in females. Furthermore, this study also showed that central AVP is not involved in regulation of the preference for volatile, airborne odors, but modulates the preference for involatile chemicals detected by the vomeronasal organs.

Disclosures: **K. Shimizu:** None. **K. Nakamura:** None. **Y. Kondo:** None.

Poster

672. Neural and Contextual Modulation of Sexual Behavior

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Program #/Poster #: 672.07/N16

Topic: F.02. Behavioral Neuroendocrinology

Support: PASSHE:FPDC Grant #3538222789.1
Edinboro University USRC Grant #3513186643

Title: The effects of a long-acting gonadotropin-releasing hormone receptor antagonist on sexual reward in male rats

Authors: *L. E. KAPP, H. A. DUFALA, C. M. DINGLE, W. R. HAWLEY;
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Abstract: The rewarding aspects of sexual behaviors serve to reinforce the subsequent expression of the behaviors themselves. In male rats, gonadectomy reduces the preference for

environments previously associated with sexual behaviors, which is indicative of sexual reward. In this study, sexual reward and consummatory sexual behaviors in male rats were examined following treatment with degarelix, a long-acting gonadotropin-releasing hormone (GnRH) receptor antagonist that has been used to attenuate androgen receptor signaling as part of the treatment for prostate cancer. The rewarding aspects of sexual behavior were assessed in a three-chambered conditioned place preference (CPP) maze that featured distinct visual cues on the external walls of the end chambers. Male rats received a set of sexual training trials and a single probe trial once a week for four consecutive weeks in order to establish and examine their preference for the sex-associated side. Twenty-four hours after the final pre-drug probe trial, half of the rats were administered degarelix (1.5 mg/kg) and the other half were administered a vehicle control (5% mannitol). One week later, all rats were tested on a post-drug probe trial to reassess their preference for the sex-associated side of the maze. Degarelix significantly reduced the preference for the sex-associated environment relative to the opposite end-chamber that was not associated with sexual experience. Consummatory sexual behaviors were examined once a week over the course of the following three weeks. Results revealed that degarelix treated rats exhibited deficits in nearly all aspects of sexual behavior, including the latency to achieve first mount, intromission, and ejaculation, as well as the total number of intromissions and ejaculations.
Degarelix also significantly reduced the weights of the androgen-sensitive bulbourethral glands and seminal vesicles, which confirmed the drug's bioactivity. The results from this study are the first to uncover the effects of a long-acting GnRH receptor antagonist on sexual reward and provide an important step for future studies that seek to understand the biochemical factors that modulate sexual reward in animal models of androgen deprivation therapy. Given that the reduction in the rewarding aspects of sexual behavior that results from androgen deprivation therapies may produce adverse consequences to psychological health and relationship satisfaction, the ultimate goal of future studies would be to identify alternative pharmacotherapies or behavioral interventions that maintain the rewarding aspects of sexual behavior independent of androgen signaling.

Disclosures: **L.E. Kapp:** None. **H.A. Dufala:** None. **C.M. Dingle:** None. **W.R. Hawley:** None.

Poster

672. Neural and Contextual Modulation of Sexual Behavior

Location: Hall A

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Program #/Poster #: 672.08/N17

Topic: F.02. Behavioral Neuroendocrinology

Support: PASSHE: FPDC grant #3538222789.1
Edinboro University USRC grant #3513186643

Title: Administration of a gonadotropin-releasing hormone receptor antagonist reduces sexual incentive motivation in male rats: The role of sociosexual stimulation

Authors: P. A. GREEN, L. E. KAPP, H. A. DUFALA, J. L. BARNES, J. L. BARWELL, C. M. DINGLE, *W. R. HAWLEY;
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Abstract: For those suffering with prostate cancer, treatment with the long-acting gonadotropin-releasing hormone (GnRH) receptor antagonist degarelix has been shown to decrease androgen receptor signaling and correspondingly reduce prostate-specific antigens. Unfortunately, androgen deprivation therapies such as these are associated with deficits in sexual motivation. Consequently, it was expected that administration of degarelix would also decrease sexual motivation in male rats, an effect similar to that which occurs following gonadectomy. In addition to gonadal hormones, sexual motivation is modulated by a variety of other social and environmental factors. For instance, when older male rats were allowed to mount a sexually receptive female immediately prior to testing sexual incentive motivation (SIM) they subsequently exhibited a preference for a female relative to a male sexual incentive. Therefore, because mounting behaviors in male rats can be maintained for several weeks after gonadectomy, it was expected that a brief exposure to a female sexual incentive would attenuate the effects of degarelix on SIM in male rats. Sexually experienced male rats were treated once with either a vehicle solution (5% mannitol) or a dose of degarelix (1.5 mg/kg) that rapidly and drastically reduces androgen signaling for over one month. SIM testing was conducted in a three-chambered maze that featured a male and a sexually receptive female incentive individually confined behind separate smaller stimulus chambers. A single stimulus chamber was placed into each of the larger end chambers of the maze. The first SIM test was conducted one week after treatment and subsequent tests were conducted once every 7 days thereafter. However, 15 minutes prior to each SIM test, half of the rats in each treatment condition were exposed for 10 minutes to a sexually receptive female with whom they could sexually interact with. Rats treated with degarelix spent significantly less time in the vicinity of the female relative to the male. Although a brief exposure to a sexually receptive female tended to increase levels of activity on the SIM test in degarelix treated rats, as indicated by the total number of end chamber entries, it was not sufficient to enhance the preference for a female incentive. However, this may have been due to the fact that the drug nearly abolished all mounting behavior only one week after treatment. These results stand in contrast to the effects of gonadectomy that have been reported previously as they suggest that chemical suppression of testosterone with degarelix is highly effective at rapidly reducing SIM and mounting behaviors in male rats.

Disclosures: P.A. Green: None. **L.E. Kapp:** None. **H.A. Dufala:** None. **J.L. Barnes:** None. **J.L. Barwell:** None. **C.M. Dingle:** None. **W.R. Hawley:** None.

Poster

672. Neural and Contextual Modulation of Sexual Behavior

Location: Hall A

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Program #/Poster #: 672.09/N18

Topic: F.02. Behavioral Neuroendocrinology

Support: CONACYT grant 487669
SEP-CINVESTAV 109

Title: Insulin improves sexual motivation in diabetic female rats evaluated in two paradigms

Authors: *A. K. HERNÁNDEZ-MUNIVE[1], D. REBOLLEDO-SOLLEIRO[2], A. FERNÁNDEZ-GUASTI[1];
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Abstract: The relationship between diabetes mellitus (DM) and sexual dysfunction in women has shown controversial results. The animal model mostly used to study the alterations in DM is the administration of streptozotocin (STZ), a drug that destroys B-pancreatic cells. When STZ is administered in the adult stage, the animal shows some symptoms of DM1: polyphagia, polydipsia, polyuria, hyperglycemia and weight loss. In preclinical studies, it has been reported that females treated with STZ showed an altered estrous cycle, a reduction in sexual receptivity and an increased aggressiveness, changes that were restored when insulin was exogenously administered. However, the motivational component of copulation in hyperglycemic rats has not been studied. The aim of this study was to evaluate female sexual motivation (FSM) in a model of DM1 in two paradigms: the partner preference (PP) and the incentive sexual motivation (ISM). DM1 was modeled in OVX Wistar rats by injecting STZ diluted in citrate buffer [50 mg/kg, i.p., for 2 consecutive days]. Ten days later, female rats were treated with estradiol benzoate (10 μg, -24 h) and progesterone (3 mg, -4 h). Also, a group of STZ-treated animals were administered with a long-acting insulin analogue (glargine) every 12 hours for 10 days (2-4U). Body weight was recorded at the beginning and at the end of the study and glucose levels were also reported (only animals with blood glucose values ≥ 350 mg/dl were considered for the study). For PP we registered the time in each compartment, the time of interaction with each stimulus and the preference of these animals. In the ISM test, we calculated the time that the female stays in each incentive zone and the time the female invests sniffing the wall that isolates the stimuli. In both tests, a castrated male (CM) and a sexually experienced male (SEM) were used as stimuli. STZ-treated OVX rats lost body weight and had increased blood glucose levels. In the PP test, control females spent more time with an SEM, while the hyperglycemic females stayed the same amount of time with the CM and the SEM and 4 out of 11 STZ-treated females preferred to remain in the box of the CM. Similarly, in the ISM arena, the control females spent

more time in sexual incentive zone, while the treated with STZ remained the same amount of time in the vicinity of the both stimuli, however, there was no difference between STZ and control females in the time spent sniffing the wall that isolated the stimuli. All these changes (in PP and ISM) were reversed with insulin to values comparable of those of the control group. Our data suggest that severe hyperglycemia decreases FSM and that insulin fully recovers such diminution.

Disclosures: A.K. Hernández-Munive: None. **D. Rebolledo-Solleiro:** None. **A. Fernández-Guasti:** None.

Poster

672. Neural and Contextual Modulation of Sexual Behavior

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Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 672.10/N19

Topic: F.02. Behavioral Neuroendocrinology

Support: NIH Fellowship 5F31HD094480-02

Title: Modulating sexual behavior in female rats with tibial nerve electrical stimulation

Authors: *L. L. ZIMMERMAN[1,2], G. MENTZELOPOULOS[1,3,2], H. J. PARRISH[3,2], B. D. LUMA[4], J. B. BECKER[4,5], T. M. BRUNS[1,2];
[1]Biomed. Engin., [2]Biointerfaces Inst., [3]Electrical Engin. and Computer Sci., [4]Mol. and Behavioral Neurosci. Inst., [5]Psychology, Univ. of Michigan, Ann Arbor, MI

Abstract: Female sexual dysfunction affects millions of women worldwide yet there are limited treatment options. In previous work, we have established that electrical stimulation of the tibial nerve can drive increases in vaginal blood flow in anesthetized female rats, indicating the potential to be used as a treatment for genital arousal deficiencies. Here, we are studying whether tibial nerve stimulation driven genital arousal can affect sexual motivation, which would indicate potential for treating genital arousal disorders as well as decreased sexual interest in women. Female rats were ovariectomized to eliminate hormonal control over sexual motivation and trained to use an operant apparatus. The apparatus has two chambers, with the female required to nose-poke to open a door between chambers to access a sexually active male. Nose pokes on a fixed interval (FI) 15 second schedule was used to quantify extent of sexual motivation. Once a week each rat was randomly assigned to one of five conditions: no stimulation & no hormone treatment, no stimulation & partial hormones, stimulation & no hormones, stimulation & partial hormones, no stimulation & full hormones. Tibial nerve stimulation was applied with a percutaneous wire at 20 Hz for 30 minutes at an amplitude twice the motor threshold prior to placement in apparatus. For hormone conditions, 10 μg 17 β-estradiol benzoate was administered 48 hours prior to testing, and 100 μg (partial dosing) or 500 μg (full dosing) progesterone was

administered 4-5 hours in advance. Each rat was tested twice per condition, for a total of 10 weeks of testing. To date, animals receiving stimulation without hormones, on average, nose poked more times per interval and spent more time in the male zone than animals receiving neither hormones nor stimulation, but less than animals receiving hormones without stimulation. Future studies will evaluate whether repeated tibial nerve stimulation over time has a cumulative effect on the sexual behavior of females.

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Poster

672. Neural and Contextual Modulation of Sexual Behavior

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Program #/Poster #: 672.11/N20

Topic: F.02. Behavioral Neuroendocrinology

Support: NIH Grant MH116470
NIH Grant HD095597

Title: Lateral hypothalamic control of male and female sexual motivation

Authors: *K. J. JENNINGS, W. J. GIARDINO, L. DE LECEA;
Psychiatry and Behavioral Sci., Stanford Univ., Stanford, CA

Abstract: Stimulation of the lateral hypothalamus (LHA) has long been known to facilitate sexual motivation. Among the multiple cell types that populate the LHA, neurons that produce the neuropeptide hypocretin (Hcrt, also known as orexin) are strong candidates to promote sexual motivation. Hcrt neurons drive arousal and reward-seeking behavior and are hypothesized to support expression of motivated behavior. To determine the role of LHA-Hcrt neurons in male and female sexual motivation, we first used fiber photometry to record calcium activity of LHA-Hcrt neurons while mice interacted with an opposite-sex conspecific. LHA-Hcrt calcium activity is increased during appetitive sexual behavior and decreased during consummatory sexual behaviors in both sexes. LHA-Hcrt activity is higher during appetitive behavior that progresses to consummatory behavior than during appetitive behavior that does not lead to consummatory behavior, consistent with a role in sexual motivation. We next used targeted optogenetic manipulation of LHA-Hcrt neurons during specific social behaviors to probe the causal role of LHA-Hcrt neurons in male and female sexual behavior. These data confirm the functional role of LHA-Hcrt neurons in male and female sexual motivation and broaden our understanding of LHA-Hcrt regulation of motivational and emotional states.

Disclosures: K.J. Jennings: None. **W.J. Giardino:** None. **L. de Lecea:** None.

Poster

672. Neural and Contextual Modulation of Sexual Behavior

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 672.12/N21

Topic: F.02. Behavioral Neuroendocrinology

Support: FCE Grant FCE-1-2017-1-136603
DT-CSIC, UdelaR
PEDECIBA, Biologia

Title: Sexual motivation throughout adolescence in the female rat and its c-Fos expression correlate

Authors: *D. AGRATI, M. ARMAS, G. MARIN, G. BEDO;
Facultad De Ciencias, Univ. De La Republica, Montevideo, Uruguay

Abstract: Sexual behavior in the female rat is highly motivated. However, although this behavior begins to be expressed during adolescence, sexual motivation has been poorly studied during this period. The present study aimed to explore the expression of the sexual motivation of female rats along adolescence. In order to achieve this, the incentive value of a sexually active male for middle (39-43 days-old) and late (49-53 days-old) adolescent and adult (90-110 days-old) female rats in late-proestrus was assessed in two models: a) male vs. non-receptive female preference test in a Y-maze without physical access to the stimuli, and b) emission of 50 kHz ultrasonic vocalization (USV) in response to a brief interaction without physical contact with a male or a non-receptive female. The brains of the females that underwent the USV emission test were processed 65 min after the initiation of the test for quantifying c-Fos protein expression as an index of neural activation. Results show that, although all sexually active females, regardless of their age, preferred the male over the female in the Y-maze, late-adolescent and adult rats performed more effort to obtain the male when compared to middle-adolescent rats. Accordingly, late-adolescent and adult females emitted more 50 kHz USV after interacting with a male than with a female, but the emission of USV in response to both social stimuli did not differ in the middle-adolescent group. Preliminary analysis of c-Fos expression suggests a differential activation of neural areas involved in the expression of sexual motivation among ages. These results strongly suggest that the sexual motivation of the female rat increases throughout adolescence and provide elements for understanding maturation processes of the neural circuits that regulate the sexual behavior of female rats.

Disclosures: D. Agrati: None. **M. Armas:** None. **G. Marin:** None. **G. Bedo:** None.

Poster

672. Neural and Contextual Modulation of Sexual Behavior

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 672.13/N22

Topic: F.02. Behavioral Neuroendocrinology

Support: CIHR
NSERC

Title: The facilitating effects of acute oxytocin treatment on pacing and proceptive sexual behaviours are dose-dependent

Authors: *C. E. MAC CIONNAITH[1], E. GOMEZ-PERALES[1], J. G. PFAUS[2], W. BRAKE[1]; [1]Concordia Univ., Montreal, QC, Canada; [2]Univ. Veracruzana, Veracruz, Mexico

Abstract: Several studies have reported that oxytocin (OT) administration increases lordosis quotients in female rats. However, the lordosis reflex is only one of many behaviours that are important during mating in the female rat. Proceptive behaviours (i.e. solicitations and hops and darts) and pacing are important for successful impregnation. Therefore, the current study tests the effects of different doses of oxytocin on a variety of sexual behavioural measures. Thirty female Long-Evans (LE) rats were randomised to be intraperitoneally injected with 20µg OT, 50µg OT, or saline one minute prior to copulation (n = 10 per group). Females copulated with an LE male in unilevel Plexiglass pacing chambers for 30 minutes. Trials were recorded and scored for: female entries to the male compartment, the latency to return to the male after leaving the male's compartment, solicitations, hops and darts, intromissions and ejaculations received, and the amount of time spent with a male. All behaviours were analysed with one-way ANOVAs, followed by Holm-adjusted group comparisons. Females treated with 50µg OT took longer to return to the male chamber and made fewer entries to the male's compartment compared to the 20µg OT group. They also received fewer intromissions and ejaculations. Additionally, females treated with 50µg OT made fewer hops and darts and fewer solicitations than females given 20µg OT. Conversely, 20µg OT females made more proceptive behaviours and entries to the male compartment compared to 50µg OT females. There was also a trend for females given 20µg OT to make more solicitations and hops and darts than saline treated females. Thus, OT may acutely facilitate female sexual behaviour, but these effects are dose dependent; 20µg OT facilitates sexual behaviours whereas 50µg OT is inhibitory.

Disclosures: C.E. Mac Cionnaith: None. **E. Gomez-Perales:** None. **W. Brake:** None. **J.G. Pfaus:** None.

Poster

672. Neural and Contextual Modulation of Sexual Behavior

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Program #/Poster #: 672.14/N23

Topic: F.02. Behavioral Neuroendocrinology

Support: RISE GM07163

Title: Potential progesterone regulated dopaminergic projections to β-endorphin neurons in the arcuate nucleus

Authors: *D. LE, C. E. CARLSON, S. BERMANI, M. LA FOREST, T. CHUON, M. ESKANDER, K. SINCHAK;
Biol. Sci., California State University, Long Beach, Long Beach, CA

Abstract: In ovariectomized (OVX) rats, a priming dose of 2μg of estradiol benzoate (EB) induces the release of β-endorphin (β-END) from neurons of the arcuate nucleus of the hypothalamus (ARH) that project to the medial preoptic nucleus (MPN). This activates and internalizes μ-opioid receptors (MOR), which initially inhibits sexual receptivity (lordosis). Progesterone infused into the ARH rapidly facilitates lordosis and reduces the activation of MPN MOR by upregulating membrane associated classical progesterone receptors (PGR). Our lab has shown previously that ARH PGR complex with and signals through Src family kinase (Src) on the plasma membrane in the ARH that also interacts with dopamine D1 receptor to facilitate lordosis. This PGR-Src-D1 interdependent signaling has been localized to a subpopulation of the ARH β-END neurons, suggesting that a progesterone responsive dopaminergic input to ARH β-END neurons should exist. In this experiment, we tested the hypothesis that progesterone signals through a dopaminergic neuron which projects to β-END neuron in the ARH to regulate sexual receptivity. OVX Long Evans rats were treated with 2μg EB or oil, and rats were perfused 48 hours later. Brain sections through the ARH were processed for doubled labeled immunohistochemistry for PGR-tyrosine hydroxylase (TH; marker for potential dopamine neurons), Src-TH, and β-END-TH. A subpopulation of potential dopamine neurons were immunopositive for TH and PGR, and EB treatment increased the number of TH-PGR positive ARH neurons, indicating that progesterone responsiveness was increased in potential ARH dopaminergic neurons. A subpopulation of neurons were also immunopositive for both Src and TH indicating that a similar PGR-Src mechanism could rapidly regulate the activity of these neurons. Lastly, we observed very little co-localization of β-END-TH immunoreactivity. However, TH immunopositive fibers were in close proximity to immunopositive β-END cell bodies and processes. These results support our hypothesis that progesterone may signal through PGR-Src signaling complexes to activate a subpopulation of potential dopaminergic neurons that project to β-END neurons to reduce their neurotransmission and facilitate lordosis.

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Poster

672. Neural and Contextual Modulation of Sexual Behavior

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Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 672.15/N24

Topic: F.02. Behavioral Neuroendocrinology

Support: NSF Grant 1253126 to SR

Title: From pheromone sensation to reproductive behavior: Identifying the pathway of prostaglandin sensation into the GnRH system in the zebrafish

Authors: *G. N. MCHUGH[1], A. MARCHAND[1], S. RAMAKRISHNAN[2];
[1]Biol., [2]Neurosci. Program, Univ. of Puget Sound, Tacoma, WA

Abstract: Mating, social communication, and social behaviors are modulated through pheromones. In many species this is essential for triggering behaviors associated with reproduction, and hence reproductive success. In most vertebrates studied to date, Gonadotropin Releasing Hormone neurons in the brain have been shown to control reproduction. Of the three populations of GnRH neurons, the extrahypothalamic ones in the terminal nerve associated with the olfactory bulb (TN-GnRH) have been linked to integrating chemosensory and visual stimuli from conspecifics thereby modulating reproductive behaviors. It is therefore likely that pheromonal signals from conspecifics are conveyed to the GnRH system. Prostaglandin (PG) is a pheromone released by female zebrafish to synchronize the timing of spawning behaviors with ovulation. This study investigated the potential link between prostaglandin as a pheromonal signal and TN-GnRH neurons in the brain of male zebrafish. A stable transgenic line of zebrafish with GnRH3 neurons tagged with green fluorescent protein (GFP) was used in this study. We observed behavioral responses of male zebrafish after exposure to 0.1 μM pheromonal PG or 0.1 μM vehicle control (DMSO). Male fish were individually placed in a testing tank and prostaglandin injected into one corner, following which behavior was recorded for 9 min with Ethovision 10 software. Behavioral testing showed that fish interacted with the zone of PG injection more than DMSO tests ($p=0.0432$). Fish exposed to prostaglandin also swam significantly faster ($p=0.0410$) and further ($p=0.0400$) than control treated fish during testing. Immediately after behavioral testing, we used c-*fos* immunohistochemical staining to identify cells in the olfactory bulb and telencephalon expressing immediate early genes. Zebrafish brains (n=8; 4 PG, 4 DMSO) were dissected and imaged using an inverted epifluorescent microscope at 488nm excitation / 512nm emission and 560 excitation / 645 emission. Imaging showed c-*fos* activation of cells in the terminal nerve near GnRH3-GFP neurons, but no co-localization. In order to identify potential intermediary cells, we used calretinin immunohistochemical staining

of chemosensory cells under the same imaging protocol (n=6). We found anatomical proximity between chemosensory neurons and GnRH3-GFP neurons in the terminal nerve. Prostaglandin pheromonal signals can thus be passed on to TN-GnRH3 neurons via chemosensory cells. Double labeling of chemosensory cells with calretinin, along with prostaglandin activated c-fos under a GnRH3-GFP background could confirm this connection.

Disclosures: G.N. McHugh: None. **A. Marchand:** None. **S. Ramakrishnan:** None.

Poster

672. Neural and Contextual Modulation of Sexual Behavior

Location: Hall A

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Program #/Poster #: 672.16/N25

Topic: F.02. Behavioral Neuroendocrinology

Title: Too much of a good thing: The effect of aversive distributed clitoral stimulation on odour conditioned partner partner and 50-kHz ultrasonic vocalizations

Authors: *C. A. GERSON[1], C. E. MAC CIONNAITH[1], M. RIVEST-BEAUREGARD[1], E. GOMEZ-PERALES[1], P. S. B. CLARKE[2], J. G. PFAUS[3], U. SHALEV[1];
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Abstract: Clitoral stimulation (CLS) offers a unique approach to investigating sexual conditioning and 50-kHz ultrasonic vocalizations (USVs). Adult female rats find distributed CLS rewarding as it mimics stimulation received during paced copulation. Distributed CLS induces conditioned partner preference (CPaP) and elicits 50-kHz USVs, both of which indicate reward. The reinforcing potential of CLS however shifts as properties of its application changes. For instance, female rats fail to develop CPaP for a scented male when distributed CLS is previously paired with an inaccessible male and odour. One property of CLS application our lab has yet to assess is tactile intensity, *i.e.* bristle hardness of the paintbrush used to deliver CLS. As distributed CLS is typically delivered using a soft bristle paintbrush, it is unknown whether changes in tactile intensity influences USV emission and CPaP development, and/or whether hard bristle distributed CLS is potentially aversive. To date, aversive sexual conditioning in rodents has only utilized pain as an aversive stimulus. The present study tested the hypothesis that hard bristle distributed CLS paired with an odor can induce condition partner aversion. Changes in USV emission in response to the tactile intensity of CLS administration were also assessed during odor conditioning. Forty-eight ovariectomized females were hormonally primed with estradiol benzoate and progesterone and randomly assigned to one of six conditioning groups (n = 12/group): (1) scented hard bristle CLS vs. unscented sham CLS; (2) unscented hard

bristle CLS vs. scented sham CLS;(3) scented soft bristle CLS vs. unscented sham CLS; (4) unscented soft bristle CLS vs. scented sham CLS; (5) scented hard bristle CLS vs. unscented soft bristle CLS; (6) scented soft bristle CLS vs. unscented hard bristle CLS. Distributed CLS consisted of lightly brushing the clitoris using either a soft or rough No. 4 paintbrush while sham CLS was performed by lifting the base of the tail. CLS was applied every 5 sec for 1 min after a 2 min inter-CLS interval no-CLS and repeated for 5 cycles for total session duration of 15 minutes. Vocalization recordings were conducted during the 12 alternating conditioning trials, which were followed by a final open-field partner-preference test. Preliminary behavioral results suggest a slight conditioned aversion to rough brush CLS that unexpectedly generalized to soft brush CLS. USV calls are currently being analyzed. *Keywords: Distributed Clitoral Stimulation, Ultrasonic Vocalization, Sexual Conditioning, Sexual Aversion*

Disclosures: C.A. Gerson: None. **C.E. Mac Cionnaith:** None. **M. Rivest-Beauregard:** None. **E. Gomez-Perales:** None. **P.S.B. Clarke:** None. **J.G. Pfaus:** None. **U. Shalev:** None.

Poster

672. Neural and Contextual Modulation of Sexual Behavior

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 672.17/N26

Topic: F.02. Behavioral Neuroendocrinology

Support: JSPS KAKENHI Grant Number 19J21828
JSPS KAKENHI Grant Number 26221104
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JSPS KAKENHI Grant Number 18H04881

Title: Neuroendocrinological mechanisms that mediate the coordinated regulation of reproduction and sexual behavior

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Abstract: Successful reproduction requires the coordinated regulation of gametogenesis and sexual behavior. In fact, sexual behavior is observed only when the animal is in the reproductive state. However, little is known about the neuroendocrinological mechanisms for such regulation. In the present study, we examined possible involvement of gonad-derived factors, which are secreted from mature gonads, in the regulation of sexual behavior in a teleost, medaka. Here, we developed and used a semi-automatic system to efficiently and accurately analyze sexual behavior. First, we analyzed the female sexual behavior after ovariectomy and found that the ovariectomized female stayed away from male to avoid male courtship. Administration of one of

the sex steroid hormones, estrogen, to ovariectomized females, reinstated the clasping-like behavior (clasping continued for a shorter period than the intact female) in some pairs. However, the estrogen administration did not reinstate the avoidance behavior. From these results, we considered that estrogen may play some important roles and administered Fadrozole-hydrochloride (an inhibiter of estrogen synthesis) to female. After this treatment, the females did not attain clasping with male, although they normally accepted male courtship. Second, we examined the contribution of estrogen receptors for the behavioral activation by gene-knockout analysis and found that estrogen receptor 2b (Esr2b)-deficient females did not attain clasping with male despite the normal acceptance of male courtship. Interestingly, they had normal ovary, exhibited normal secondary sex characteristics and ovulated normally; they are in the reproductive state. The present results indicate that estrogen signaling via Esr2b plays an important role in the sexual behavior sequence of female medaka as a specific activator of clasping behavior after the acceptance of male courtship. Furthermore, some kind(s) of ovary-derived non-estrogenic factors may play a role in the male acceptance. Because Esr2b is known to be expressed in some brain regions (Zempo *et al.*, 2013), the present results suggest the existence of a neuroendocrinological mechanism in which Esr2b-expressing neurons receive estrogen secreted from mature ovary and then activate clasping behavior.

Disclosures: **S. Tomihara:** None. **D. Kayo:** None. **S. Kanda:** None. **Y. Oka:** None.

Poster

672. Neural and Contextual Modulation of Sexual Behavior

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 672.18/N27

Topic: F.02. Behavioral Neuroendocrinology

Support: JSPS Grant 17H06429

Title: Sexually dimorphic neuropeptide B neurons in the ventral telencephalon, a leading candidate for the regulator of female reproductive behavior, show estrogen dependence and diurnal changes in their neuronal activities

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Abstract: Sexual reproduction requires not only gonadal maturation to attain fertility, but also reproductive-state dependent behavior so-called sexual behavior. For coordination of both under the control of the central nervous system, sex steroid signals such as estrogen (E) play pivotal roles, which is considered to be an essential regulatory system in vertebrates. Previous

physiological and histological studies in both teleosts (Koyama et al., 1984, Satou et al., 1984, Zempo et al., 2013) and mammals (Munchrath & Hofmann, 2010, Lee et al., 2014) have suggested that estrogen receptor (ER)-expressing neurons localized in several brain regions such as the preoptic area (POA), ventral telencephalon (Vs/Vp), and hypothalamus are involved in the regulation of reproductive behaviors. However, the detailed neural circuit including these neurons largely remains unclear.Our previous study discovered in medaka (*Oryzias latipes*) that neuropeptide B (Npb)-expressing neurons localized in Vs/Vp represent female-biased and E-dependent *npb* expression, which is explained by the co-expressed ERs (Hiraki et al., 2014). Therefore, in the present study, to examine possible E-dependent regulation of these neuronal functions in females, we performed neurophysiological analysis. Using female transgenic medaka whose Npb neurons are specifically labeled by GFP (*npba*:*gfp*), we analyzed spontaneous neuronal activities of Vs/Vp Npb neurons by on-cell patch clamp recording in various conditions. First, we discovered their time-of-day dependent changes. Their firing frequency in the early light period (10 AM - 2 PM) when medaka usually start to mate (Mean±SEM; 1.3±0.24 Hz) is significantly higher than that in the middle light period (2 - 6 PM) (0.59±0.11 Hz, $p<0.01$, Steel-Dwass test). Next, we used ovariectomy (OVX) in combination with E supplement (OVX+E) technique. Compared to Sham-operated individuals (1.1±0.30 Hz), OVX ones showed significantly lower frequencies (0.24±0.091 Hz, $p<0.05$, Steel-Dwass test) in their neuronal activities in the early period of the light cycles, which were restored in OVX+E ones (0.78±0.20 Hz). Furthermore, as for the firing patterns, Vs/Vp Npb neurons of Sham-operated fish occasionally showed bursting whereas OVX ones mostly showed silent type, indicating that the firing activity of Npb neurons and Npb release are dependent of E signals. Intriguingly, our previous behavioral analysis indicated that *npb* knockout female medaka have abnormality in mating (Hiraki-Kajiyama et al., in review). Taken together, the present study strongly suggests that Vs/Vp Npb neurons regulate female-specific sexual behaviors specifically in the presence of E.

Disclosures: **M. Nakajo:** None. **T. Hiraki-Kajiyama:** None. **K. Okubo:** None.

Poster

672. Neural and Contextual Modulation of Sexual Behavior

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 672.19/N28

Topic: F.02. Behavioral Neuroendocrinology

Title: Steroid-independent spatial working memory is associated with steroid-independent sexual behavior in b6d2f1 male mice

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[3]Psychology, Univ. of Massachusetts, Boston, Boston, MA

Abstract: In rodents, gonadal steroids play a critical role in the modulation of a wide array of behaviors, including social interaction and cognitive performance. Animals generally experience a reduction or complete inhibition of male sexual behavior following castration. Similarly, castration is associated with decreased performance of spatial, working, and reference learning and memory in males of many species; administration of replacement steroids, including testosterone or estradiol, increases performance on a variety of cognitive tests to levels observed prior to castration. However, between individuals and across species, the role of steroids on these behaviors is highly variable. In a prior study in our lab, two proteins involved in cognitive behavior, amyloid precursor protein and tau, were shown to play a significant role in steroid-independent male sex behavior in B6D2F1 hybrid male mice. Thus, we used this mouse model, in which a large proportion of the males retains the complete repertoire of male reproductive behavior long after castration, to probe a potential relationship between steroid-independent male sexual behavior and steroid-independent cognition. After identifying males as either "maters" (retaining steroid-independent male sex behavior) or "non-maters," animals were tested in an 8-arm radial arm maze. Maters outperformed non-maters in the number of errors committed during the maze ($p < 0.01$). We also observed a trend that maters completed the maze more quickly than non-maters ($p < 0.10$). Our data demonstrate that retention of male sexual behavior and cognitive performance in the absence of gonadal steroids may be linked and warrant further investigation into potential mechanisms underlying these behaviors. Specifically, we plan to further investigate the role of *amyloid precursor protein* and *microtubule associated protein tau* in the hippocampus. Furthermore, we found that the animals' weight had a group-specific effect when predicting number of errors and was included as a covariate in corresponding analyses. These results indicate that the predictive value of weight may reflect different responses to food deprivation or greater motivation to seek food rewards in the maze, identifying additional future routes of inquiry and compelling us to compare expression of genes involved in metabolism, such as leptin receptor b (*Ob-Rb)*, and genes related to motivation, such as dopamine receptor 2 (*D2R*).

Disclosures: C.D. David: None. **B.N. Wyrosdic:** None. **H. Wan:** None. **S. Yitbarek:** None. **J. Park:** None.

Poster

672. Neural and Contextual Modulation of Sexual Behavior

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 672.20/N29

Topic: F.03. Neuroendocrine Processes

Support: CONACyT 338459

Title: Influence of maternal conditions in sexual preference of male progeny

Authors: *A. HERNANDEZ-GONZALEZ, A. FERNANDEZ-GUASTI;
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Abstract: Sexual preference is typically presented in the same way among all species: males usually prefer an estrous female for sexual interaction while receptive females generally prefer a sexually active male. However, also in all species, there is a subpopulation of males with same-sex preference. The most studied reason underlying this preference is a decrease in androgens aromatization in certain brain areas during development that leads to an altered sexual differentiation process. However, the experimental inhibition of aromatase in rats only produces a same sex preference in around half of the subjects. Multiparity and gestational stress have also been proposed as causal factors for same-sex preference. Here we evaluated the possible involvement of multiparity, gestational stress and aromatase inhibition on sexual preference and sexual behavior of the male progeny. We evaluated the role of these factors individually and their putative interaction. We used males whose mothers were primiparous or multiparous (4 or more deliveries); stressed (restriction stress for the last 10 gestation days) or non-stressed; and treatment with the aromatase inhibitor, letrozole (0.56µg/kg/from G10 to delivery). Sexual preference was established in a three-compartment cage, where animals could choose between a sexually experienced male and a receptive female.
We found that letrozole induced a 40% of males with preference for another male, 30% of prenatally stressed males presented same sex preference, and there was a lack of interaction between letrozole and gestational stress because only 50% of males submitted to both treatments had same-sex preference. A 34% of the male progeny of multiparous dams preferred the sexually active male.
High levels of feminine sexual behavior were displayed by males with same sex preference regardless of the cause (gestational stress, multiparity or aromatase inhibition), indicating that all treatments interfered with the defeminization process.
Present data suggest that stress and the inhibition of aromatase do not interact to produce same-sex preference and that multiparity may play an important role in this phenomenon.

Disclosures: A. Hernandez-Gonzalez: None. **A. Fernandez-Guasti:** None.

Poster

672. Neural and Contextual Modulation of Sexual Behavior

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 672.21/N30

Topic: F.02. Behavioral Neuroendocrinology

Title: Rapid changes in sociosexual behaviors around transition to and from behavioral estrus, in female rats housed in a seminatural environment

Authors: *O. LE MOENE[1], **E. HERNANDEZ-ARTEAGA**[2], X. CHU[3], A. AGMO[4];
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Abstract: Intact female rats display sexual behaviors only during a portion of the estrus cycle. This portion, behavioral estrus, coincides with the proestrus/estrus phase as determined by vaginal cytology, and with peak serum concentrations of estradiol and progesterone. In standard experimental setups, intact females gradually changes from complete non-receptivity to full receptivity in the beginning of behavioral estrus and vice versa at the end of estrus. However, in naturalistic settings, the change in receptivity is almost instantaneous. In order to eliminate possible rapid fluctuations in ovarian steroids as causes of the sudden on- and offset of sexual activity, we assessed the changes in sociosexual behaviors around the beginning and end of behavioral estrus in ovariectomized females sequentially treated with estradiol benzoate (18 μg/kg) and progesterone (1 mg/rat). Females were housed in a seminatural environment, in groups of three males and four females. We scored female and male behavior during the 8 minutes preceding and following both the first and last lordosis of behavioral estrus. Immediately before the first lordosis, there was a sharp increase in female paracopulatory behaviors and male pursuit of the females. According to a co-occurrence analysis, the beginning of behavioral estrus was characterized by both pro- and anti-social behaviors. Male sexual behavior was absent before the beginning of estrus. The end of estrus was marked by a sudden decrease in female paracopulatory behavior, as well as male pursuit of the females and male sexual activity. The behavioral changes associated with both the beginning and end of behavioral estrus suggest that the females became attractive to the males only when fully receptive and that they lost this attractivity while still being fully receptive. In fact, it is known that receptivity requires less hormone exposure than attractivity. Both during transition into and out of behavioral estrus, most behavioral changes occurred within three minutes. Since these rapid changes cannot correlate with ovarian hormone fluctuations in these ovariectomized females, the almost instantaneous transition may be caused by mechanisms similar to a phase shift in the function of critical structures within the brain.

Disclosures: O. Le Moene: None. **E. Hernandez-Arteaga:** None. **X. Chu:** None. **A. Agmo:** None.

Poster

673. Hormone Modulation of Behavior and Physiology IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 673.01/N31

Topic: F.03. Neuroendocrine Processes

Support: NKFI K115984
NKFI K128278

Title: Proestrus evokes transcriptional changes in genes encoding ion channel and calcium homeostasis-regulating proteins in GnRH neurons of mice

Authors: *Z. LIPOSITS[1,2], N. SOLYMOSI[3], I. FARKAS[4], C. VASTAGH[5];
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Abstract: In late proestrus, GnRH neurons exhibit increased firing (*Farkas et al., PLoS One, 2013*) and frequency of mPSCs (*Farkas et al., eNeuro, 2018*). These events are indicative of a proestrus-driven plasticity of GnRH neurons with involvement of ion channels. This study examined the effects of proestrus on expression of genes encoding ion channel and calcium homeostasis-regulating proteins in GnRH neurons of regularly cycling, GnRH-GFP transgenic mice (*Suter et al., Endocrinology, 2010*). Met- and proestrous mice were sacrificed between 16:00 and 18:00 h. LCM was used for collecting GnRH neurons that were studied by Mouse Genome 430 PM Arrays and q-RT-PCR. Voltage-gated sodium channels responded with upregulation of the alpha subunits (*Scn2a1, Scn3a* and *Scn9a*). Within the voltage-gated potassium channel class, *Kcna1, Kcnd3, Kcnh3 and Kcnq2* were upregulated, while others (*Kcna4, Kcnc3, Kcnd2* and *Kcng1*) underwent downregulation. It also had impact on inwardly rectifying potassium channel subunits manifested in enhanced expression of *Kcnj9* and *Kcnj10* genes, whereas *Kcnj1, Kcnj11* and *Kcnj12* subunit genes were downregulated. The two-pore domain potassium channel subfamily also showed differential expression with upregulation of *Kcnk1* and reduced expression of 3 subunit genes (*Kcnk7, Kcnk12* and *Kcnk16*). Changes in expression of chloride channels involved both the voltage-gated (*Clcn3* and *Clcn6*) and the intracellular (*Clic1*) subtypes. Regarding the pore-forming alpha 1 subunits of voltage-gated calcium channels, two (*Cacna1b and Cacna1h*) were upregulated, while *Cacna1g* showed downregulation. The ancillary subunits were also differentially regulated (*Cacna2d1, Cacna2d2, Cacnb1, Cacnb3, Cacnb4, Cacng5, Cacng6* and *Cacng8*). Genes encoding proteins regulating the intracellular calcium homeostasis were also influenced (*Calb1, Hpca, Hpcal1, Hpcal4, Cabp7, Cab 39l, Cib2*). The findings indicate that the altering gonadal hormone milieu in proestrus contributes to remodeling of ion channels which is a prerequisite of preovulatory GnRH surge.

Disclosures: Z. Liposits: None. **N. Solymosi:** None. **I. Farkas:** None. **C. Vastagh:** None.

Poster

673. Hormone Modulation of Behavior and Physiology IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 673.02/N32

Topic: F.03. Neuroendocrine Processes

Support: JSPS KAKENHI Grant Number 17K15157
JSPS KAKENHI Grant Number 26221104
JSPS KAKENHI Grant Number 18H04881
JSPS KAKENHI Grant Number 18K19323

Title: Coexpression of glutamate and multiple neuropeptides in the midbrain GnRH neurons suggests various neuromodulatory functions

Authors: *C. UMATANI[1], S. KANDA[2], T. KARIGO[3], Y. OKA[1];
[1]The Univ. of Tokyo, Tokyo, Japan; [2]AORI, Univ. Tokyo, Chiba, Japan; [3]Biol. and Biol. engineering, Caltech, Pasadena, CA

Abstract: Vertebrates generally have three paralogous genes for gonadotropin releasing hormone (GnRH). One of *gnrh* paralogues, *gnrh2,* is expressed in the midbrain tegmentum neurons, and this expression is the most conserved among vertebrates and may play important roles (Okubo et al., 2008, Muske et al, 1993). Midbrain GnRH2 neurons project broadly to the whole brain except the pituitary, show pacemaker-like action potential firing, and are suggested to show neuromodulation via GnRH2 peptide release (Kanda et al., 2010, Karigo and Oka, 2013). In addition, intracerebroventricular injection of GnRH2 suggested that GnRH2 decrease food intake in goldfish and zebrafish. However, a recent study reported that gnrh2/3 double KO zebrafish can grow almost normally (Marvel et al., 2018), and the function of GnRH2 is still controversial. For a functional characterization of the GnRH2 neuronal system, we examined the possible transmitter co-expression by single cell RNA-seq followed by confirmation with dual *in situ* hybridization using Japanese medaka (*Oryzias latipes*). Here, we found that all midbrain GnRH2 neurons express corticotropin releasing hormone (*crh*) and cocaine- and amphetamine-regulated transcript (*cart*) in addition to *gnrh2*. About 45 % of CRH neurons in the midbrain tegmentum express *gnrh2*. One of the *cart* paralogues, *cartch4* (*cart* in chromosome 4), is expressed only in the midbrain GnRH2 neurons. There was no sexual difference in either *crh* or *cartch4* expression in the midbrain GnRH2 neurons. Unlike the terminal nerve GnRH3 neurons, which also have neuromodulatory functions and show regular pacemaker activities (Umatani et al., 2015, Umatani and Oka, 2018), the midbrain GnRH2 neurons were suggested to express neither GnRH receptors nor NPFF receptors, whose receptors are important for regulation of pacemaker firing of terminal nerve GnRH3 neurons (Abe and Oka, 2000, Saito et al., 2010). Thus, firing patterns of midbrain GnRH2 neurons may be regulated by different mechanisms

from the terminal nerve GnRH3 neurons. On the other hand, the midbrain GnRH2 neurons expressed vesicular glutamate transporter as in the terminal nerve GnRH3 neurons. Thus, midbrain GnRH2 neurons were suggested to release glutamate in addition to three neuropeptides: GnRH2, CRH, and CARTch4. Because CRH plays an important role in stress responses and the expression of *cartch4* was not affected by fasting (Murashita and Kurokawa, 2011), the midbrain GnRH2 neurons may have various neuromodulatory functions as well as a regulation of food intake.

Disclosures: C. Umatani: None. **S. Kanda:** None. **T. Karigo:** None. **Y. Oka:** None.

Poster

673. Hormone Modulation of Behavior and Physiology IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 673.03/N33

Topic: F.03. Neuroendocrine Processes

Support: NKFI K115984
NKFI K128278

Title: Secretin regulates excitatory gabaergic neurotransmission to GnRH neurons via retrograde no signaling pathway in mice

Authors: *V. CSILLAG[1,2], I. FARKAS[3], C. VASTAGH[4], Z. LIPOSITS[5,6];
[1]Roska Tamas Doctoral Sch. of Sci. and Technology, Pazmany Peter Catholic Univ., Budapest, Hungary; [2]Lab. of Endocrine Neurobio., Hungarian Acad. of Sci., Budapest, Hungary; [3]Lab. of Reproductive Neurobio., Inst. of Exptl. Medicine, Hungarian Acad, Budapest, Hungary; [4]Lab. of Endocrine Neurobio., Inst. of Exptl. Med., Budapest, Hungary; [5]Inst. of Exptl. Medicine, HAS, Budapest, Hungary; [6]Dept. of Neurosci., Pazmany Peter Catholic University, Fac. of Information Technol. and Bionics, Budapest, Hungary

Abstract: Metabolic hormones influence reproduction in accordance with the actual energy balance. This control may occur at multiple levels of the HPG axis, although the majority of these interactions takes place centrally in the hypothalamus. It has been shown earlier (Kimura et al., 1987), that secretin, a member of the gut-brain hormone family, modulates the luteinizing hormone (LH) level, albeit the underlying mechanisms have not been examined till date. In order to elucidate the involved cellular mechanisms, *in vitro* electrophysiological experiments were carried out in GnRH-GFP neurons of male mice. Whole-cell patch-clamp measurements demonstrated increased frequency of the postsynaptic currents (sPSCs) (118±2.64 %) and that of the GABAergic miniature postsynaptic currents (mPSCs) (147.6±19.19 %) after 100 nM secretin administration. Resting membrane potential also became depolarized by 12.74±4.539 mV. Frequency of evoked action potentials also increased to 144.3±10.8 %. The secretin-triggered

elevation of the frequency of mPSCs was prevented by using either a secretin receptor antagonist (3μM) or intracellularly applied G-protein-coupled receptor blocker (GDP-β-S; 2mM) supporting the involvement of secretin receptor in the mechanism. Concerning the known downstream pathway to secretin receptor, intracellular blockade of protein kinase A (PKA) activity with KT-5720 (2μM) or intracellular inhibition of the neuronal nitric oxide synthase (nNOS) by NPLA (1μM) attenuated the stimulatory effect of secretin on mPSCs. These data suggest that the direct activation of GnRH neurons via secretin receptor occurs through the cAMP/PKA/nNOS signaling pathway, resulting in nitric oxide release. In turn, NO can bind to its receptor, the soluble guanylyl cyclase (sGC), expressed in GABAergic axon terminals innervating GnRH neurons (Farkas et al., 2016). The NO-sGC interaction in the presynaptic axon terminals leads to increased vesicular GABA release which, in turn, excites GnRH neurons via GABA-A receptors.

Disclosures: V. Csillag: None. **I. Farkas:** None. **C. Vastagh:** None. **Z. Liposits:** None.

Poster

673. Hormone Modulation of Behavior and Physiology IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 673.04/N34

Topic: F.03. Neuroendocrine Processes

Support: BB/S001255/1
EP/N014391/1

Title: Modulation of leteinizing hormone pulse frequency by optogenetic stimulation of arcuate nucleus kisspeptin neurones along the oestrus cycle

Authors: *M. VOLIOTIS[1], X. LI[3], R. DE BURGH[3], G. LASS[3], K. T. O'BYRNE[3], **K. TSANEVA-ATANASOVA**[2];
[2]Mathematics, [1]Univ. of Exeter, Exeter, United Kingdom; [3]King's Col. London, London, United Kingdom

Abstract: Gonadotrophin-releasing hormone (GnRH) is secreted in a pulsatile manner under the control of the neural oscillator known as the hypothalamic GnRH pulse generator. Evidence suggests that this neural construct comprises kisspeptin neurones in the arcuate nucleus (ARC) of the hypothalamus that co-express neurokinin B (NKB) and Dynorphin (Dyn), also known as KNDy. What initiates and maintains the rhythmic activation of the KNDy neural network to drive pulsatile secretion of GnRH is unknown. We have developed a mathematical model of the KNDy neural network, which revealed that the level of network excitability controls the network oscillatory dynamics. Furthermore, mathematical analysis predicts that alterations of network excitability can have distinct effect on pulse generator frequency depending on the levels of sex-

steroids modulating the balance between NKB and Dyn signalling. To test this model prediction we used optogenetics by injecting a viral vector carrying channelrhodopsin into the ARC of female Kiss-Cre mice. The implanted fibre-optic canulae in the ARC allows for optic stimulation of KNDy neurones. LH dynamics was monitored by collecting serial blood samples (5µl, tail-tip) at 5min intervals for 2.5h. In line with our model predictions, continuous optic stimulation at 5Hz (473nm, 5ms) for 90min increased LH pulse frequency in estrous animals, but decreased frequency in diestrous animals. Taken together these data demonstrate that a continuous low frequency stimulation of KNDy neurones modulates the mode of LH secretion depending on the sex steroid background.

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Poster

673. Hormone Modulation of Behavior and Physiology IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 673.05/N35

Topic: F.03. Neuroendocrine Processes

Support: JSPS KAKENHI Grant No JP16K08523

Title: Excitatory GABAergic inputs to GnRH neurons are required for female reproduction

Authors: *M. WATANABE, A. FUKUDA;
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Abstract: Gonadotropin-releasing hormone (GnRH) neurons form the final common pathway for the central regulation of reproduction. γ-aminobutyric acid (GABA) has long been thought to be one of the major players in the regulation of GnRH secretions. While GABA is generally considered to be an inhibitory neurotransmitter in the adult brain, GABA has been reported to excite GnRH neurons *in vitro* experiments. However, the functional significance of the excitatory action of GABA on GnRH neurons *in vivo* remains entirely elusive. Intracellular Cl^- concentration ($[Cl^-]_i$) determines the polarity of $GABA_A$ mediated synaptic input. GABA acts excitatory when $[Cl^-]_i$ is high, due to the high expression of the Na^+-K^+-$2Cl^-$ cotransporter (NKCC1), which includes Cl^- into the cell, and the low expression of the K^+-Cl^- cotransporter (KCC2), which excludes Cl^- out of the cell. To examine the precise physiological functional role of the excitatory action of GABA *in vivo*, we generated a transgenic mouse (GnRH-tTA::KCC2-tetO) in which KCC2 can be induced selectively to GnRH neurons using tetracycline controlled gene expression system. In this mouse, GABA action could be reversibly switched from excitatory to inhibitory *in vivo* selectively in GnRH neurons in specific time point. Application of muscimol, $GABA_A$ receptor agonist, inhibited the spontaneous firing of GnRH neurons in

acute slice of GnRH-tTA::KCC2 tetO mice. Female GnRH-tTA::KCC2-tetO mice failed to exhibit the estrous cyclicity, ovulation and pregnancy. Ovarian histology revealed an abundance of immature follicles. Furthermore, female GnRH-tTA::KCC2-tetO mice showed advanced vaginal opening. On the other hand, male GnRH-tTA::KCC2-tetO mice showed the normal fertility. These results suggest that the excitatory action of GABA on GnRH neurons play a crucial role in the female reproduction.

Disclosures: M. Watanabe: None. **A. Fukuda:** None.

Poster

673. Hormone Modulation of Behavior and Physiology IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 673.06/N36

Topic: F.03. Neuroendocrine Processes

Support: NCARS Hatch 02622

Title: Feed restriction reduces neurokinin B expression in young male sheep

Authors: A. N. RENWICK, J. R. SOMMER, C. M. MERKLEY, ***C. C. NESTOR**;
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Abstract: The central integration of internal and external cues ultimately control reproduction via regulation of hypothalamic gonadotropin-releasing hormone (GnRH) neurons, which are the final common pathway from the brain controlling luteinizing hormone (LH) secretion from the anterior pituitary. While undernutrition is known to suppress GnRH/LH secretion, the central mechanisms that govern this regulation remain to be determined. Based on growing evidence that KNDy (Kisspeptin/Neurokinin B/Dynorphin) neurons represent the GnRH pulse generator, and the important role for NKB signaling in GnRH/LH pulse generation, we hypothesized that undernutrition would reduce the number of NKB neurons in the arcuate nucleus (ARC) of the hypothalamus of male sheep. Six wethers (approximately 5 months of age) were evenly divided into a fed to maintain body weight (Fed) group or a feed restricted to lose 15-20% of pre-study body weight (FR) group. Weekly blood samples (every 12 minutes for 4.5 hours) were taken via jugular venipuncture and plasma was stored at -20°C until the time of radioimmunoassay. Weekly body weights were recorded and feed amounts were adjusted to achieve desired body weights. At Week 13, animals were euthanized following blood collection, and brain tissue containing the hypothalamus was collected. Hypothalamic tissue was sectioned and immunohistochemistry for NKB in the ARC was performed. At Week 13, the average percent change in body weight was clearly evident (Fed, 10.23 $\pm$ 7.2% vs FR, -17.03 ± 2.8%), and although not significantly different between Fed and FR groups, mean LH was dramatically reduced in two of three FR wethers compared to controls. The number of NKB-immunopositive

neurons was significantly less in FR animals (26.4 ± 9 cells/hemi-section), compared to Fed animals (89.2 ± 23 cells/hemi-section). Therefore, the reduction in NKB cell numbers observed here may be an important upstream contributor to the decrease in GnRH/LH pulses that occur during chronic negative energy balance. Further, together with our previous work showing a decrease in kisspeptin neurons with feed restriction, this work provides the first evidence that NKB plays a role in the central mechanism governing GnRH/LH secretion during times of undernutrition in male sheep.

Disclosures: A.N. Renwick: None. **J.R. Sommer:** None. **C.M. Merkley:** None. **C.C. Nestor:** None.

Poster

673. Hormone Modulation of Behavior and Physiology IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 673.07/N37

Topic: F.03. Neuroendocrine Processes

Support: NIH Grant K99 HD096120 to A.M.M
NIH Grant R01 HD039916 to M.N.L

Title: Synaptic input to kisspeptin/neurokinin B/dynorphin (KNDy) neurons is reduced in a mouse model of polycystic ovarian syndrome

Authors: *A. M. MOORE, L. M. COOLEN, M. N. LEHMAN;
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Abstract: Polycystic ovarian syndrome (PCOS) is the leading cause of infertility in reproductive age women. PCOS women display increased luteinizing hormone (LH) pulse frequency, indicative of increased pulsatile gonadotropin-releasing hormone (GnRH) release due to impaired central steroid hormone feedback. Neurons in the arcuate nucleus that co-express kisspeptin, neurokinin B and dynorphin (KNDy cells) are postulated to mediate steroid hormone feedback and are implicated as the GnRH/LH pulse generator. We hypothesized altered synaptic input by upstream populations regulating KNDy neuron activity may result in LH hypersecretion in PCOS. To investigate this, we used a prenatal androgen (PNA)-induced mouse model of PCOS to study excitatory glutamatergic synaptic input to KNDy cells. Pregnant Kiss1-Cre/yellow fluorescent protein (YFP) mice were injected with dihydrotestosterone (250µg) or sesame oil vehicle on days 16, 17 and 18 of pregnancy. PNA (n=4) female and prenatal vehicle-treated (PNV) male (n=3) and female (n=4) offspring were studied as adults. Triple-label immunofluorescence was performed on coronal brain sections for YFP (marker for kisspeptin), synaptophysin (SYN; synaptic terminal marker) and vesicular glutamate transporter 2 (vGluT2). KNDy soma in rostral, middle and caudal arcuate regions were imaged (10 cells/region/animal)

using confocal microscopy and the density of closely-apposed triple-labeled (SYN+vGluT2+YFP), double-labeled (SYN+vGluT2) and single-labeled SYN puncta analyzed. The density of SYN+vGluT2+YFP ($p<0.01$) and SYN+vGluT2 ($p<0.05$) inputs to KNDy soma was lower in PNA females compared to PNV males and females, indicating PNA treatment causes loss of glutamatergic input to KNDy cells from both kisspeptin and non-kisspeptin glutamatergic cells. In addition, the density of SYN inputs was lower in PNA females compared to PNV males and females ($p<0.05$), signifying loss of synaptic input from a non-glutamatergic source. These data indicate PNA treatment reduces synaptic input to KNDy neurons from multiple neuronal phenotypes. The mechanism by which reduced glutamatergic input increases LH in PNA mice is unclear, although loss of glutamatergic kisspeptin input may represent reduced KNDy-KNDy connections that impair steroid hormone feedback.

Disclosures: **A.M. Moore:** None. **L.M. Coolen:** None. **M.N. Lehman:** None.

Poster

673. Hormone Modulation of Behavior and Physiology IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 673.08/N38

Topic: F.03. Neuroendocrine Processes

Support: NIH grant R21 HD092009

Title: Physiological characterization of GnRH neurons derived from human embryonic stem cells

Authors: B. I. FORDYCE[1], C. R. JOHNSTON[1], K. L. KEEN[1], *E. TERASAWA[2]; [1]Primate Ctr., Univ. of Wisconsin, Madison, WI; [2]Pediatrics and Primate Ctr., Univ. of Wisconsin Madison, Madison, WI

Abstract: The pulsatile release of the gonadotropin-releasing hormone (GnRH) is critical for mammalian reproductive function. Consequently, hypogonadotropic hypogonadism (IHH) patients who do not have GnRH neurons or their upstream regulatory neurons in the hypothalamus are not able to conceive and need gonadal steroid hormone treatments for their entire lives. As part of a long-term goal to use GnRH neurons derived from IHH patient's induced pluripotent stem cells (iPSC) as a treatment tool, this lab was recently successful in generating GnRH neurons from human embryonic stem cells (hESC) and human-iPSC. With the ultimate goal in mind, the present study evaluated characteristics of GnRH neurons derived from hESC. Differentiated GnRH neurons were perifused with artificial cerebrospinal fluid over a period of six hours, and perifusates were continuously collected in fractions at 10 min intervals. Various known exocytotic stimuli for GnRH neurons were applied for 20 min periods at 90 min intervals, and GnRH levels in the perifusates were measured via radioimmunoassay. After the

experiments, cells were fixed and subjected to immunohistochemical analysis to confirm the presence of GnRH neurons. Results are summarized: First, we found that hESC-derived GnRH neurons released the GnRH peptide in a pulsatile manner with an inter-pulse interval of 59.5±3.3 min, which is very similar to the interval in primary GnRH neurons derived from monkey fetuses (46.6 ± 4.0 min) as well as *in vivo* release (43.5 ± 1.8 min) in the adult monkey hypothalamus. Second, we found that hESC-derived GnRH neurons respond to kisspeptin, neurokinin B, estradiol, and high potassium by significantly increasing GnRH release (all at $p<0.01$). The question of whether iPSC-derived GnRH neurons behave similar to hESC-derived GnRH neurons is currently under examination. Collectively, the results indicate that hESC-derived GnRH neurons exhibit physiological characteristics similar to those in primary GnRH neurons *in vitro* as well as in the rhesus-monkey hypothalamus *in vivo*.

Disclosures: B.I. Fordyce: None. **C.R. Johnston:** None. **K.L. Keen:** None. **E. Terasawa:** None.

Poster

673. Hormone Modulation of Behavior and Physiology IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 673.09/N39

Topic: F.03. Neuroendocrine Processes

Support: Health Research Council of New Zealand Project Grant #16-027

Title: Projections of suprachiasmatic nucleus vasopressin neurons regulate preoptic kisspeptin neuron electrical activity

Authors: *B. B. JAMIESON, R. E. CAMPBELL, R. PIET;
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Abstract: In female rodents, appropriate timing of the surge of gonadotropin secretion that triggers ovulation is critical to their reproductive success. The central circadian clock in the suprachiasmatic nucleus (SCN) is thought to time the preovulatory surge by activating circuitry that ultimately controls gonadotropin secretion. We have used an anatomical and functional approach to investigate the innervation of preoptic area (POA) kisspeptin neurons, which are thought to drive the preovulatory surge, by a group of SCN neurons that produce vasopressin (AVP).Diestrous female *AVP-ires2-cre* mice, which express cre recombinase (cre) in AVP neurons, were injected in the SCN with an adeno-associated viral (AAV) vector carrying a cre-dependent sequence for the fluorescent reporter mCherry. This revealed innervation of the POA by SCN AVP neurons, closely apposing 44.6 ± 6.6% (N = 6 mice) of POA kisspeptin neurons, and suggesting putative synaptic inputs. Diestrous and proestrous *AVP-ires2-cre* mice expressing the green fluorescent protein (GFP) in kisspeptin neurons were injected in the SCN with an AAV

carrying a cre-dependent sequence for channelrhodopsin (ChR2), and brain slices were taken for patch-clamp electrophysiological recordings. In whole-cell voltage clamp recordings, the vast majority (92%) of POA GFP-expressing kisspeptin neurons (n = 26, 9 mice) did not display fast postsynaptic currents in response to brief blue-light stimulation of ChR2-expressing axons in diestrous or in proestrous mice. High-frequency blue-light stimulation (20 Hz, 60 s) did, however, increase action potential firing in 59% of kisspeptin neurons recorded in the cell-attached patch clamp configuration (n = 17, 9 mice; $p < 0.05$ vs control). Further, this response appears to occur in proestrus (n = 8, 4 mice; $p < 0.05$ vs control) rather than diestrus (n = 9, 5 mice; $p = 0.4$ vs control; two-way ANOVA). Using the vasopressin 1 receptor (V1R) antagonist, Manning compound, blue light-evoked increases in action potential firing were prevented (n = 8, 4 mice; $p > 0.99$ vs control), indicating that this response was mediated by V1R activation.This work suggests that although SCN AVP neurons project to the POA, they may not communicate with POA kisspeptin neurons via fast amino acid neurotransmission, but rather through the release of AVP acting at V1 receptors. This reveals a mechanism through which the biological clock may control the POA kisspeptin neurons and stimulate the onset of the preovulatory surge release of gonadotropins.

Disclosures: B.B. Jamieson: None. **R.E. Campbell:** None. **R. Piet:** None.

Poster

673. Hormone Modulation of Behavior and Physiology IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 673.10/N40

Topic: F.03. Neuroendocrine Processes

Support: DGAPA-PAPIIT Grant 215619

Title: Asymmetries on the estradiol receptors, kisspeptin and GnRH content between the left and right hypothalamus during the estrous cycle of the rat

Authors: *C. C. SILVA-MENDEZ[1], E. OLVERA[2], A. FLORES[3], R. LIBRADO[3], I. ARRIETA[3], R. GUTIÉRREZ[3], R. DOMÍNGUEZ[3], M.-E. CRUZ[3];
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Abstract: Ovarian functions are regulated by the hypothalamic-pituitary-ovarian axis. At the hypothalamus, neurons located at the preoptic and anterior hypothalamic area synthetize the gonadotropin releasing hormone (GnRH). GnRH stimulates the secretion of the luteinizing hormone and the follicle stimulating hormone, which in turn will modulate processes as ovulation and hormone secretion. The estradiol secreted by the ovaries exerts positive and

negative feedback on the hypothalamus by binding to its receptors at the kisspeptin-cells located at the anteroventral periventricular area and the arcuate nucleus, respectively. We and others have shown anatomic and functional asymmetries between the left and right hypothalamic centers related to ovarian regulation. Since those asymmetries depends on the estrogenic environment, we hypothesized that the content of key proteins involved on the hypothalamic integration of ovarian signals i.e. estradiol receptors, kisspeptin and GnRH, is asymmetric depending on the stage of the estrous cycle and the time of the day. Groups of 24 intact rats were euthanized at 08:00, 11:00, 14:00 and 17:00 hours of each stage of the estrous cycle. Brains were extracted and the left and right hypothalamus were dissected from the preoptic area to the mediobasal hypothalamus and processed for western-blot analysis of protein content. We found that, in estrous, estradiol receptor-α (ERα) content was similar in both sides of the brain while those of estradiol receptor-β (ERβ) and kisspeptin were asymmetric on most of the time points analyzed. At metestrous, no differences on the content of the three proteins were found. In diestrous, ERα on the left side was similar during all time points, on the other side, the content on the right side displayed a sinusoidal pattern with a peak during the morning. ERβ was consistently higher while kisspeptin showed no differences. At proestrous, ERα and ERβ on the left, but not on the right side showed a sinusoidal pattern with a peak concomitant with the preovulatory rise on gonadotropin serum levels. Kisspeptin and GnRH content on the right side decreased during the afternoon and no changes on the left side were detected. We concluded that the central regulatory mechanisms of ovarian functions that involves the estradiol receptors, kisspeptin and GnRH on the left and right sides of the hypothalamus are asymmetric. These asymmetries depends on the stage of the estrous cycle and the time of the day.

Disclosures: C.C. Silva-Mendez: None. **E. Olvera:** None. **A. Flores:** None. **R. Librado:** None. **I. Arrieta:** None. **R. Gutiérrez:** None. **R. Domínguez:** None. **M. Cruz:** None.

Poster

673. Hormone Modulation of Behavior and Physiology IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 673.11/N41

Topic: F.03. Neuroendocrine Processes

Support: University of Michigan Rackham Precandidacy Grant
NIH HD 090567

Title: Unraveling the subsets of MCH neurons associated with reproductive control

Authors: *B. G. BEEKLY, C. F. ELIAS;
Mol. and Integrative Physiol., Univ. of Michigan, Ann Arbor, MI

Abstract: Pulsatile release of luteinizing hormone (LH) is necessary for reproductive development and function. Due to the complexity of the hypothalamic-pituitary-gonadal (HPG) axis, the factors governing LH release remain incompletely understood. Melanin-concentrating hormone (MCH) neurons have well-characterized roles in many fundamental processes, but while they project to reproductive control sites such as the medial preoptic nucleus and the median eminence, the nature of their effect on the HPG axis is unclear. This is due in part to the heterogeneity of MCH neurons and their widespread distribution. In rats, two populations of MCH neurons have been neurochemically defined: a medial group expressing cocaine- and amphetamine-related transcript (CART) and targeting cortex, rostral brainstem, and hypothalamic nuclei associated with reproductive control; and a lateral, CART-negative group targeting the caudal brainstem. Based on their projections, we hypothesize that MCH/CART neurons can induce pituitary LH release. We used immunohistochemistry and viral tracing methods in MCH neurons to elucidate their neurochemical profile and projection patterns. We observe that in mice, as in rats, medial MCH neurons colocalize with CART and project to reproductive control sites including the medial and ventrolateral preoptic areas. Interestingly, our initial studies also suggest that the MCH/CART system is sexually dimorphic. In the regions examined, males have more CART neurons, fewer MCH neurons, and a lower percentage of total CART neurons expressing MCH. We also used chemogenetic technology to probe the functional differences in these populations. By activating anatomically distinct subsets of MCH neurons and analyzing serum LH levels, we found that stimulating medial groups of MCH neurons increased blood LH while more lateral MCH neurons did not achieve this effect. Collectively, these data indicate that medial MCH/CART neurons modulate the HPG axis. Further studies will be performed to evaluate the physiological relevance of these findings.

Disclosures: B.G. Beekly: None. **C.F. Elias:** None.

Poster

673. Hormone Modulation of Behavior and Physiology IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 673.12/N42

Topic: F.03. Neuroendocrine Processes

Support: NIH R37HD34860

Title: Relation of firing to release in gonadotropin-releasing hormone (GnRH) neurons

Authors: *X. CHEN[1], R. A. DEFAZIO[1], S. M. MOENTER[2];
[1]Mol. and Integrative Physiol., [2]Mol. and Integrative Physiology, Intrnl. Medicine, and Obstetrics and Gyne, Univ. of Michigan, Ann Arbor, MI

Abstract: In vertebrates, the secretion of the gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) by the pituitary is triggered by the pulsatile release of GnRH from neurons located in the preoptic area of the hypothalamus. In brain slices, GnRH neurons often exhibit an episodic action potential firing activity that is regulated by steroid feedback and resembles the pattern of LH release. There is no direct evidence, however, showing how GnRH neuron firing rate relates to GnRH release. To begin to study this, long-term (1 to 1.5 h) simultaneous measures of spontaneous firing rate using extracellular recording and GnRH release using fast-scan cyclic voltammetry (FSCV) were made in sagittal brain slices from gonad-intact male GnRH-GFP mice. Slices were scanned for pairs of GnRH neurons with overlapping processes; GnRH release was monitored from where the GFP-identified cells/processes overlapped, and firing was recorded from one (n=5) or both (n=1) of the GnRH neurons. When GnRH neurons were active (61-742 spikes/10min), the number of GnRH release events and release duration were higher than when neurons were quiescent (0-20 spikes/10min) (events/10min: 6.5±0.5 vs. 1.7±0.5, $p<0.0001$; duration/10min: 215.3±17.2 vs. 35.6±10.4s, $p<0.0001$; n=22 active and 17 quiescent 10-min bins from 6 mice). In contrast, within periods of neuronal activity the coordination between firing rate and GnRH release was less distinct. Kisspeptin triggered both GnRH neuron firing and GnRH release. Interestingly, preliminary data reveal GnRH release occurs as much as 175s before firing during kisspeptin treatment, consistent with reports that release in the preoptic area can be action potential independent. Combined current-clamp and FSCV recordings were used to examine the effects of membrane depolarization without spikes. Depolarization of the membrane potential to ~-40mV for 500ms initiated GnRH release in the absence of action potentials (n=2 cells). These early results suggest a clear but loose correlation between GnRH neuron firing and GnRH release. On the one hand, high GnRH neuron activity appears required to trigger robust GnRH release; on the other hand, firing frequency and GnRH concentration change in active GnRH neurons are not tightly coordinated. Depolarization alone without spikes can also initiate release. Future work will use current-clamp to regulate the number of spikes and examine how steroid feedback alters firing rate to release coupling.

Disclosures: **X. Chen:** None. **R.A. DeFazio:** None. **S.M. Moenter:** None.

Poster

673. Hormone Modulation of Behavior and Physiology IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 673.13/N43

Topic: F.03. Neuroendocrine Processes

Support: NIH R01 HD41469

Title: Corticotropin-releasing hormone (CRH) has no effect on arcuate kisspeptin neuron firing activity in female mice

Authors: *C. PHUMSATITPONG[1], S. M. MOENTER[2];
[1]Mol. and Integrative Physiol., [2]Mol. and Integrative Physiology, Intrnl. Medicine, and Obstetrics and Gyne, Univ. of Michigan, Ann Arbor, MI

Abstract: Stress has been shown to alter the reproductive system via several possible target sites. Corticotropin-releasing hormone (CRH) increases gonadotropin-releasing hormone (GnRH) activity via CRHR1 and reduces this activity via CRHR2; both of these actions require estradiol. Elevated GABA transmission mediates, at least in part, the excitatory actions of CRH, but the mechanisms for inhibitory effects are unknown. Kisspeptin neurons in the hypothalamic arcuate nucleus provide estradiol-sensitive activation of GnRH neurons and various stressors (restraint, metabolic stress and immunological stress) or CRH peptide can decrease *Kiss1* mRNA expression in these cells. Arcuate kisspeptin neurons appear to express CRH receptors by immunofluorescence. We hypothesized that CRH inhibits arcuate kisspeptin neuron firing activity and that this response is modulated by estradiol. To test this, mice expressing GFP under the Tac2 promoter (coexpressed with *Kiss1*) were ovariectomized and either implanted with a capsule producing a physiological circulating level of estradiol (OVX+E) or not treated further (OVX). Targeted extracellular recordings of firing rate were made of arcuate kisspeptin neurons in the afternoon during estradiol positive feedback. Basal, bath-application of CRH, and wash out periods were examined. Basal firing rate was higher in OVX than OVX+E mice ($p<0.01$), indicating estradiol regulation of arcuate kisspeptin neurons is different from anteroventral periventricular kisspeptin neurons. CRH (100nM) did not alter firing rate of arcuate kisspeptin neurons in the OVX+E group (n=6, con 0.09±0.05 Hz, CRH 0.09±0.04, wash 0.25±0.14 Hz, $p>0.9$). In the OVX group, firing rate in some (2 of 7) kisspeptin neurons increased by ≥30% after CRH treatment, but continued to show further increases in activity during the wash period (n=7, con 0.64±0.27 Hz, CRH 0.75±0.29 Hz, wash 1.03±0.24 Hz, $p=0.045$ con vs CRH). To distinguish a technical from a biological phenomenon, we performed a vehicle-treatment experiment. A similar pattern of a mild increase during the vehicle treatment followed by continued increase during the wash was observed (OVX+E n=4, con 0.18±0.11 Hz, vehicle 0.26±0.18 Hz, wash 0.77±0.55 Hz, $p>0.2$; OVX n=5, con 0.87±0.34 Hz, vehicle 0.91±0.38 Hz, wash 1.89±0.65 Hz, $p>0.5$). These data suggest the increase in firing rate that is observed during CRH treatment in OVX group is a technical phenomenon. While it remains possible that a biological response is masked by this technical change, the results suggest that under these conditions CRH does not acutely alter arcuate kisspeptin neuronal activity regardless of estradiol status in female mice.

Disclosures: C. Phumsatitpong: None. **S.M. Moenter:** None.

Poster

673. Hormone Modulation of Behavior and Physiology IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 673.14/N44

Topic: F.03. Neuroendocrine Processes

Support: NIH R01 HD41469
NIH F31 HD097830

Title: Three types of voltage-gated potassium currents in AVPV kisspeptin neurons

Authors: *J. R. STARRETT[1], S. M. MOENTER[2];
[1]Mol. and Integrative Physiol., [2]Mol. and Integrative Physiology, Intrnl. Medicine, and Obstetrics and Gyne, Univ. of Michigan, Ann Arbor, MI

Abstract: Ovulation is stimulated by a switch in gonadotropin-releasing hormone (GnRH) and luteinizing hormone (LH) release from repeated brief episodes (pulses) to a continuous surge lasting several hours. Pulses are regulated by estradiol negative feedback and the surge is initiated by estradiol positive feedback. Interestingly, GnRH neurons do not express detectable levels of estrogen receptor α, which is needed for both negative and positive feedback. Feedback thus likely involves ERα-expressing afferents. The neuropeptide kisspeptin (Kiss1) excites GnRH neurons. Most *Kiss1*-expressing neurons in the anteroventral periventricular (AVPV) nucleus express ERαand estradiol increases the firing rate of these cells, suggesting they may convey positive feedback to GnRH neurons. The mechanisms by which estradiol increases firing of AVPV-Kiss1 cells are not completely understood. Voltage-gated potassium currents strongly influence neuronal firing activity and can be regulated by steroids. We tested the hypothesis that voltage-gated potassium currents are modulated by estrous cycle stage. Voltage-clamp recordings were made of AVPV-Kiss1 neurons in brain slices from Kiss1-GFP mice on the afternoon of diestrus (negative feedback) and proestrus (positive feedback). The macroscopic K^+current was found to consist of three components: a fast-inactivating, a slow-inactivating and a non-inactivating component, likely mediated by distinct populations of channels. We compared the pharmacology of the two transient components. The fast-inactivating component was relatively resistant to tetraethylammonium (TEA, 20 mM) but was blocked by 4-aminopyridine (4-AP, 5mM), suggesting it is mediated by Kv4 channels. The slow-inactivating component was blocked by TEA and was comparatively more resistant to 4-AP. Fast and slow components displayed different voltage-dependence of activation. The fast component began to activate at membrane potentials close to the action potential threshold (~40-50 mV), suggesting it may affect spike initiation, whereas the slow component began to activate at more depolarized potentials (~ -10 mV), suggesting it may modulate spike width and neurosecretion. Preliminary data from pharmacological studies suggest the amplitude of the fast component may be increased

on proestrus. Computational models are being developed to test if estrous cycle modulation of these currents contributes to the increases in AVPV-Kiss1 neuron firing frequency and bursting observed during estradiol positive feedback.

Disclosures: J.R. Starrett: None. **S.M. Moenter:** None.

Poster

673. Hormone Modulation of Behavior and Physiology IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 673.15/N45

Topic: F.02. Behavioral Neuroendocrinology

Support: University at Buffalo Research Foundation, Award #64755

Title: Sex-specific consequences of post-weaning social isolation on social behavior, affective behavior, and kisspeptin neural circuitry in Long Evans rats

Authors: *B. L. KINLEY[1], D. M. WALKER[2], R. F. KYNE[1], N. VENTURA[1], E. J. NESTLER[2], M. J. PAUL[1];
[1]Psychology, Univ. at Buffalo, SUNY, Buffalo, NY; [2]Nash Family Dept. of Neurosci. and Friedman Brain Inst., Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Childhood and adolescence are critical periods for social and affective development. However, they are also times of increased vulnerability to stress. For example, post-weaning social isolation (PSI) can lead to long-term behavioral and neural changes that persist into adulthood. The neuropeptide, kisspeptin, plays a critical role in reproduction, including the onset of puberty, and recent studies suggest that extra-hypothalamic kisspeptin cell groups may also influence affective behaviors. Kisspeptin cells and fibers increase markedly during early adolescence. To our knowledge, however, no one has tested whether PSI impacts the development of kisspeptin circuitry. In this study, we tested whether PSI has a lasting impact on social behavior, affective behavior, and kisspeptin cells and fibers in medial amygdala (MeA) and lateral septum (LS) of male and female Long Evans rats. Rats were weaned at 21 days of age and housed either alone (Isolated) or in groups of 2-3 rats/cage (Group-housed). After 3 weeks of isolation, Isolated rats were group-housed for the remainder of the experiment. At 10 weeks of age, all rats were tested in Social Preference, Marble Burying, and Light/Dark Box tests, with 1 day between behavioral tests. Rats were euthanized 1-2 days after the Light/Dark Box test, and brains were removed and processed for kisspeptin immunohistochemistry. Isolated males showed a lower social preference score, buried more marbles, and spent more time in the light zone of the light/dark box than their group-housed counterparts. Isolated and Group-housed females did not differ in these measures, although time in the light zone of the Light/Dark Box test approached significance (Isolated females > Group-housed females, P=0.06, Fisher's PLSD).

Kisspeptin staining in Group-housed rats was sexually dimorphic, with greater numbers of cells in the MeA of males, but greater fiber staining in the LS of females. Preliminary analyses indicate that PSI had no effect on the number of kisspeptin cells in the MeA, but selectively increased kisspeptin fiber staining in the LS of males. These findings demonstrate sex-specific consequences of PSI on social behavior, affective behavior, and kisspeptin neural circuitry.

Disclosures: B.L. Kinley: None. **D.M. Walker:** None. **R.F. Kyne:** None. **N. Ventura:** None. **E.J. Nestler:** None. **M.J. Paul:** None.

Poster

673. Hormone Modulation of Behavior and Physiology IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 673.16/N46

Topic: F.03. Neuroendocrine Processes

Support: USDA 2010-65206-20647
Auburn CVM Animal Health and Disease Grant

Title: Kisspeptin and the neuroendocrine regulation of growth hormone release

Authors: *C. D. FORADORI[1], B. K. WHITLOCK[2], J. A. DANIEL[3], A. D. ZIMMERMAN[1], L. O. MACKAY[1], C. C. READ[1], B. P. STEELE[1], J. L. SARTIN[1];
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Abstract: Kisspeptin (Kp) is a neuropeptide which is widely accepted as a critical regulator of the neuroendocrine control of reproduction in all mammals. Kp is the most potent stimulator of hypothalamic gonadotrophin releasing hormone (GnRH) release ever studied. Kp, by way of its stimulation of GnRH release, causes luteinizing hormone and follicle stimulating hormone release, leading to subsequent stimulation of gonadal steroid synthesis, gamete maturation, and ovulation. Although Kp is a stimulator of GnRH secretion and therefore the hypothalamic-pituitary-gonadal axis, new findings suggest Kp can also regulate additional neuroendocrine processes including the release of growth hormone (GH). We have shown that central delivery of Kp causes a robust rise in plasma GH in fasted but not fed sheep. We postulate that Kp works with the established neurocircuity implicated in the control of GH release. GH release from somatotropes of the pituitary is under direct control of GH releasing hormone (GHRH) and somatostatin (SS). GHRH and SS are secreted by cells in the arcuate and periventricular nuclei, respectively, and transported to the pituitary via the hypophyseal portal vascular. Somatotropes are stimulated by GHRH and inhibited by SS. Another cell group expressing neuropeptide Y (NPY) is upstream of GHRH and SS cells. Activation of NPY neurons in the arcuate nucleus of

the hypothalamus has been shown to increase GH release working through GHRH and SS cells. Our proposed model linking Kp to the NPY-GHRH/SS control of GH release is supported by findings from our lab that 1) Central Kp treatment induces GH release, 2) Kp fibers contact NPY cells, 3) NPY cells express the Kp receptor which increases in the fasted state, 4) pretreatment with a NPY receptor antagonist blocks the effects of Kp-induced GH release, and 5) Kp infusion stimulates NPY and GHRH cells and inhibits SS cells. However, as stated above, Kp can only induce GH in short-term fasted animals. In examining GH release associated with short-term fasting, the prominent role of the gut derived peptide ghrelin was considered to be a potential intermediary. Indeed, when systemic ghrelin release is blocked in fasted animals or if fasted animals are pretreated with a ghrelin receptor antagonist, Kp-induced GH was eliminated or reduced, suggesting the presence of ghrelin is required for Kp-induced GH release in fasted animals. Our findings support the hypothesis that during short-term fasting, systemic ghrelin concentrations increase, leading to alterations in the NPY-GHRH-SS system permitting Kp activation of NPY cells. In turn, NPY stimulates GHRH cells and inhibits SS cells, resulting in GH release from somatotropes.

Disclosures: C.D. Foradori: None. **B.K. Whitlock:** None. **J.A. Daniel:** None. **A.D. Zimmerman:** None. **L.O. Mackay:** None. **C.C. Read:** None. **B.P. Steele:** None. **J.L. Sartin:** None.

Poster

673. Hormone Modulation of Behavior and Physiology IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 673.17/O1

Topic: F.03. Neuroendocrine Processes

Support: NIH R01 HD082135

Title: Colocalization of NK3R and KOR mRNA in KNDy and non-KNDy neurons in the ovine arcuate nucleus

Authors: *W. HE[1], L. M. COOLEN[1], R. L. GOODMAN[2], M. N. LEHMAN[1];
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Abstract: Compelling evidence in sheep and other species suggest that KNDy (kisspeptin/neurokinin B/dynorphin) neurons of the arcuate nucleus (ARC) are responsible for the pulsatile secretion of gonadotropin-releasing hormone (GnRH). Neurokinin B (NKB) is hypothesized to mediate the initiation of GnRH pulses by acting on neurokinin 3 (NK3R/*TAC3R*) receptors within the KNDy network. In contrast, dynorphin (DYN) by acting on kappa opioid receptor (KOR) in KNDy and GnRH cells, has been linked to termination of GnRH pulses. However, it is unknown if there are other NKB or DYN-responsive neuronal populations

in the ARC that may contribute to the regulation of KNDy neurons and pulse generation. Therefore, we used RNAscope, a sensitive *in situ* hybridization technique that allows detection of multiple mRNA transcripts in the same cell, to examine kisspeptin, *TAC3R* and *KOR* co-expression in the ARC of luteal phase ewes. Adult ewes (n=4) were perfused, hypothalami sectioned coronally (12 µm), and RNAscope using ovine-specific probes were used to analyze the expression of *TAC3R*, *KOR*, and *kisspeptin* (as marker for KNDy cells). Results showed that *KOR* and *TAC3R* mRNAs are co-expressed in 94% of KNDy cells. However, the KNDy cells only constitute 33% of total *KOR* cells and 52% of total *NK3R* cells in the ovine ARC, suggesting the presence of a non-KNDy neuronal population that also respond to DYN and/or NKB. Among this non-KNDy population, *KOR*/*TAC3R* and *KOR*-only expressing cells constitute the majority with 40% and 56%, respectively. Hence, only a very small portion of ARC cells express *TAC3R* only: 98% of total *TAC3R* cells co-express either KNDy and/or *KOR* and 91% of non-KNDy *TAC3R* cells co-express *KOR*. Together, these findings indicate three populations of ARC neurons that are potentially involved with GnRH pulse secretion: KNDy cells expressing both *TAC3R* and *KOR*, non-KNDy cells either co-expressing *KOR* and*TAC3R* or *KOR* alone. It is also notable that all *TAC3R* cells are either KNDy and/or *KOR* positive and together could be defining different components of the NKB responsive pulse generator.

Disclosures: W. He: None. **L.M. Coolen:** None. **R.L. Goodman:** None. **M.N. Lehman:** None.

Poster

673. Hormone Modulation of Behavior and Physiology IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 673.18/O2

Topic: F.03. Neuroendocrine Processes

Support: CONACyT: FC 2016-2/ 2319

Title: Morphological characterization of the intrinsic neurons in the ovary of young and senescent rats

Authors: *J. M. BRAVO[1], A. ESPINOSA[2], Y. CRUZ[3], C. MORAN[2];
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Abstract: The extrinsic innervation of the ovary participates regulating their activity; like as follicular development, steroidogenesis, ovulation and reproductive cycles. The intrinsic innervation of the ovaries has been shown in various mammals, including the Wistar rat. The aim of the present study was to recognize the intrinsic neurons of the ovaries and their biochemical characteristics in young and senescence rats. We used adult female rat CII ZV strain of 3, 12 and 15 months old. The identification of the neurons was performed using the

immunohistofluorescence techniques to Neu-N and tyrosine hidroxylase (TH) antibodies, using ovarian slices made with cryostat. The results show immunoreactivity to Neu-N and TH in the interstitial gland, around the follicles and corpus luteum. The measurement of the neurons was performed in neurons immunopositive to Neu-N. Neuron diameter was longer in old rats (15 months: 12.2±3.0 μm, 12 months: 10.8±2.5 μm, 3 months: 8.7±1.4μm. $p < 0.01$ ANOVA followed by Tukey); the area of the perikarya was also higher in old animals (15 months: 87.5±0.5 μm^2, 12 months: 60.3±0.5 μm^2 and 3 months: 62.9±1.1 μm^2, $p < 0.01$ ANOVA Followed by tukey). Moreover the number of neurons decreases in older the animals; thus we can infer that there is an aging-related compensatory effect that involves anatomical and functional plasticity of the neuronal system of the ovary, extrinsic and intrinsic. Our results suggest the participation of the innervation in the maintenance of ovarian functions through the reproductive life span of females.

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Poster

673. Hormone Modulation of Behavior and Physiology IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 673.19/O3

Topic: F.03. Neuroendocrine Processes

Support: CONACYT 331854

Title: Prolactin and testosterone regulate the activity of MMP9 in LNCaP cells

Authors: *M. JIMÉNEZ BUENDÍA[1], J. LARA REYES[1], M. HERNANDEZ[3], G. E. ARANDA-ABREU[4], J. MANZO[2], J. M. SUÁREZ MEDELLÍN[1], D. HERRERA-COVARRUBIAS[2], C. A. PÉREZ ESTUDILLO[1], A. AQUINO GÁLVEZ[5], M. MENDOZA[6], F. ROJAS-DURÁN[2];
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Abstract: The hypothalamus-pituitary axis is responsible for regulating the hormone levels of prolactin (PRL) and testosterone. PRL is a polypeptide hormone synthesized and secreted mainly by specialized cells of the adenohypophysis. Testosterone is a steroid hormone synthesized, in greater proportion, by Leydig cells. Both PRL and T are necessary for the proper functioning of the prostate. In pathological processes, such as prostate cancer, there has been an important relationship between PRL and testosterone, and there are studies that relate both hormones to the

regulation of the activity and gene expression of matrix metalloproteases (MMPs); being MMP2 and MMP9 the most studied. MMPs are highly linked to the ability of cancer cells to migrate and their level of malignancy, so the increase in these is related to the progression and development of cancer. Therefore, the activity of MMP2 and MMP9 was evaluated in culture media of LNCaP cells stimulated with PRL (50 nM) and testosterone (0.1 nM), or with both hormones, it was observed that MMP9 increases its activity in the treatments with PRL, Testosterone and both hormones. The results show that in the treatment with 0.1nM of testosterone it decreases the expression of STAT3, while the expression of STAT5 is increased in the treatment with both hormones. The cells treated with PRL, testosterone or both had different structural changes. The cells treated with 50 nM of PRL were characterized for presenting blebs, the cells treated with 0.1 nM of testosterone formed extensions of actin filaments (lamellipodia and filopodia). In conclusion, PRL and testosterone induce migration in LNCaP cells with formation of blebs, lamelipodia and filopodia, regulating the activation of MMP9 that is correlated with the STAT5 and STAT3 pathways.

Disclosures: M. Jiménez Buendía: None. **J. Lara reyes:** None. **M. Hernandez:** None. **G.E. Aranda-Abreu:** None. **J. Manzo:** None. **J.M. Suárez Medellín:** None. **D. Herrera-Covarrubias:** None. **C.A. Pérez Estudillo:** None. **A. Aquino Gálvez:** None. **M. Mendoza:** None. **F. Rojas-Durán:** None.

Poster

673. Hormone Modulation of Behavior and Physiology IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 673.20/O4

Topic: F.03. Neuroendocrine Processes

Support: CONACYT/622677

Title: Effect of prolactin and estradiol in MMP2 activity in conditioned medium from MCF-7 cells

Authors: *J. LARA REYES[1], M. G. JIMENEZ BUENDIA[2], M. HERNÁNDEZ AGUILAR[4], G. E. ARANDA-ABREU[4], J. MANZO DENES[5], D. HERRERA COVARRUBIAS[4], J. SUAREZ MEDELLIN[4], C. A. PEREZ-ESTUDILLO[4], C. SAMPIERI RAMIREZ[6], A. AQUINO GÁLVEZ[7], F. ROJAS-DURÁN[3];
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Abstract: Prolactin (PRL) is a polypeptide hormone synthesized and secreted mainly by specialized cells of the pituitary gland. Estradiol (E_2) is a sexual steroid hormone of the estrogen group and it is the most potent natural estrogen in humans. The release of both hormones is controlled by neural stimuli and their levels are regulated by the hypothalamic-pituitary axis. PRL participates in the development of the mammary gland and in the production of milk proteins in pregnancy and lactation. It exerts diverse biological effects through its interaction with specific membrane receptors that are widely distributed in the organism. E_2 has effects on the growth, development and differentiation of tissues, although its main action is observed in reproductive organs. In addition to both their physiological functions, it has been shown that they also participate in the development of pathologies such as breast cancer, however, it is not clear whether these hormones have any involvement in cell migration, a crucial step in the development of metastasis, and in the regulation of the activity of matrix metalloprotease 2 (MMP-2), that is related to the cell migration process. We found that PRL (2 nM) increased cell migration in MCF-7 cells and E_2 seems to have no effect and we evaluated the effect of stimulation with PRL and E_2 in MMP-2 activity in the conditioned medium from MCF-7 cells.

Disclosures: J. Lara Reyes: None. **M.G. Jimenez Buendia:** None. **M. Hernández Aguilar:** None. **G.E. Aranda-Abreu:** None. **J. Manzo Denes:** None. **D. Herrera Covarrubias:** None. **J. Suarez Medellin:** None. **C.A. Perez-Estudillo:** None. **C. Sampieri Ramirez:** None. **A. Aquino Gálvez:** None. **F. Rojas-Durán:** None.

Poster

673. Hormone Modulation of Behavior and Physiology IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 673.21/O5

Topic: F.03. Neuroendocrine Processes

Support: NIH R01 MH-109471
NIH P30 ES-025128

Title: Estradiol rapidly modulates excitatory synapse properties in a sex and region specific manner in the nucleus accumbens core and caudate putamen

Authors: *A. A. KRENTZEL, L. BARRETT, J. MEITZEN;
North Carolina State Univ., Raleigh, NC

Abstract: Estradiol acutely facilitates sex differences in striatal-dependent behaviors and neurotransmitter release where females are more sensitive to the rapid actions than males; however, little is understood of the mechanism. In striatal regions in adult rodents, estrogen receptors feature exclusively membrane expression both on terminals and dendrites. This suggests that estradiol can directly modulate striatal neurons or the terminal projections onto

those neurons. We tested whether estradiol rapidly modulates excitatory synapse properties onto medium spiny neurons (MSNs) of two striatal regions, the nucleus accumbens core and caudate-putamen in adult (P60-P90) female and male rats. Using whole-cell patch clamp, we recorded MSN intrinsic properties to determine if these properties were predictive of estrogen sensitivity. We then recorded mini-excitatory post-synaptic currents (mEPSC) and bath applied 100nM 17β-estradiol to record the changes to mEPSC frequency, amplitude, and decay. Estradiol exhibited bidirectional and sex-specific acute effects in the nucleus accumbens core: mEPSC frequency robustly decreased in response to estradiol in female MSNs, and mEPSC amplitude moderately increased in response to estradiol in both males and female MSNs. This increase in mEPSC amplitude is associated with more excitable MSNs. No MSN intrinsic electrical property associated with changes in mEPSC frequency or decay. Estradiol did not acutely modulate mEPSC properties in the caudate-putamen of either sex. This is the first demonstration of acute estradiol action on MSN excitatory synapse function. Importantly, female-specific sensitivity in the nucleus accumbens may explain female-biased sex differences observed in striatal behaviors. A robust decrease in mEPSC frequency for females suggests pre-synaptic changes to excitatory terminals projections into the core, providing a potential mechanism to explore in future studies.

Disclosures: **A.A. Krentzel:** None. **L. Barrett:** None. **J. Meitzen:** None.

Poster

673. Hormone Modulation of Behavior and Physiology IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 673.22/O6

Topic: F.03. Neuroendocrine Processes

Support: Wenner Gren Stiftelserna
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StratNeuro Karolinska Institutet

Title: Estrogen controls the electrical properties of mouse tuberoinfundibular dopamine (TIDA) neurons: A novel substrate for sex hormone control of prolactin secretion

Authors: J. FERRARIS[1,2], R. AMMARI[1], *C. BROBERGER[1,2];
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Abstract: Neuroendocrine tuberoinfundibular dopamine (TIDA) neurons tonically inhibit pituitary prolactin secretion. After parturition elevated prolactin activates a number of maternal

functions, including lactation, but the hormone also exhibits a peak during proestrus in rodents. This peak depends on a decrease in dopaminergic tone triggered by estradiol (E2), partly by inhibition of dopamine synthesis. However, the membrane properties and firing pattern of TIDA neurons provide an additional level of control in the lactotropic axis. Furthermore, E2 is now known to modulate neuronal electrophysiology by both acute and chronic actions. These observations raise the possibility that sex hormones control of TIDA neurons may involve regulation of the excitability and discharge configuration of these neurons.
To address this issue, we used whole-cell patch clamp recordings in acute hypothalamic slices from postpubertal female mice expressing tdTomato under control of the dopamine transporter promoter. Recordings were performed during a) natural variations of sex hormones (estrous cycle), b) chronic changes in hormone levels (ovariectomy) and c) acute application of E2 in vitro.
Similar to males, TIDA neurons in female mice exhibited a spectrum of firing patterns from silent, to tonic to phasic. In males, the absolute majority of TIDA neurons can are regular oscillators. However, 50% of the cells exhibited tonic firing during estrus whereas, during diestrus, 70% of cells showed an oscillatory pattern. Ovariectomy altered the distribution of firing patterns among TIDA neurons, in which the firing frequency was increased, and action potential amplitude decreased. In response to bath application of E2, TIDA neurons depolarized, an effect also observed in the presence of tetrodotoxin, suggesting a role for postsynaptic modulation. The depolarization was dose-dependent and at higher concentrations resulted in depolarization block, with successive stunting and the abolishment of action potentials.
These findings indicate that the membrane properties of TIDA neurons may be subject to both acute and long-term regulation by gonadal steroids. This modulation may be involved in shaping the serum profile of prolactin during both the estrous cycle and in the nursing mother.

Disclosures: **J. Ferraris:** None. **R. Ammari:** None. **C. Broberger:** None.

Poster

673. Hormone Modulation of Behavior and Physiology IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 673.23/O7

Topic: F.03. Neuroendocrine Processes

Support: NIH OD010662 Midwest Proteome Center

Title: Characterization of phoenixin and thimet oligopeptidase (EP24.15) in neural circuits associated with the regulation of neuroendocrine processes

Authors: J. Z. GLUCKSMAN[1], M. R. DEJOSEPH[2], K. D. PHILIBERT[3], *J. H. URBAN[2]; [1]Ctr. for Neurobio. of Stress Resilience and Psychiatric Disorders, Rosalind Franklin Univ. of Med. and Scien, North Chicago, IL; [2]Ctr. for Neurobio. of Stress Resilience and Psychiatric

Disorders, [3]3Biochemistry and Mol. Biol. and Ctr. for Proteomics and Mol. Therapeut. and Midwest, Chicago Med. Sch/Rosalind Franklin Univ. Med. & Sci., North Chicago, IL

Abstract: The recently identified neuropeptide phoenixin (Phx) is distributed throughout the hypothalamus, central amygdala (CeA) and bed nucleus of the stria terminalis (BST). It has received attention for its role in the regulation of a number of homeostatic neuroendocrine systems including anxiety, vasopressin release and reproductive hormone secretion where Phx increases GnRH peptide release and receptor expression, increases Kisspeptin (Kiss) mRNA, and modulates ovarian cyclicity. The responses to neuropeptides are not only mediated by the local release of the neuropeptide, but also by modification of the peptide through enzymatic processing in the synaptic space. This enzymatic processing can shift the affinity of the peptide for various receptor subtypes, or in many cases, degrades the peptide thereby inactivating it and its downstream actions. EP24.15 (EC 3.4.24.15, thimet oligopeptidase) is a neuropeptide processing metalloenzyme that is expressed throughout the hypothalamus and other brain regions. EP24.15 plays a major role in the regulation of GnRH by processing the hormone and thus, inactivating binding to the GnRH receptor. As we have shown recently, EP24.15 not only modifies GnRH but other neuropeptides such as Kiss and dynorphin that are part of the reproductive neuroendocrine circuit. These current studies were designed to demonstrate the physiological and biochemical regulation of Phx in male and female animals in the context of reproduction by examining the association of Phx with EP24.15 within the hypothalamus. Using an immunohistochemical approach, we demonstrated Phx immunoreactivity in areas of the brain related to stress (CeA; BST) and reproduction (hypothalamic arcuate nucleus); EP24.15 was also highly expressed in these regions. To determine whether Phx was a substrate for EP24.15 we employed a combination of *in silico* structural models, mass spectrometry, enzyme kinetics, and high resolution, respectively. Enzyme kinetics indicated a single cleavage site in Phx and that the Km and Vmax for this reaction were comparable to published values for GnRH and Kiss. The data demonstrates that EP24.15 can potentially cleave Phx *in vivo* as an additional layer of control to the elaborate mechanism of reproduction. A better understanding of novel, regulated peptides that integrate stress and reproductive processes will provide insight into brain circuitry for moderating reproductive function.

Disclosures: J.Z. Glucksman: None. **M.R. DeJoseph:** None. **K.D. Philibert:** None. **J.H. Urban:** None.

Poster

673. Hormone Modulation of Behavior and Physiology IV

Location: Hall A

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Program #/Poster #: 673.24/O8

Topic: F.03. Neuroendocrine Processes

Support: CONACYT: CB-238744
DGAPA-UNAM-PAPIIT-IN216918

Title: Gabaergic cells expressing estrogen receptors in limbic and hypothalamic regions are sensitive to testosterone levels

Authors: *L. ZAVALA[1], V. S. HERNANDEZ[1], O. R. HERNANDEZ[1], L. E. EIDEN[2], L. ZHANG[1];
[1]Natl. Autonomus Univ. of Mexico, Mexico City, Mexico; [2]Sec Molec Neurosci, NIH, NIMH-IRP, Bethesda, MD

Abstract: We have previously reported the existence of a novel cell population in the medio-central nucleus of the lateral habenula complex of the rat, which consists in GABAergic and estrogen receptive neurons (GERNs). These cells co-express SLC32A1, the RNA encoding for the vesicular GABA transporter, and ERα, the RNA encoding for the oestrogen receptor α. The GERNs in habenula are shown to integrate glutamatergic input from hypothalamic neurons containing vasopressin and orexin, as well as from serotonin and TH positive neurons in the raphe nuclei and SN/VTA. All those afferent neurons are androgen receptive (express androgen receptor) and the oestrogen synthase aromatase are found at their axon terminals. In this work we further investigate the presence of GERNs in other limbic regions of the brain and how the testosterone levels modulate their density. Using the RNAscope technique, we compared the effect of testosterone up-regulation (testosterone supplementation) or downregulation (castration) on the density of GERN in male rats. Preliminary results show that castration produced a significant decrease in GERN's density in BNST (56.9%), LS (86.12%), DG (33.4%) to control rats (100%). Testosterone supplementation caused a significant increase in GERN density at DG (4 folds). These results suggest that testosterone can induce a subpopulation of neurons expressing ERα to express a GABAergic phenothype thus influencing the information processing in the limbic system.

Disclosures: L. Zavala: None. **V.S. Hernandez:** None. **O.R. Hernandez:** None. **L.E. Eiden:** None. **L. Zhang:** None.

Poster

673. Hormone Modulation of Behavior and Physiology IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 673.25/O9

Topic: F.02. Behavioral Neuroendocrinology

Support: NNSFC31271095

Title: Effects of social closeness on the menstrual synchronization in young college females

Authors: K. CAO[1], X. ZHANG[1], ***R. ZHANG**[2,1];
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Abstract: Most organisms exhibit biological rhythms by synchronizing their behavioral and physiological activities with cyclic changes in the environment. Circadian time-keeping mechanisms preserve homeostasis by synchronizing internal physiology with predictable variations in the environment. The women's menstrual cycle are subjected to the lunar circadian regulation with a period around 29.5 days. In current study, we confirmed, as previously reported, women's menstrual circle were synchronized, at variable extent, in the same dormitory. Then, we asked how and why women's menstrual circle were regulated and affected reciprocally by investigating their saliva endocrinology profile and social behaviors pattern. Total 163, aged 18 -19 years old college female students who live in total 36 dormitories (4-6 people/room) were recruited. By questionnaire and survey, we collected information include 1) monthly menstrual circle dated in both solar and lunar calendar; 2) food preference (carbohydrates, protein, fat, snacks); 3) monthly social events; We measured the students' 1) bodyweight and body composition; 2) body temperature at start and end day of menstrual circle, and non-menstrual circle day. The inner social status and the closeness among individuals in the same dormitory were investigated through a designed conflict scene behavior observation that was performed in a blinded manner to both the participants and observers. The saliva cortisol, testosterone and melatonin concentration were measured by ELISA. We found that the bodyweight, basal metabolic rate, and their social status (dominant, subordinate, irrelated relationship) are related to the menstrual synchronization. We conclude that menstrual-related biological rhythms are individually regulated by their own endogenous profile. The exogenous social closeness reciprocally impacted on the menstrual circle among young female students.

Disclosures: K. Cao: None. **X. Zhang:** None. **R. Zhang:** None.

Poster

673. Hormone Modulation of Behavior and Physiology IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 673.26/O10

Topic: F.03. Neuroendocrine Processes

Support: Arnold & Mabel Beckman Foundation Beckman Scholars Program (SDS)

Title: Association of the vaginal microbiota with menstruation, mood, and diet in healthy, young women

Authors: *S. D. SONG[1], K. ACHARYA[1], C. DEVENEY[2], M. R. WALTHER-ANTONIO[3], M. J. TETEL[1], N. CHIA[4];

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Abstract: The human microbiome, the microorganisms and their metabolites that reside in and on the human body, profoundly influences health and disease. However, studies of the vaginal microbiota, the microbes residing in the vaginal tract, are few and limited in scope. The vaginal microbiota is critical for maintaining women's health, and vaginal microbial dysbiosis is implicated in endometrial and ovarian cancers. However, very little is known about the endogenous factors that influence vaginal microbial composition and stability. The present study tests the hypotheses that vaginal microbial composition is associated with menstruation, contraceptive use, mood, and diet. Volunteer participants from a college provided daily vaginal swab samples for 2 months, while recording menstruation, contraceptive use, mood, and daily diet using a mobile application. Diet data were linked to nutritional information provided by the college's dining food provider. Vaginal microbial diversity, as measured using the Shannon Index, was significantly greater during menses (Wilcoxon signed rank, $p < 0.001$). This increase in diversity was even more dramatic among participants not using contraceptives (paired t-test, $p = 0.005$, 95% CI [0.27, 0.97]) than those using contraceptives (paired t-test, $p = 0.021$, 95% CI [0.05, 0.43]). Preliminary analyses revealed trends between vaginal microbial diversity and mood, with higher diversity on average corresponding to higher happiness ratings ($R^2 = 0.37$, $p = 0.28$) and greater mood variability ($R^2 = 0.36$, $p = 0.28$). However, these trends did not reach significance, likely due to the low number of participants with usable mood data ($n = 5$). Diet analyses reveal that those following a vegetarian or vegan diet tend to have increased average vaginal microbial diversity compared to non-vegetarians (Wilcoxon rank sum, $p = 0.18$). This trend also did not reach significance due to few participants following a vegetarian or vegan diet ($n = 5$). We are currently analyzing temporal effects of mood and diet on the vaginal microbiota. Our goal is to establish baseline knowledge on how healthy vaginal microbiota fluctuates over time, and the role of ovarian hormones, mood, and diet in this dynamic. Ultimately, our goal is to track these participants for 10-20 years in the hope of identifying early biomarkers of reproductive tract cancers in women.

Disclosures: S.D. Song: None. **K. Acharya:** None. **C. Deveney:** None. **M.R. Walther-Antonio:** None. **M.J. Tetel:** None. **N. Chia:** None.

Poster

673. Hormone Modulation of Behavior and Physiology IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 673.27/O11

Topic: F.03. Neuroendocrine Processes

Support: NIH Grant P50: DA039841

NIH Grant R01: DA037927

Title: Genomic profiling of spontaneous X chromosome nondisjunction mice reveals Turner syndrome relevant pathways

Authors: *U. DATTA, M. SAUL, V. PHILIP, E. CHESLER;
The Jackson Lab., Bar Harbor, ME

Abstract: Turner's syndrome is a developmental disorder due to sex chromosome nondisjunction and an XO genotype. Patients have short stature, hormonal and cognitive characteristics, marked with non-verbal learning disability, dyscalculia, and social cognitive impairments. This has been assumed to be attributed to pseudoautosomal gene function. Diversity Outbred mice have an elevated frequency of these events (about 1%). Like their human counterparts, XO female mice lack a second X chromosome and thus may serve as a naturally occurring murine model of Turner's syndrome. Derived from the same eight founders as those of the Collaborative Cross inbred strains through randomized breeding, the Diversity Outbred population harbors a high level of allelic diversity and heterozygosity, thereby representing the heterogeneity of the affected population. In the present study, Diversity Outbred mice were classified as males or females based on genotype information. XO females were identified by lack of heterozygosity on X chromosome. Males with partial duplication of the X chromosome were also identified by heterozygous calls on the distal portion of the X chromosome. Examination of the genotypes on the sex chromosomes revealed six XO females (out of 432 total females) and twelve males (out of 429 total males) with partial X chromosome duplication. Preliminary analysis of global gene expression in striatum was carried out using RNA-seq on 3 XO females. A total of 783 differentially expressed genes were identified, of which 146 genes were up-regulated and 637 genes were down-regulated in XO females compared to euploid females. Among the downregulated genes was Xist, a non-coding RNA involved in X inactivation. GeneWeaver identified a significant overlap with CREB- and zif268-regulated neuronal plasticity related genes. Interesting downregulated candidates include the X-encoded magnesium transporter gene Magt1 and the NMDA receptor subunit gene Grin2a. Further interrogation of these genes and mechanisms may help explain the neurobiological basis of deficits in Turner's syndrome.

Disclosures: U. Datta: None. **M. Saul:** None. **V. Philip:** None. **E. Chesler:** None.

Poster

674. Neuroinflammation: Pathophysiological Consequences

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 674.01/O12

Topic: F.05. Neuroimmunology

Support: 2017 APS Future Leader in Pain Research
NIH R01 NS073939

Title: Neuroimmune mechanisms of latent pain sensitization after chemotherapy

Authors: *G. LAUMET[1,2], K. B. CLARK[2], J. D. EDRALIN[2], X. HUO[2], B. PENG[2], R. DANTZER[3], C. J. HEIJNEN[4], L. GENDRON[6], A. KAVELAARS[5];
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Abstract: The episodic nature of chronic pain has been described in animal models as latent pain sensitization. For example after remission from inflammatory or postsurgical pain, assessed by normalization of mechanical pain threshold, injection of opioid receptor inverse agonists reinstates pain hypersensitivity (Campillo et al., Eur J Pharmacol 2011; Corder et al., Science 2013; Walwyn et al., J Neurosci 2016). To investigate whether latent sensitization is also occurring in neuropathic pain and neuroimmune mechanisms are involved, male and female mice were treated with 3 daily injections of cisplatin (2 mg/kg) to induce a transient neuropathic pain. Mice developed mechanical pain hypersensitivity that resolved after 3 weeks. Interleukin (IL)-10 was significantly upregulated in the spinal cord during and after remission from cisplatin-induced neuropathic pain. One week after remission, injection of a neutralizing antibody anti-IL-10 reinstated mechanical pain hypersensitivity in both male and female mice treated with cisplatin whereas the same treatment had no effect on naïve mice. To determine the downstream mechanism of the reinstatement of pain hypersensitivity by inhibition of IL-10 signaling, we performed RNA-sequencing analysis of dorsal root ganglion (DRG) tissue. Remission and reinstatement of pain hypersensitivity were associated with a change in gene expression of more than 250 genes. Bioinformatics analysis identified *Oprd1* as the main regulator of the balance between remission and reinstatement of pain. *Oprd1* encodes the delta opioid receptor (DOR) which has already been implicated in latent sensitization after inflammatory pain (Walwyn et al., J Neurosci 2016). Q-PCR data confirmed that *Oprd1* is upregulated in the DRG during remission and that this upregulation is mediated by IL-10 signaling. IL-10 signaling is also necessary for DOR agonist-induced analgesia. Furthermore naltrindole, a DOR antagonist, reinstated pain hypersensitivity after remission from neuropathic pain in both sexes. In conclusion, upregulation of *Oprd1* in the DRG by spinal IL-10 is necessary to maintain remission from neuropathic pain. Recurrence of chronic pain may result from the dysregulation of IL-10 - DOR interaction.

Disclosures: G. Laumet: None. **K.B. Clark:** None. **J.D. Edralin:** None. **X. Huo:** None. **B. Peng:** None. **R. Dantzer:** None. **C.J. Heijnen:** None. **L. Gendron:** None. **A. Kavelaars:** None.

Poster

674. Neuroinflammation: Pathophysiological Consequences

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 674.02/O13

Topic: F.05. Neuroimmunology

Support: K22NS096030
American Pain Society Future Leaders Award

Title: Toll-like receptor 4 expressed on LysozymeM^{+} immune cells mediates neuropathic mechanical hypersensitivity development in male, but not female mice

Authors: *T. A. SZABO-PARDI, L. R. BARRON, N. M. AGALAVE, M. D. BURTON; Brain and Behavioral Sci., Univ. of Texas at Dallas, Richardson, TX

Abstract: Chronic pain is a disease affecting more than 1 billion people worldwide. Understanding how the immune system promotes inflammation and pro-nociception following traumatic injury is paramount to the development of effective therapeutics to combat neuropathic pain. It is well accepted that neuropathic pain is maintained in part by microglia, however mechanisms of neuropathic pain development present a point of treatment to prevent maturation of chronic neuropathic pain. Recent literature has delved deeper into the interface of neuro-immune interactions which have brought to light sexual dimorphisms in pain development that warrant further investigation. Studies provide a direct link between TLR4 activation and neuropathic pain in male mice, however, the specific cells expressing TLR4 that are responsible for these effects remains a point of contention. Toll-like receptor 4 (TLR4) is a pattern recognition receptor (PRR) expressed on various cell types, including cells of the innate immune system with activation leading to pro-inflammatory cytokine production and tissue sensitization. This study focuses on investigating peripheral actions of LysozymeM^{+} (LysM) immune cell activation and infiltration via TLR4 in the dorsal root ganglia (DRG), along with its effects on behavioral pain phenotypes. We hypothesize neuropathic pain in males is dependent on TLR4 expressed on peripheral LysM^{+} cells while females utilize an alternative signaling pathway. We have employed two unique *Cre*/LoxP transgenic models that allow for specific deletion or reactivation of a floxed TLR4 allele utilizing LysM as a promoter of *Cre* expression. We used a spared-nerve injury (SNI) model of neuropathic pain after which mice are subject to von Frey and cold allodynia measures. In addition, we assayed recruitment and polarization of macrophages and T-cells in the DRG following SNI using flow cytometry. Results indicate that TLR4 acting on LysM^{+} peripheral immune cells is both necessary and sufficient to produce neuropathic mechanical hypersensitivity during early timepoints following SNI in male, but not female mice. No differences are observed in cold allodynia. Lastly, flow cytometry reveals male mice have enhanced anti-inflammatory (M2) macrophage polarization 3D post-SNI as compared

to females. We have observed a robust, sexually dimorphic effect when TLR4 is removed from $LysM^+$ peripheral immune cells. Our data suggest that TLR4 acting on immune cells mediates neuropathic pain development in male, but not female mice.

Disclosures: T.A. Szabo-Pardi: None. **L.R. Barron:** None. **N.M. Agalave:** None. **M.D. Burton:** None.

Poster

674. Neuroinflammation: Pathophysiological Consequences

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 674.03/O14

Topic: F.05. Neuroimmunology

Support: NCCIH P50 AT008661-01

Title: Gut microbiota derived dietary polyphenol metabolites promote cognitive resilience to anxiety and depression through immunological mechanisms of the gut-brain-axis

Authors: *S. WESTFALL, F. CARACCI, T. FROLINGER, U. IQBAL, G. M. PASINETTI; Neurol., Icahn Sch. of Med. At Mount Sinai, New York, NY

Abstract: Neuroinflammation promotes stress-induced neuropsychiatric disorders including depression and anxiety. Recently, we showed that gut microbiota-derived metabolites mitigate chronic inflammation and microglia activation promoting cognitive resilience to depression and anxiety; however, the metabolites' anti-inflammatory mechanisms remain to be elucidated. The gut-brain-axis describes a battery of humoral and neuronal modes of bidirectional communication between the gut and the brain that heavily influence the immune system's development and resistance to external stress. The purpose of this study is to dissect how modulating immune-mediated GBA signaling with an optimized synbiotic can protect against neuroinflammation and its associated disorders. The synbiotic, combining dietary polyphenol-rich prebiotics and probiotics, was designed and tested using a novel *in vitro* model of the human gastrointestinal tract called the A-BIOME (A bioreactor imitation of the microbiota ecosystem) and optimized for metabolite production. The polyphenolic precursor is a Bioactive Dietary Polyphenol Preparation (BDPP) containing grapeseed extract, concord grape powder and resveratrol and once combined with probiotics, production of plasma- and brain-bioavailable metabolites was significantly enhanced. Following 28 days of chronic unpredictable stress (CUS) in mice, the synbiotic promoted resilience to depressive-like behavior to a greater extent than BDPP alone, but to the same extent as BDPP in metrics of anxiety-like behavior. Circulating and central levels of proinflammatory cytokines, including IL-1β, TNFα and IL-6 elevated by the CUS protocol, were also reduced by the synbiotic to a greater extent than BDPP. Biochemical analyses confirmed the altered immune profile indicating that the synbiotic could be acting on

mechanisms of sterile inflammation including NLRP3 inflammasome activation in peripheral monocytes, intestinal enteroendocrine cells or brain-derived microglia, altered recruitment of lymphocyte subsets to the brain, or modulation of microglia activation in the prefrontal cortex. Nanostring immunophenotyping technology revealed that the synbiotic promotes differentiation of regulatory T cells over cytotoxic T cells, reducing the neuroinflammatory phenotype and associated neuropsychiatric phenotypes. Overall, synbiotics can normalize the production of bioactive polyphenolic metabolites with neuroactive properties and used as novel therapeutic strategies for neuroinflammatory conditions including depression, anxiety, Alzheimer's disease and multiple sclerosis.

Disclosures: S. Westfall: None. **F. Caracci:** None. **T. Frolinger:** None. **U. Iqbal:** None. **G.M. Pasinetti:** None.

Poster

674. Neuroinflammation: Pathophysiological Consequences

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 674.04/O15

Topic: F.05. Neuroimmunology

Support: NIDA Grant DA044308
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NARSAD Young Investigator Awards
Leon Levy Foundation
Seaver Family Foundation

Title: Investigating GM-CSF as a mediator of gut-brain signaling in addiction-like behaviors

Authors: *K. E. LUCERNE[1], E. S. CALIPARI[2], A. GODINO[3], D. D. KIRALY[4];
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Abstract: Recent work suggests that the resident bacteria of the gastrointestinal tract, collectively dubbed the gut microbiome, can have profound effects on brain and behavior including in multiple neuropsychiatric diseases. While the majority of work in this field has focused on affective, neurodevelopmental, and neurodegenerative disorders, our group has demonstrated that depletion of the gut microbiome markedly alters the rewarding properties of cocaine. While the precise mechanisms underlying gut-brain communication are not fully understood, one potential mechanism is via the extensive effects of the gut microbiome on immune system function. To investigate potential gut-immune-brain signaling in models of

addiction, we performed quantitative multiplex serum cytokine analysis on animals with a normal microbiome or antibiotic-induced microbiome depletion that were administered either cocaine or saline. While many cytokines were altered either by microbiome depletion or cocaine treatment, there were few that demonstrated a strong interaction between the conditions. Of particular note was granulocyte-macrophage colony-stimulating factor (GM-CSF) which was robustly increased by cocaine only in animals with a normal gut microbiome. Enzyme linked immunosorbent assay (ELISA) confirmed the cocaine-induced increase of GM-CSF in animals with normal gut microbiome that were self-administering cocaine. Interestingly, GM-CSF expression showed a positive correlation with levels of drug intake over the self-administration sessions. To assess the role of GM-CSF as a mediator of gut brain signaling in behavioral response to cocaine we utilized a cocaine conditioned place preference (CPP) assay. For these studies animals either drank control water or had their microbiome depleted with antibiotics, and also received daily injections of GM-CSF (10μg/kg) or vehicle throughout cocaine CPP in a 2x2 design. Microbiome-depleted animals that received vehicle injections developed a robust place preference for low doses of cocaine in agreement with our previously published findings. However, microbiome-depleted animals that received injections of GM-CSF displayed place preference similar to control levels. Taken together, these data suggest that cocaine-induced GM-CSF signaling is dependent on a normal gut microbiome and plays a key role in the rewarding effects of cocaine. This introduces a new line of gut-immune-brain communication with clinical translational potential.

Disclosures: **K.E. Lucerne:** None. **E.S. Calipari:** None. **A. Godino:** None. **D.D. Kiraly:** None.

Poster

674. Neuroinflammation: Pathophysiological Consequences

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 674.05/O16

Topic: F.05. Neuroimmunology

Support: NIH/NIDA 1-R00-DA032681
NIH/NIDA 1-R01-DA044311
2017 PhRMA Foundation Research Starter Grant

Title: Neuroinflammatory modulation of nicotine dependence

Authors: *E. L. ANDERSON[1], A. O. ADELUYI[1], J. R. TURNER[2];
[1]Col. of Pharm., Univ. of South Carolina, Columbia, SC; [2]Col. of Pharm., Univ. of Kentucky, Lexington, KY

Abstract: Introduction: Neuroinflammation and associated gliosis has been demonstrated to be a primary mediator of many neurological disorders, including in CNS trauma, ischemia, stroke, and neurodegenerative diseases. However, while their role has been extensively examined in neurology, this is much less true in psychiatry, especially in substance use disorders. It is thought that discrete microenvironments in the select brain regions may polarize the immune effector cells, namely microglia, to a reactive state. We examined these changes in the nucleus accumbens (ventral striatum), which is a region reliably shown to underpin many behavioral characteristics of substance use disorders as well as the withdrawal symptomology.
Methods and Results: Our preliminary IHC and qPCR data indicates that significant neuroinflammation can be detected in the ventral, but not the dorsal striatum, following withdrawal from chronic nicotine in mice. Furthermore, previous studies have suggested that microglial activation can contribute to neuronal damage through release of reactive oxygen and nitrogen species and inflammatory cytokines. In line with these findings, we detect significantly increased levels of both reactive oxygen species as well as pro-inflammatory cytokines in the ventral, but not dorsal, striatum.
Significance and Conclusions: Our current experiments investigate whether pharmacological compounds possessing both structurally and mechanistically distinct mechanisms for inhibiting microglial activation, such as ibudilast and minocycline, will reduce the molecular hallmarks of neuroinflammation during nicotine withdrawal. Further, because these processes are known to be able to regulate nicotine-induced upregulation and assembly of nicotinic acetylcholine receptors, a phenomenon that can be correlated to anxiety-like nicotine withdrawal behaviors, future studies will examine the effects of these inhibitors on modulating nicotinic receptor expression.

Disclosures: E.L. Anderson: None. **A.O. Adeluyi:** None. **J.R. Turner:** None.

Poster

674. Neuroinflammation: Pathophysiological Consequences

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 674.06/O17

Topic: F.05. Neuroimmunology

Support: DFG Grand SPP 1738

Title: microRNAs in inflammatory neurodegeneration and multiple sclerosis

Authors: *I. WINKLER[1], J. ENGLER[1], G. SALINAS[2], L. BAL[1], B. SCHATTLING[1], O. PLESS[3], M. FRIESE[1];
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Abstract: Multiple sclerosis (MS) is a chronic-inflammatory disease of the central nervous system (CNS) characterised by CNS immune cell infiltration, axonal demyelination and neurodegeneration. Chronic CNS inflammation results in neuronal stress response networks with alteration of synaptic signalling and signal transduction, thereby perpetuating neurodegeneration and consecutive neurological deficits. Coordination of translation by microRNAs (miRNAs) is a fundamental mechanism to respond to changes in the cellular environment. However, whether and how inflammation impacts on neuronal gene expression by regulating miRNAs and whether this determines neurodegeneration is unknown. By comparing healthy and inflamed neuronal transcriptomes and miRNome we demonstrate that mRNA transcripts involved in synaptic signaling and plasticity are significantly under-represented in inflamed neurons, while at the same time newly identified inflammation induced miRNAs are predicted to target these transcripts. Of these miRNA candidates, miR-92a was identified most prominently induced. Mechanistically, we identified exogenous glutamate to regulate miR-92a expression in primary neurons, while concomitantly the predicted target mRNA cytoplasmic polyadenylation element-binding protein 3 (CPEB3) was downregulated. Luciferase reporter assays proved a direct inhibition of CPEB3 translation mediated by miR-92a. Further, to investigate miR-92a function during neuroinflammation, we performed EAE in respective knock-out mice. Specific deletion of miR-92a led to an accelerated EAE disease course and clinical symptoms, implying a neuroprotective role of miR-92a upregulation. Currently, we decipher the interaction network of miR-92a and CPEB3 and its implications for neuronal survival during inflammation. Together, we present a new approach offering an understanding of miRNAs governing synaptic function and contributing to neuronal integrity during CNS inflammation. This will provide insights into the role of miRNAs in the pathogenesis of MS and opportunities for intervening in MS-associated neurodegeneration.

Disclosures: I. Winkler: None. **J. Engler:** None. **G. Salinas:** None. **L. Bal:** None. **B. Schattling:** None. **O. Pless:** None. **M. Friese:** None.

Poster

674. Neuroinflammation: Pathophysiological Consequences

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 674.07/O18

Topic: F.05. Neuroimmunology

Support: NIH Grant NS093057
AHA fellowship 17POST33660421

Title: Characterization of a unique microglia subtype in secondary thalamic injury after ischemic stroke

Authors: *Z. CAO[1,2], S. HARVEY[1,2], T. C. CHIANG[1,2], M. Y. CHENG[1,2], G. K. STEINBERG[1,2];
[1]Neurosurg., Stanford Univ., Stanford, CA; [2]Stanford Stroke Ctr., Stanford, CA

Abstract: Introduction: Stroke affects brain connectivity and causes network-wide deficits. In particular, the ipsilesional thalamus undergoes degeneration after cortical stroke and impedes functional recovery. Previously we demonstrated that neuroinflammatory responses are critically involved in the development of secondary thalamic injury. In this study, we focus on characterizing microglia changes in the secondary thalamic injury after stroke. **Methods**: Left middle cerebral artery was permanently occluded to generate cortical ischemic stroke in male C57BL6J mice (12-15 weeks). Brain sections were collected from post-stroke days (PD) 1, 3, 7, 14, 28, 56 and 84. Immunostaining was used to detect microglia/macrophage activation (Iba-1, Tmem119 and CD11c) in the ipsilesional thalamus (iTH). Flow cytometry was used to analyze iTH samples collected at PD28. Furthermore, qPCR was used to quantify the expression of microglia-associated genes in iTH among Naïve, PD7 and PD28 groups. **Results**: In iTH, Iba-1$^+$ cells exhibited ramified morphology at PD1, became hyper-ramified between PD3-7, and appeared as rod-shaped at PD14. Bushy/amoeboid microglia/macrophages were shown at PD28. At PD 56-84, most microglia/macrophages returned back to resting/ramified status. These morphological changes suggested a gradual and progressive activation of microglia/macrophages in iTH. Iba-1$^+$Tmem119+ cells were observed at early phases (PD1-7), but the expression of Tmem119 significantly decreased between PD14-56. Interestingly, a population of CD11c$^+$ cells appeared in the thalamic injured area between PD14-28 and most were Iba-1$^+$, suggesting they were CD11c$^+$ microglia/macrophages. Flow cytometry analysis further confirmed that resident microglia (CD45^{int} CD11b$^+$) are the major population and CD11c$^+$ microglia is a subtype of microglia in iTH at PD28. Several microglial activation related genes (CD11c, Trem2, CX3CR1, CSF1R and TLR2) were significantly increased at PD28 iTH compared to naïve and PD7. **Conclusion**: Our results show that dynamic microglia changes occurs during the development of secondary thalamic injury, with progressive changes in morphology and gene expressions. In addition, we have identified a unique subtype of microglia (CD11c$^+$) in the secondary thalamic injury. Future studies will explore the roles of CD11c$^+$ microglia in the secondary thalamic injury and long-term stroke outcome.

Disclosures: Z. Cao: None. **S. Harvey:** None. **T.C. Chiang:** None. **M.Y. Cheng:** None. **G.K. Steinberg:** None.

Poster

674. Neuroinflammation: Pathophysiological Consequences

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 674.08/O19

Topic: F.05. Neuroimmunology

Support: NIH Grant K22NS096030

Title: Long-term high fat diet precipitates peripheral sensitization independent of obesity in female mice

Authors: *J. A. TIERNEY[1], M. D. BURTON[2];
[2]Behavioral and Brain Sci., [1]Univ. of Texas at Dallas, Richardson, TX

Abstract: Worldwide there were 422 million adults over the age of 18 diagnosed with type II diabetes, as of 2014. Up to 50% of people diagnosed with diabetes will develop painful diabetic neuropathy (PDN) at some point. It is known that free fatty acids (FFAs), which are a large component of western diet (WD), lead to obesity, “metainflammation”, and type II diabetes. Free fatty acids have been proposed to interact with various receptors in the digestive and immune system to mediate inflammation and metabolic disorder. Our hypothesis is that circulating free fatty acids contribute to the pain associated with PDN. To test this hypothesis we utilized a diet regimen where animals had ad libitum access to high-fat diet (HFD) containing 60% of calories from fat for over 40 weeks. Male and female C57/B6 mice were placed on HFD or kept on chow diet at 6 weeks of age and weighed once every week. At 13 weeks on diet we began assessing mechanical hypersensitivity using the von Frey up-down method, thermal sensitivity at 4°C and 50°C, and fasting glucose levels once per week until week 29. At week 29 a Glucose Tolerance Test was performed to assess glucose insensitivity. Male mice on HFD gained significant weight and reached obesity levels by week 12 on diet, whereas the female mice on HFD gained weight, but never reached significant levels of obesity. For over 40 weeks long-term HFD caused peripheral mechanical hypersensitivity in male and female mice starting 17 weeks after diet initiation. Female mice developed mechanical hypersentivity in the absence of obesity and glucose insensitivity, whereas male mice did develop glucose insensitivity when assessed with a GTT at week 29 on diet. There were no significant differences observed in standard hot plate, or cold plate tests. However, at week 39 on diet dynamic hot and cold sensitivity was tested and both male and female mice on HFD were more sensitive to changes in temperature. These results show that diets high in saturated fats play a role in the development of pain in both males and females in the presence or absence of obesity.

Disclosures: J.A. Tierney: None. **M.D. Burton:** None.

Poster

674. Neuroinflammation: Pathophysiological Consequences

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 674.09/O20

Topic: F.05. Neuroimmunology

Support: Seaver Foundation

Title: Gut-brain interactions in a mouse model of Phelan-McDermid syndrome

Authors: *A. OSMAN, N. MERVOSH, D. D. KIRALY;
Dept. of Psychiatry, Ichan Sch. of Med. At Mount Sinai, New York, NY

Abstract: Phelan-McDermid syndrome (PMS) is a neurodevelopmental disorder caused by haploinsufficiency of the Shank3 gene. PMS has been identified as one of the most frequent monogenic causes of Autism Spectrum Disorder (ASD). Despite its high prevalence, there are currently few FDA-approved pharmacotherapies for treatment of ASD including PMS. In recent years, a mounting body of evidence has demonstrated that the gut microbiome, can influence brain development and behavior. A significant subset of patients with ASD also present with gastrointestinal disturbances, and sequencing of the gut microbiota has shown alterations in the bacterial makeup of stool from patients with ASD. To identify a possible role for gut microbiome in the development of ASD, we used a mouse model of PMS in which exons 4-22 of the Shank3 gene have been deleted resulting in total knockdown of Shank3 expression ($Shank3^{KO}$). We then investigated the effect of Shank3 deletion on the microbiome and metabolome as well as the effects of a depleted gut microbiome on autism-like behaviors in the $Shank3^{KO}$ model. 16s sequencing of cecal contents demonstrated that $Shank3^{KO}$ results in marked shifts in microbiome composition at the phylum and class levels. $Shank3^{KO}$ mice also displayed altered levels of numerous amino acids and short chain fatty acid metabolites – effects that were exacerbated by Abx treatment. For behavioral experiments wildtype, heterozygous and homozygous $Shank3^{KO}$ littermates were divided into control and antibiotic-depletion (Abx) groups at weaning (postnatal day 21). The Abx group received a cocktail of broad spectrum non-absorbable antibiotics daily via drinking water. On postnatal day 60 animals were subjected to behavioral testing using three-chambered social interaction, marble burying and open field. Behaviorally, $Shank3^{KO}$ KO mice demonstrated decreased social interaction, a deficit which was exacerbated by microbiome depletion. Medial prefrontal cortex (mPFC) was dissected from animals following behavioral testing to assess pathways linked to this gene x microbiome interaction. Preliminary pathway analysis shows that multiple synaptic plasticity-related pathways are differentially affected by microbiome depletion in $Shank3^{KO}$ mice. Taken together our results demonstrate that shank3 KO results in significant changes to the gut flora and metabolome which may be linked to the social deficits observed in these animals. Additionally, the autistic-like behaviors in $Shank3^{KO}$ mice are exacerbated by depletion of the gut microbiome. These findings suggest the possibility of gene x microbiome interactions in this translationally relevant model of autism spectrum disorder.

Disclosures: **A. Osman:** None. **N. Mervosh:** None. **D.D. Kiraly:** None.

Poster

674. Neuroinflammation: Pathophysiological Consequences

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 674.10/O21

Topic: F.05. Neuroimmunology

Support: NIH R35GM118182

Title: Optogenetic stimulation of glutamatergic and cholinergic potentials in the vagus nerve mediating peripheral neuroimmune signaling

Authors: *E. H. CHANG[1], T. TSAAVA[3], A. M. KRESSEL[4], S. S. CHAVAN[2], K. J. TRACEY[2];
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Abstract: The inflammatory reflex is a neural circuit that relays information between the periphery and the brain via the vagus nerve to regulate levels of peripheral inflammatory cytokines. The reflex is comprised of sensory afferents and motor efferent fibers within the vagus nerve, each mediated by a different neurotransmitter system. Sensory afferent information from the periphery to the brainstem is glutamatergic in nature and represents about 80% of all fibers within the vagus nerve. Motor efferents originate in the brainstem to innervate target organs, such as the heart and spleen, and use cholinergic signaling. To examine the neural signaling that is associated with sensory afferent and motor efferent activation, we used nerve cuff electrodes combined with optogenetics to record light-evoked compound action potentials (CAPs). We used three strains of transgenic mice expressing light sensitive channelrhodopsin (ChR2) in distinct genetically defined neuronal populations. Light-evoked CAPs were recorded from TRPV1-ChR2-YFP, Vglut2-ChR2-YFP, and ChAT-ChR2-YFP mice. Two-channel cuff electrodes placed onto the cervical vagus nerve recorded CAPs in response to light pulses (473 nm light at 1, 10, or 20 Hz, 60 s between trains) delivered by a fiber optic. For sensory afferent activation, TRPV1-ChR2 evoked CAPs were characterized by rapid rise times with peak-to-peak amplitudes of 3.55 ± 0.02 mV (mean ± SEM). Vglut2-ChR2 evoked CAPs were multimodal and characterized by substantially larger mean amplitudes 10.21 ± 0.07 mV. In comparison, motor efferent activation of ChAT-ChR2 evoked CAPs had a mean peak amplitude of 1.8 ± 0.02 mV, significantly than TRPV1 (Mann-Whitney, $P<0.005$) and VGlut2 CAPs ($P<0.0001$). These large differences in sensory afferent and motor efferent light-evoked activation may be attributed to the number of fibers represented by each group. Immunohistochemical analysis of vagus nerves cross-sections from TRPV1-ChR2-YFP mice (n = 4) showed that TRPV1 fibers occupy the majority of the cross-sectional area and do not overlap with labeled myelinated fibers. Additional immunohistochemical analysis will show whether ChAT-positive fibers account for <20% of the vagus nerve. These fiber-specific CAPs can help us to understand the nature of signals within the sensory and motor arcs of the mouse vagus nerve. Once coupled to peripheral cytokine measures, they can provide insights into the type of neural activation necessary to activate the inflammatory reflex. These findings are also relevant to emerging neuromodulation and bioelectronic approaches aiming to activate specific nerve fibers or neurotransmitter populations for therapeutic benefit.

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Poster

674. Neuroinflammation: Pathophysiological Consequences

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 674.11/O22

Topic: F.05. Neuroimmunology

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NARSAD Young Investigator Grant from BBRF

Title: The role of microglia in the sculpting of developing stress circuits by early-life adversity

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Abstract: BACKGROUND: Early-life adversity can have a profound and lifelong impact on an individual's risk for emotional disorders such as depression by modulating the maturation of brain circuits. We find that early-life exposure to an impoverished environment and unpredictable maternal care (in a limited bedding and nesting [LBN] paradigm) provokes major alterations in cognitive and emotional function, including anhedonia, accompanied by aberrant connectivity between the hippocampal-limbic system and reward/pleasure-related regions. Within the hypothalamus, this early-life adversity causes an increase in the number of excitatory synapses onto corticotropin-releasing hormone (CRH)-expressing neurons in the paraventricular nucleus (PVN). Such synaptic changes suffice to induce large-scale and enduring epigenomic changes in the expression of neuronal genes, including *Crh*. However, the mechanisms by which early-life adversity modulates synapse development or persistence in developing brain circuits remain unknown. Here, we test the hypothesis that microglia contribute to normal synapse reduction on CRH neurons in the developing PVN, and that adverse early-life experiences interfere with this function.
METHODS: To interrogate microglial function, we employed dual-reporter transgenic mice with visible CRH+ neurons and microglia and two-photon time-lapse imaging in acute slices of the PVN. We obtained these hypothalamic slices from P8 mice that were reared in LBN or control cages from P2 to P8. We visualized live microglial process dynamics and their interactions with CRH+ neurons. In fixed tissue, we utilized 3D-reconstruction confocal

microscopy and immuno-detection of synaptic markers to quantify in high-resolution the developmental trajectory of synapse density and engulfment by microglia.
RESULTS: Early-life adversity augmented the number of vGlut2+/PSD95+ excitatory synapses onto CRH+ neurons by the end of the LBN experience (P10), without altering the number of CRH+ neurons or microglia. Inhibition of microglia increased the density of excitatory synapses onto CRH+ neurons, phenocopying adversity. Live-imaging revealed that microglial process dynamics were diminished in the PVN of LBN mice, along with decreased microglial engulfment of excitatory synapses.
CONCLUSIONS: Microglia are potential contributors to early-life experience-dependent sculpting of stress-sensitive circuits. Ongoing studies include manipulation of microglial function during development to assess if this prevents stress-related emotional disorders in adulthood, thereby providing novel targets for therapeutics or preventative interventions.

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Poster

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Topic: F.05. Neuroimmunology

Support: CONACyT IFC 2015-1 project 115

Title: Hypothalamic and pulmonary vasopressin production during tuberculosis: A link to pathogenesis

Authors: *M. A. ZETTER[1], J. BARRIOS[1], B. MARQUINA-CASTILLO[1], D. MATA[1], A. QUINTANAR-STEPHANO[2], R. HERNANDEZ-PANDO[1];
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Abstract: Tuberculosis (TB) is a highly prevalent chronic infectious disease characterized by granulomatous inflammation and immunopathology that affect primarily the lungs but also interferes with host metabolism and neuroendocrine function. Vasopressin (VP), a well-recognized stress hormone is apparently overproduced and responsible for altered water metabolism during TB. Due to the immunomodulatory effects of VP, here we tried to elucidate whether it influences the pathophysiology of pulmonary TB using a Balb/c mouse model of progressive infection. Our findings indicate that as active pulmonary TB progressed, hypothalamic VP mRNA increase, reaching an acme on the first month of infection,

characterized by a protective immune phenotype in our mice model, to then decrease. Additionally, VP mRNA was detected at the infected lung and contained inside macrophages within the granuloma, the histopathological hallmark of TB since early infection. During pneumonic process, VP was found in foamy macrophages, which are deleterious to the control of infection. Functional studies using pharmacologic compounds showed that agonism of VP receptor provoked marked fibrosis, higher bacilli burdens and increased synthesis of the cytokine TGFβ at lungs. Conversely, non-selective blockade of VpR improved protective immunity reflected in increased inflammatory areas and reduced pulmonary bacterial loads. These effects were a consequence of vasopressinergic inhibition of bacterial clearance by alveolar macrophages, as cell culture assays showed. We conclude that hypothalamic VP synthesis is induced during the onset of pulmonary infection, and produced at the infected lung during late stages, worsening immunopathology and hampering bacilli elimination. These observations highlight the pathophysiological effects of Vp during chronic peripheral inflammation and suggest the possible manipulation of the vasopressinergic system by tubercle bacilli. Furthermore, our results suggest that mycobacteria could drive vasopressin-mediated behavioral changes in infected individuals. Additional research is needed to understand these points.

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Poster

674. Neuroinflammation: Pathophysiological Consequences

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Topic: F.05. Neuroimmunology

Support: NINR Divisions of Intramural Research

Title: Inflammatory signals from the periphery to the brain can mediate fatigue-like behavior in a mouse model of radiation therapy

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Abstract: Fatigue is a common and distressing symptom following radiation therapy for cancer, and it can be frequently undertreated in clinical practice. The neurobiology underlying fatigue is poorly understood, though it is believed inflammatory signals may play a role, as pro-inflammatory cytokines can induce fatigue symptoms in humans and fatigue-like behavior in animals. To help understand how inflammation may lead to fatigue, we use our previously established mouse model of radiation-induced fatigue, in which male mice receive radiation targeted to their pelvic region to mimic treatments for prostate cancer. Mice exposed to this

peripherally-targeted irradiation show a substantial reduction in voluntary running wheel activity (VWRA), which we interpret as fatigue. In current experiments, we first establish that inflammation is contributing to the fatigue by using minocycline, an antibiotic and anti-inflammatory drug, and by using mice lacking MyD88, an important immune signaling adaptor protein. We found that both minocycline-treated mice and MyD88 knockout mice showed a smaller decline in VWRA than control mice after irradiation. In addition, we tested an array of cytokines and other biomarkers in both blood and brain to investigate possible molecular mechanisms both for the fatigue induced by radiation and for its reversal by the two anti-inflammatory manipulations. We found substantial changes in immune signaling in the blood as well as in the brain, which may help us understand how peripheral inflammation signals the brain to produce fatigue-like changes in behavior.

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Poster

674. Neuroinflammation: Pathophysiological Consequences

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Title: Inflammatory biomarkers in depression and schizophrenia -comparison in patients and healthy control participants

Authors: *F. KLAUS[1], F. CATHOMAS[1], K. GÜTTER[1], M. HARTMANN-RIEMER[1], R. SCHLEGEL[1], E. SEIFRITZ[1], S. KAISER[2];
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Abstract: Depression (major depressive disorder, MDD) and schizophrenia (SZ) are heterogeneous mental disorders with a high burden on the individual and societal level as well as limited treatment options. According to the current state of research, the etiology of both is multi-factorial and recent evidence suggests that a subgroup of patients display a pro-inflammatory state. However, studies that directly compare blood biomarkers across different diagnostic entities remain sparse. In order to generate further knowledge about underlying

pathomechanisms, we assessed peripheral inflammation-related biomarkers. We examined patients meeting the DSM-IV criteria for schizophrenia (male/female (M/F): 31/14), MDD (M/F: 18/26) and healthy controls (HC) (M/F: 9/10). Inclusion age was 18-65 years. Exclusion criteria were: any neuropsychiatric diagnosis (HC), any other than the above mentioned DSM-IV Axis I disorders (patients), any autoimmune or chronic inflammatory disorder, anti-inflammatory drugs or any acute infections. C-reactive Protein (CRP), cytokines and chemokines were assessed in plasma / serum using the Olink Inflammation panel, analyzing 92 inflammation-related proteins. We used one-way analysis of variance (ANOVA) to investigate the differences of the inflammation variables between the three groups. To correct for multiple comparisons, overall significant values of the ANOVA were corrected using the false discovery rate (FDR). Post-hoc comparisons using Bonferroni were applied only to biomarker parameters that remained significant after FDR-correction. Analysis of covariance (ANCOVA) was conducted to control for BMI, age and sex as covariates. Several inflammatory biomarkers were elevated in SZ (including CRP, CXCL11, FGF21, IL6, MCP3, TRAIL) and MDD (including FGF21, TRAIL), with some cytokines being decreased in SZ (including CCL28, CXCL11) and in MDD (including DNER, IL18, MCP2) compared to healthy participants. Analysis of covariance revealed that BMI and age influenced CRP, CCL28, IL6 (no significant differences after introduction of covariates) and DNER, TRAIL (no significant differences after introduction of covariates in HC vs MDD). The preliminary results of this exploratory study support the hypothesis of an underlying inflammatory process in SZ and MDD. Further investigation of associations with biomarker alterations and clinical symptoms could potentially identify transdiagnostic subgroups and foster hypothesis-generation on underlying pathomechanisms in order to inspire new therapeutic targets for severe mental illnesses.

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Poster

674. Neuroinflammation: Pathophysiological Consequences

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Topic: F.05. Neuroimmunology

Support: Hillblom Network for the Prevention of Age-Associated Cognitive Decline
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Title: Irritability and its associations with immuno-vascular risk factors in the aging brain

Authors: *D. COTTER, M. YOU, S. WEINER-LIGHT, N. DJUKIC, M. ALTENDAHL, S. M. WALTERS, C. A. LINDBERGH, A. M. STAFFARONI, W. RIVERA-CONTRERAS, A. KARYDAS, Y. COBIGO, A. WOLF, J. KRAMER, F. ELAHI, K. CASALETTO;
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Abstract: Introduction
Neuropsychiatric symptoms have been associated with immuno-vascular disorders as early as the 19th century. Age-associated neurovascular changes are pervasive and contribute to functional decline. Anecdotally, clinicians report increased irritability in patients with CVD. Despite this, there is very little evidential support for irritability as a marker of compromised cerebrovascular health. To address this gap, we examined the link between irritability and quantitative measures of immuno-vascular risk such as white matter integrity, systemic inflammation, and clinical vascular risk factors.
Methods
370 older adults with diagnoses ranging from typical aging to mild cognitive impairment (MCI) (age M=71, 55.2% female, education M=17.5, 91% CDR=0) underwent a comprehensive neurobehavioral examination and fasting blood draw, to quantify plasma-based inflammatory markers. Irritability was assessed using the Neuropsychiatric Inventory Questionnaire (NPI-Q), which evaluates both presence (Yes/No) and severity (mild, moderate, severe) of symptoms. A subset (N=290) underwent a 3T brain MRI within 6 months of the neurobehavioral examination, blood draw, and NPI-Q. Measures of white matter integrity included fractional anisotropy (FA) and mean diffusivity (MD). Systolic blood pressure (BP) was used as a clinical vascular risk factor. Results were analyzed using multivariable regression models controlling for age, gender, and education.
Results
Greater severity of irritability was significantly related to lower FA and higher MD (FA $\beta = -0.11$, $p < 0.04$; MD $\beta = 0.12$, $p < 0.02$), increased TNF-α ($\beta = 0.11$, $p < 0.03$), and systolic BP ($\beta = 3.05$, $p < 0.03$). There were no significant associations between irritability and white matter hyperintensity volumes, nor with other markers of systemic inflammation (IL-6, CRP).
Conclusions
Neuropsychiatric symptoms are common comorbidities of neurodegeneration, and could be considered prodromal. Our data indicate that irritability is linked with both systemic molecular measures of inflammation and CNS structural consequences of its dysregulation. In addition, irritability is associated with systolic BP, an important vascular risk factor. Given that inflammation and white matter changes are known risk factors for neurodegeneration, irritability may be a symptomatic harbinger of age-associated immuno-vascular dysregulation. Future research should aim to define the mechanisms related to the nuanced interplay between neuroinflammation and psychiatric symptomatology.

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Poster

674. Neuroinflammation: Pathophysiological Consequences

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 674.16/O27

Topic: F.05. Neuroimmunology

Title: Toll-like receptor 4 contributes to sex-specific cocaine-induced behaviors

Authors: *J. S. ARCENEAUX[1,2,3], D. T. KASHIMA[2,4], C. A. GRUETER[2,5], B. A. GRUETER[1,2,3,5];
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Abstract: Substance use disorders (SUDs) affect more than 7% (19.7 million people) of the US population. While men are twice as likely to develop SUDs, women are more sensitive to the negative consequences of drugs of abuse and have increased propensity of relapse to drug-seeking behavior. Toll-like receptor 4 (TLR4), a component of the innate immune system, is implicated in drug-related behavior. However, the contribution of TLR4 to the temporal components of cocaine experience is largely unknown. To determine the contribution of TLR4 to cocaine-induced behavior, the behavioral properties of wildtype (WT) and TLR4 knockout mice (TLR4.KO) were compared following cocaine exposure. Locomotor sensitization and place conditioning assays were used to elucidate how TLR4 modulates cocaine-induced behavior. We find that TLR4 deficiency results in differential expression of cocaine-induced locomotor sensitization between males and females. While both male and female TLR4.KO mice had reduced locomotor responding during the development of cocaine sensitization, female TLR4.KO mice exhibited robust enhancement of sensitization expression following a challenge dose of cocaine. In addition, female TLR4.KO mice had prolonged retention of associative memory following cocaine exposure and displayed reinstatement following a subthreshold dose of cocaine. Taken together, these results suggest TLR4 contributes to behavioral adaptations in response to cocaine experience.

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Poster

674. Neuroinflammation: Pathophysiological Consequences

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Program #/Poster #: 674.17/O28

Topic: F.05. Neuroimmunology

Support: NIDA Grant RO1 DA034721
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Title: Hippocampal neuroimmune signaling mediates heroin-conditioned suppression of peripheral nitric oxide

Authors: *J. E. PANICCIA, C. L. LEBONVILLE, S. V. PAREKH, M. E. JONES, *D. T. L. LYSLE;
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Abstract: Heroin and heroin-paired cues impair the peripheral immune response to pathogens. Specifically, exposure to heroin-conditioned stimuli (CS) is sufficient to elicit pronounced suppression of peripheral measures of nitric oxide (NO) production in response to a lipopolysaccharide (LPS) challenge. Our laboratory has established that the cytokine interleukin-1β (IL-1β) within the dorsal hippocampus (DH) is critical during CS exposure for the heroin-conditioned response to occur. The current set of experiments built on these findings and examined the role of DH IL-1 receptor type 1 (IL-1R1) during presentation of these heroin-paired cues. In experiment 1, male rats underwent five conditioning sessions in which heroin (1 mg/kg, s.c.) was paired with a distinct context for 1 h every other day. This context served as the CS. Six days following the last conditioning session, animals received bilateral intra-DH infusions of either IL-1 receptor antagonist (IL-1RA; 1.25 μg/0.6 μL per hemisphere) or vehicle 30 min prior to CS exposure or home cage stay. Immediately following 60 min in the heroin-paired context, or equivalent time in home cage, all rats were administered LPS (1 mg/kg, s.c.) to induce an immune response and tissue was collected 6 h later. Direct antagonism of IL-1R1 within the DH significantly blocked heroin-conditioned suppression of peripheral NO production. Thus, experiment 2 examined the consequence of CS exposure on both IL-1β and IL-1R1 protein within the dentate gyrus, CA3, and CA1 subregions of the DH. Rats underwent the conditioning procedure outlined above, and on test day, tissue was collected at 4 time points: 0, 30, 60, or 120 min post CS onset. Interestingly, we observed a time-dependent, sub-region specific increase in IL-1R1 immunoreactivity within the dentate gyrus 120 min following CS onset. Additionally, there were no significant differences detected in DH IL-1β expression. Collectively, these studies establish that stimulation of DH IL-1R1 is required for the context-heroin association driving conditioned immunomodulation, and that changes in receptor

expression, rather than IL-1β itself, mediate this heroin-conditioned response.
Key words: Opioids, interleukin, conditioning

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Poster

674. Neuroinflammation: Pathophysiological Consequences

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Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 674.18/O29

Topic: F.05. Neuroimmunology

Title: Cytokine alterations differentially influence context-dependent amphetamine locomotor sensitization in female Long Evans rats

Authors: *B. PLOTKIN[1], C. A. CALHOUN[2], B. M. MASON[3], J. GALINDO[4], C. VALENCIA[4], S. DONALDSON[5];
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Abstract: The development of sensitization to psychostimulants such as amphetamine suggests that repeated exposure causes neuroplasticity changes that are persistent. Indeed neural changes have been reported in critical learning and reward-related brain systems following chronic amphetamine and recently, alterations in central chemokines and cytokines have also been noted. The current investigation was designed to evaluate the sex differences in the context-dependent effects of repeated, intermittent amphetamine (AMPH; 4.0 mg/kg, 4 days, every 48 h). Adult Long Evans male and female rats (n=7-10 per group) were divided into context-dependent (locomotor activity cages) groups CD+SAL and CD+AMPH, and context-independent (CI; home cage injections) groups CI+SAL and CI+AMPH. All animals were administered a low dose (1.0 mg/kg AMPH) CHALLENGE in the LMA cages following a 3-day withdrawal. Animals were sacrificed on the final day of testing and brains were flash frozen and stored at -80 C for immunohistochemistry. Results indicate that AMPH-treated males and females displayed increased LMA including distance traveled, vertical counts, and stereotypies on the CHALLENGE day. Interestingly, CD+AMPH groups displayed the greatest CHALENGE day responses, highlighting the importance of contextual drug associations. Immunohistochemical data support these behavioral differences with the largest increases in protein levels for the chemokine CXCL12 and its canonical receptor, CXCR4, in the medial prefrontal cortex (mPFC), striatum (STR), and ventral tegmental area (VTA) of CD+AMPH animals. In sum, our results provide evidence for sex-dependent differences in response to an intermittent AMPH regimen and reveal that AMPH exposure after withdrawal in a *familiar* environment increases sensitization. These behavioral differences parallel increases in CXCL12 and CXCR4 proteins,

implicating a potential interaction of neuroimmune activation and contextual cues in AMPH sensitization.

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Poster

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Program #/Poster #: 674.19/O30

Topic: F.05. Neuroimmunology

Support: 1ZIAMH001090-36

Title: Neutrophil-mediated effects at the meningeal barrier following chronic stress

Authors: *S. L. KIGAR[1], C. T. HIGHAM[1], N. E. WRIGLEY[1], V. H. SUN[2], M. L. LEHMANN[1], A. ELKAHLOUN[3], M. HERKENHAM[1];
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Abstract: Chronic stress is a potent risk factor in the etiology of depression, and both stress and depression are associated with holistic changes to organismal immunity. Bidirectional communication pathways between the brain and peripheral immune systems have been described (Herkenham & Kigar, 2016), though less is known about how chronic stress changes the dialogue. Our lab has recently shown that neurovascular events (NVEs) associated with damage to the blood brain barrier (BBB) are evident in the brain parenchyma of chronically stressed animals exhibiting depressive-like behavior (Menard et al., 2017; Lehmann et al., 2018). Damage to the BBB allows for direct interaction of the peripheral immune system and brain, precipitating a sterile injury response and subsequent wound resolution by immune cells. Interestingly, patients who have recently experienced a stroke or traumatic brain injury—conditions associated with overt damage to the BBB and massive infiltration of peripheral immune cells into the brain—are at heightened risk for development of major depression (Pedroso et al., 2016; Jorge et al., 2004), suggesting depression may be causally linked with BBB damage. Understanding the mechanisms preceding appearance of these NVEs is thus of high priority for developing novel, effective treatments for depression. To address this, using multiparametric flow cytometry, we first examined the spatiotemporal dynamics of the peripheral immune response to chronic social defeat (CSD) in mice via accumulating exposure to stress. CSD stress is a well-characterized, ethologically validated model to induce depressive- and anxious-like behavior in rodents. Our results strongly imply activation and trafficking of neutrophils into the leptomeninges from circulating blood over time. Further, meningeal single

cell RNA sequencing reveals pericyte decline in CSD-stressed animals. Pericytes are a critical cellular component of the neurovascular unit that support BBB-integrity, and are sensitive to reactive oxygen species (ROS)-induced apoptosis (Amano, 2005). Work exploring the putative role for neutrophil-induced pericyte apoptosis via ROS-release as a causative pathway for BBB-breakdown is ongoing.

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Poster

674. Neuroinflammation: Pathophysiological Consequences

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Topic: F.05. Neuroimmunology

Support: NIH Grant R15HD082638
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NYU NIEHS Center Pilot Projects

Title: Developmental consequences of prenatal electronic cigarette aerosol exposure on offspring behavior and neuroinflammation

Authors: *F. CHACE-DONAHUE[1], A. KAZAKOVA[1], J. S. CHURCH[1], J. L. BLUM[2], J. R. RATNER[2], J. T. ZELIKOFF[2], J. J. SCHWARTZER[1];
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Abstract: In an effort to decrease the rates of smoking tobacco, electronic cigarettes (e-cigs) have been proposed as an effective smoking cessation tool. Despite the growing popularity of e-cigs, little is known about their toxicological impacts. This is particularly concerning given that e-cig use is marketed as a “safer alternative” to conventional tobacco cigarettes during pregnancy for both the mother and fetus. To examine the behavioral and developmental consequences of maternal e-cig use, pregnant female CD-1 mice were randomly assigned to one of three treatment groups (n=9 per group) and exposed daily to either filtered air (control), propylene glycol and vegetable glycerol (50:50 PGVG, vehicle), or to PGVG with 16mg/ml nicotine. Whole-body exposures were carried out for 3 hours per day throughout gestation. Adult male and female offspring from each treatment group were assessed for learning & memory deficits using the Novel Object Recognition task, social-emotional processing using the Social Approach task, anxiety-like behavior using the Elevated Plus Maze, resignation or depressive-like behavior using the Forced Swim Task, and repetitive motor stereotypies using the Marble Burying task. Nicotine-exposed male offspring exhibited hyperactivity in several tasks and reduced resignation

in the forced swim task. In addition, adult female offspring of dams exposed throughout gestation to PGVG plus nicotine displayed a small but significant increase in body weight. At the time of sacrifice following behavior measurements, male and female brains were examined for region-specific differences in cytokine expression using multiplex immunoassays to identify the neuroimmunological consequences of maternal e-cig use on offspring brain development. These findings provide substantial evidence of adverse developmental consequences of maternal e-cig use during pregnancy and persistent behavioral changes in adult offspring.

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Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 674.21/O32

Topic: F.05. Neuroimmunology

Title: Breast cancer hijacks the brain to impair memory in mice

Authors: *S. KENT[1], S. N. DE LUCA[1], A. ARMSTRONG[1], A. K. WALKER[2];
[1]La Trobe Univ., Bundoora, Australia; [2]Neurosci. Res. Australia, Randwick, Australia

Abstract: Cognitive impairment and mood-related symptoms are highly prevalent in cancer patients with non-central nervous system tumors; common symptoms include learning, memory and concentration difficulties. Until recently these symptoms have been attributed to chemotherapy (referred to as ‘chemobrain’). However, recent clinical studies show that so-called ‘chemobrain’ can present prior to cancer treatment. These findings suggest that the stress of a cancer diagnosis or the tumour itself may be responsible for cognitive impairment in some cancer patients. We recently demonstrated using mouse models of syngenic, orthotopic breast cancer that a solid peripheral tumour alone is sufficient to induce hippocampal-dependent memory impairment via (neuro)inflammation. Whether triple negative breast cancer is capable of inducing hippocampal independent memory impairment or mood-related symptoms remained unknown, and the neurocellular culprits responsible for these symptoms in triple negative breast have not been explored. Here, we investigated hippocampal-dependent and hippocampal independent fear conditioning and depression-like behaviour using sucrose preference in response to two orthotopic, syngenic mouse models of mammary adenocarcinoma. 4T1.2 tumor cells syngenic to BALB/C mice or E0771 tumor cells syngenic to C57BL/6J mice vs vehicle were injected into the left 4^{th} mammary fat pad. Tumors induced depression-like behaviour indicated by reduced sucrose preference ($p < 0.05$), and in contrast to previous findings showing poorer novel object recognition, tumours enhanced hippocampal-dependent fear conditioned memory ($p < 0.05$). No difference is hippocampal-independent memory was observed. It is

possible that increased freezing in the fear conditioning task is due to increased sensitivity to shock in tumour bearing mice caused by inflammation. Tumour bearing mice exhibited splenomegaly indicating elevated peripheral inflammation and increased microglial activation in the hippocampus ($p < 0.05$). Examination of cytokine gene expression in the hippocampus confirmed increases in pro-inflammatory cytokines *Il1b* and *Tnfa* and reductions in anti-inflammatory *Il10*. Taken together, these findings suggest that a solid peripheral tumour is sufficient to induce depression-like behaviour and modulate hippocampal-dependent memory which coincides with markers of peripheral and central inflammation. Future research should investigate whether tumour-induced neuropathy may explain differential findings between hippocampal-dependent memory tasks.

Disclosures: S. Kent: None. **S.N. De Luca:** None. **A. Armstrong:** None. **A.K. Walker:** None.

Poster

674. Neuroinflammation: Pathophysiological Consequences

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 674.22/O33

Topic: F.05. Neuroimmunology

Support: FWO PhD fellowship Strategic basic Research

Title: A20: A predisposing factor for neurolupus?

Authors: *C. DAEMS[1], Z. CALLAERTS-VEGH[2], G. VAN LOO[3], R. D'HOOGE[2], P. CALLAERTS[1];
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Abstract: Neuropsychiatric lupus (NPSLE) refers to the neurological and psychiatric symptoms seen in patients with systemic lupus erythematosus (SLE). An important question regarding the pathogenesis of NPSLE is whether the symptoms are caused primarily by intrinsic mechanisms in the CNS or develop as a consequence of systemic autoimmunity. Even though, significant insights have already been gained from studies using SLE mouse models, none of these models are based on genes that are associated with SLE.
In this research, the influence of *TNFAIP3* heterozygosity on behavior and CNS associated defects were evaluated in a C57BL6 mouse model. *TNFAIP3* is a well-known susceptibility locus for SLE and encodes the ubiquitin-editing enzyme, A20. This protein is a strong negative regulator of the nuclear factor-κB (NF-κB) pathway. Its important anti-inflammatory function has been shown in an A20 loss-of-function mouse model, where animals died prematurely due to severe organ inflammation.
Females and males at the age of 10±2 weeks were subjected to an extensive behavioral analysis,

evaluating motor function, emotional and social behavior, cognitive function and disease-related behavior. A20 heterozygous mice ($A20^{+/-}$) showed subtle cognitive defects in comparison to wildtype littermates. Evaluation of the neuroinflammatory profile uncovered the presence of pro-inflammatory and anti-inflammatory mediators in the hippocampus of male $A20^{+/-}$ mice. The presence of a subtle cognitive deficit and the increased neuroinflammatory profile in hippocampi of A20 heterozygous mice suggests that A20 heterozygosity predisposes to deficits in brain homeostasis maintenance.
Besides a genetic predisposition, environmental factors are known to have an important contribution to the development of neuropsychiatric symptoms. In order to mimic the disease pathogenesis more closely, an immune challenge (LPS) was delivered in the cerebroventricular system. This challenge further exacerbates behavioral impairments, related to anxiety, cognitive function and sensorimotor gating. The deficits were predominantly present in females, which suggests an important contribution of hormonal factors in inflammation and behavioral changes in NPSLE.
We propose that A20 heterozygosity is predisposing for NPSLE, and that further mechanistic insight and possible therapeutic interventions can be studied in this mouse model that recapitulates key hallmarks of the disease.

Disclosures: **C. Daems:** None. **Z. Callaerts-Vegh:** None. **G. van Loo:** None. **R. D'Hooge:** None. **P. Callaerts:** None.

Poster

675. Neuroinflammation: Neurophysiological Responses

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 675.01/O34

Topic: F.05. Neuroimmunology

Support: NIH Grant R15AG052935

Title: Differential effects of TLR4 deficiency on hippocampal neurogenesis in male and female adult and aged mice

Authors: *M. G. CONNOLLY[1], O. L. YOST[1], M. E. GIEDRAITIS[2], O. V. POTTER[3], L. S. MATHENY[1], C. E. RINDOKS[1], R. A. KOHMAN[1];
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Abstract: Toll-like receptor 4 (TLR4) is primarily responsible for initiating an innate immune response following pathogen recognition. However, TLR4 is also expressed on neural progenitor cells and has been reported to regulate hippocampal neurogenesis. For instance, young male TLR4 knockout mice show increases in new cell proliferation and the proportion of doublecortin

(DCX) positive cells (Rolls et al., 2007). Currently, it is unknown if these changes are present in both sexes and persist with aging. Therefore, the present study evaluated whether TLR4 deficiency alters hippocampal neurogenesis in young (3-4 months) and aged (18-20 months) male and female TLR4 deficient (TLR4−/−; B6.B10ScN-Tlr4lps-del/JthJ) and wild type (WT) mice. New cell survival was evaluated by quantifying bromodeoxyuridine (BrdU)-positive cells in the granular cell layer of the hippocampus 32 days after BrdU exposure. Results showed that young TLR4-/- females had a greater number of BrdU positive cells than TLR4-/- males and WT females, indicating enhanced new cell survival in young TLR4-/- females. Aged WT mice showed the expected decrease in new cell survival compared to young WT mice and this deficit was maintained in the aged TLR4-/- mice. Additional measures currently in progress will determine whether TLR4-/- mice show altered new cell differentiation by comparing proportions of BrdU-positive cells that co-label with a neuron or astrocyte marker. Further, differences in proliferation rates are being evaluated by quantifying Ki-67-positive cells. Preliminary results show that the absence of TLR4 regulates new cell survival in a sex- and age-dependent manner.

Disclosures: M.G. Connolly: None. **O.L. Yost:** None. **M.E. Giedraitis:** None. **O.V. Potter:** None. **L.S. Matheny:** None. **C.E. Rindoks:** None. **R.A. Kohman:** None.

Poster

675. Neuroinflammation: Neurophysiological Responses

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 675.02/O35

Topic: F.05. Neuroimmunology

Support: Dept of Biology, Univ. of KY laboratory funds
personal funds (RLC)

Title: The effects of bacterial endotoxin LPS on neural function in various animal models

Authors: *R. L. COOPER[1], M. MCNABB[1], C. SAELINGER[1], C. BALLINGER BOONE[1], A. GREENHALGH[1], O. ISTAS[1], M. STANBACK[1], A. STANBACK[1], O. ANYAGALIGBO[1], J. BERNARD[1], M. L. DANLEY[1], S. M. BIERBOWER[2], A. GHOWERI[3], O. THIBAULT[3]; [1]Biol., Univ. of Kentucky Dept. of Biol., Lexington, KY; [2]Biol., William Paterson Univ., Wayne, NJ; [3]Pharmacol. and Nutritional Sci., Univ. of Kentucky, Lexington, KY

Abstract: The endotoxic effect from gram negative bacteria is primarily due to the lipopolysaccharides (LPS). LPS activates the innate immune response through a Toll-like receptor 4 (TLR4) known as the CD14/TLR4/MD2 receptor complex in mammals. The Toll receptors are conserved from primates to insects. However, in insects the peptidoglycan recognition proteins (PGRPs) are the receptors which respond to LPS from gram negative bacteria. These PGRPs activate the Immune Deficient (IMD) signaling cascade. There is a

family of these receptors known in Drosophila melanogaster but their expression profiles in different tissues has yet to be fully elucidated. We examined a variety of model preparations to better understand the acute actions of exposure to LPS of Serratia marcescens to better understand the varied mechanisms of action. There is a differential, dose dependent effect of LPS in increasing and decreasing HR heart rate (HR) in the larval medicinal blow fly (Phaenicia sericata) and a fruit fly (Drosophila melanogaster). LPS depressed evoked and miniature (quantal) EJPs while hyperpolarizing the skeletal muscle in larval Drosophila, but increased EJPs with no effect on muscle membrane potential at the crayfish NMJ. Both NMJs are glutamatergic. LPS had no effect on sensory transduction of proprioceptive sensory neurons in crayfish and blue crab. LPS at the cholinergic frog NMJ depressed synaptic transmission with no effect on muscle membrane potential. LPS depressed sensory-CNS-motor nerve circuits in both crayfish and larval Drosophila. Synaptically-evoked population spikes in field CA1 of the mouse hippocampus were also significantly reduced by acute LPS applications. The varied effects of LPS in different model systems paves the way to examining differential cellular mechanisms induced by acute exposure to LPS.

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Poster

675. Neuroinflammation: Neurophysiological Responses

Location: Hall A

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Program #/Poster #: 675.03/O36

Topic: F.05. Neuroimmunology

Support: Exploratory Research for Advanced Technology (JPMJER1801)
Precursory Research for Embryonic Science and Technology (JPMJPR1785)

Title: Optogenetic activation of dopaminergic neurons in ventral tegmental area induces peripheral immune responses

Authors: *T. KAYAMA, Y. IKEGAYA, T. SASAKI;
Grad. Sch. of Pharmaceut. Sci., The Univ. of Tokyo, Tokyo, Japan

Abstract: Dopaminergic neurons in the ventral tegmental area (VTA) is a main part of the brain reward system. Recent reports using a Designer Receptors Exclusively Activated by Designer Drugs technology have demonstrated that pharmacogenetical activation of VTA dopaminergic neurons induces activation of peripheral immunity system, which resulted in increases in the resistance for bacterial infection and the reduction of cancer volume (Shaanan et al., 2016;

2018). However, the pharmacogenetic method has a limited temporal resolution and it is thus impossible to precisely estimate how long and when the activation of VTA neurons was required to induce immune responses. In this study, we addressed to create an experimental system that more accurately replicates physiological conditions by utilizing an optogenetic approach. Here, we crossed DAT-Cre with RCL-ChR2(H134R)/EYFP mice, yielding a bigenic mouse line in which the expression of ChR2 is driven by dopamine transporter (DAT)-promoter, which has been proven to be dopaminergic neuron specific. In these transgenic male mice, photostimulation was applied to the VTA for 12 hours and their serum samples were collected from the caudal vein 3, 9, 24 hours after the photostimulation. The Bio-plex multiple cytokine assay system revealed that the serum concentrations of several types of immune-related cytokines were increased, compared with sham control groups, demonstrating that increased activity of dopaminergic VTA neurons leads to the activation of the peripheral immune system. Similar tests were applied to two additional mouse groups; one in which a male mouse was kept housed with a single female mouse for 10 days, and the other in which a male mouse was kept housed in an enriched environment with several toys and a running wheel for 10 days. Especially in the former animal group, but not the latter animal group, the concentrations of a subset of cytokines were increased, similar to the VTA photostimulation group. These results suggest that housing with female mice are effective to mobilize immune responses through the activation of the VTA reward system. We are now testing detailed physiological mechanisms by using a multi-channel electrode array system.

Disclosures: **T. Kayama:** None. **Y. Ikegaya:** None. **T. Sasaki:** None.

Poster

675. Neuroinflammation: Neurophysiological Responses

Location: Hall A

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Program #/Poster #: 675.04/O37

Topic: F.05. Neuroimmunology

Support: NIH grant U01-AA020935
NIH grant R01-AA024095

Title: The endogenous neurosteroid (3α,5α)3-hydroxypregnan-20-one (3α,5α-THP) inhibits pro-inflammatory toll-like receptor (TLR)-MyD88-dependent signaling in immune cells and brain

Authors: *I. BALAN[1], T. O'BUCKLEY[1], R. SCHLEICHER[1], G. BOERO[1], L. AURELIAN[2], L. A. MORROW[1];
[1]Univ. of North Carolina, Chapel Hill, NC; [2]Stanford Univ. Sch. of Med., Stanford, CA

Abstract: 3α,5α-THP has protective activity in addictions, depression, traumatic injury and epilepsy. These conditions are regulated by multiple TLRs, suggesting that 3α,5α-THP may

inhibit TLR signaling. We have recently shown that 3α,5α-THP inhibits TLR4 activation in RAW264.7 macrophages and the brain of alcohol-preferring (P) rats. However, its effect on other TLR signals and the potential difference between males and females, are currently unknown. We examined the effect of 3α,5α-THP on agonist-induced activation of the TLR2 and TLR7 signals, which are MyD88-dependent and the TLR3 signal, which is TRIF-dependent in RAW264.7 cells. We found that Pam3Cys (10 μg/ml; 24h) activates TLR2 signaling, evidenced by increased levels of TRAF6, pERK1/2, pCREB and pATF-2. Increased expression was completely inhibited by 3α,5α-THP (1 μM, $p<0.05$). Imiquimod (1 μg/ml; 24h) activated TLR7 signaling, resulting in pIRF7 increase (30%) that was completely inhibited by 3α,5α-THP (1 μM, $p<0.05$). By contrast 3α,5α-THP did not inhibit the Poly-IC- (TLR3 agonist; 25 μg/ml; 24h) induced increase in CXCL10, suggesting that 3α,5α-THP selectively inhibits the activation of signals that function through MyD88. Consistent with the findings for RAW264.7 cells, 3α,5α-THP inhibited MCP-1 and pIRF7, but had no effect on pIRF3 levels in P rat nucleus accumbens (NAc). We found a sex difference in baseline MCP-1 (55% higher in male vs. female) and pIRF7 (45% higher in female vs. male). In both sexes, 3α,5α-THP (15 mg/kg; IP) administration significantly reduced the levels of MCP-1 (40% in females; 25% in males) and pIRF7 (55% in males and females). 3α,5α-THP inhibition of MCP-1 levels was also found in the P rat ventral tegmental area, amygdala, hypothalamus and hippocampus, indicating that 3α,5α-THP inhibits pro-inflammatory TLR signal activation throughout brain. However, TLR activation can also increase anti-inflammatory signals and we have previously shown that P rats have significantly lower levels of the TLR4-associated anti-inflammatory chemokine CX3CL1 in the NAc than their non-alcohol preferring NP counterparts. Significantly, 3α,5α-THP administration increased the NAc levels of CX3CL1 in both female (45%, $p<0.05$) and male (30%, $p<0.05$) P rats, suggesting that it corrects a neuroimmune imbalance in P rats. Collectively, the data indicate that the 3α,5α-THP therapeutic potential involves modulation of MyD88-dependent TLR signaling pathways resulting in diminished pro-inflammatory signal activation, both in immune cells and throughout the brain.

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Poster

675. Neuroinflammation: Neurophysiological Responses

Location: Hall A

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Program #/Poster #: 675.05/O38

Topic: F.05. Neuroimmunology

Support: DARPA grant # N66001-16-2-4054. Bremner

Title: Levels of pituitary adenylate cyclase-activating polypeptide (PACAP) in traumatic stress and the modulatory effect of noninvasive cervical vagus nerve stimulation (nVNS)

Authors: Y. JIAO[1], Y. KO[4], N. Z. GUREL[6], A. HANKUS[2], S. L. LADD[7], M. T. WITTBRODT[8], L. SHALLENBERGER[5], N. MURRAH[2], M. HUANG[5], A. HAFFER[10], J. ALKHALAF[3], H. JUNG[6], O. LEVANTSEVYCH[2], J. A. NYE[9], M. H. SHANDHI[6], V. VACCARINO[5], A. J. SHAH[11], O. T. INAN[6], J. D. BREMNER[12], ***B. D. PEARCE**[13]; [1]Epidemiology, [3]Cardiol., [2]Emory (RSPH), Atlanta, GA; [4]Dept. of Biostatistics and Bioinformatics, [5]Dept. of Epidemiology, Rollins Sch. of Publ. Hlth., Atlanta, GA; [6]Sch. of Electrical and Computer Engin., Georgia Inst. of Technol., Atlanta, GA; [7]Dept. of Psychiatry and Behavioral Sci. and Dept. of Radiology, [8]Dept. of Psychiatry and Behavioral Sci., [9]Dept. of Radiology, Emory Univ. Sch. of Med., Atlanta, GA; [10]Emory, Atlanta, GA; [11]Dept. of Epidemiology, Dept. of Intrnl. Med. (Cardiology), [12]Dept. of Psychiatry and Behavioral Sciences, Dept. of Radiology, Rollins Sch. of Publ. Health, Emory Univ. Sch. of Med., Atlanta, GA; [13]Epidemiology/Neuroscience Program, Emory Univ., Atlanta, GA

Abstract: Background: Prior studies suggest that the neuropeptide, PACAP, is dysregulated in post-traumatic stress disorder (PTSD). Studies *in vitro* and animal models have confirmed that PACAP signaling plays an essential role in stress homeostasis. However, there is a lack of studies in humans examining longitudinal changes in PACAP in relation to experimentally-controlled trauma recall or other stressful paradigms. The anatomical distribution of PACAP suggests it may be regulated by the vagus nerve, which could explain some neuroimmune functions ascribed to PACAP. Noninvasive cervical vagus nerve stimulation (nVNS) is used experimentally in treating neuropsychiatric disorders. In the current study we examined longitudinal changes in PACAP in an experimental paradigm that also examined the influence of nVNS.

Methods: A total of 36 subjects with previous traumatic experienced were recruited (12 with PTSD diagnosis) for a multi-day double-blinded study of nVNS. After a baseline psychological and health assessment, patients were randomly assigned to nVNS stimulation or sham stimulation, and underwent a protocol that includes both trauma recall and non-personalized mental stressors. Blood was collected at baseline (day 1 before any experimental stressor or VNS) and after the stressors on days 1, 2 and 3. Linear mixed-effects models were used to assess changes in PACAP over time (in response to stressors) and its relation to the nVNS stimulation. The ratio of PACAP to baseline levels was compared over the three days of the protocol. Linear regression was used to examine the correlation between the concentrations of PACAP and other immune molecules (log-transformed).

Results: Adjusted for age, sex, BMI, race, and education level, PACAP blood levels continuously increased during the procedure (1st day: 9%, 95%CI: [1.00, 1.18]; 2nd day: 14%, 95%CI: [1.04, 1.25]; 3rd day: 15%, 95%CI: [1.03, 1.28]). This increase was consistently lower in the VNS compared to the sham stimulated group. The log PACAP concentration was significantly, positively associated with (log) IFN-γ (β=0.14, p=0.022) and ghrelin (β=0.15, p=0.05), and significantly negatively correlated with IL6 (β=-0.13, p=0.048), IL13 (β=-0.25, p=0.006), and IL5 (β=-0.27, p=0.013).

Conclusions: This is the first report of PACAP in humans undergoing a trauma recall paradigm.

Trauma or stressful tasks were associated with increased PACAP blood levels. However, the association in VNS treatment to PACAP blood levels still needs to be established in a Phase 2 study. Combined with correlated inflammatory cytokines, PACAP may be a biomarker to show or predict the treatment effect of VNS in PTSD.

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Poster

675. Neuroinflammation: Neurophysiological Responses

Location: Hall A

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Program #/Poster #: 675.06/O39

Topic: F.05. Neuroimmunology

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NNSFC 91432114
NNSFC 91632302
Beijing Municipal Government

Title: Inflammatory challenges inflict dramatic transcriptional responses in pituitary gland at single-cell level

Authors: *T. YAN, R. WANG, R. LIN, M. LUO;
Natl. Inst. of Biol. Sci., Beijing, China

Abstract: Immune challenges such as viral or bacterial infections cause tissue inflammations and have profound effects on the hypothalamic-pituitary-adrenal (HPA) axis. Pituitary gland is the endocrine center of the brain and is actively involved in the regulation of inflammatory events. However, very little is known about the transcriptional response of pituitary cells during immune challenge. In this study, we established inflammatory mouse models using immune stimuli such as lipopolysaccharides (LPS) and polyinosinic:polycytidylic acid (poly I:C) with a series of doses and durations, and performed single-cell RNA sequencing (Smart-seq2) on over 4000 individual cells from mouse pituitary gland. Concordantly, we identified 6 major cell clusters (Somatotropes, Corticotropes, Melanotropes, Lactotropes, Thyrotropes, Gonadotropes) in the pituitary gland with corresponding markers, which is consistent with previous knowledge. Within these cells, short-term, high-dose LPS administration invoked dramatic increase of

mRNA levels in genes related to immune response. The transcriptional state of these cells returned to normal after 3-5 weeks of recovery, but some genes appeared to be upregulated compared to control group. Pseudo-time analysis of single-cell transcriptome trajectory also confirmed that the procedure of inflammatory response was followed by recovery to normal state. The results from this study extends our knowledge of the transcriptional response of pituitary single cell during inflammatory challenge, and provide valuable information regarding the hormonal regulation with HPA-axis during inflammatory responses.
(T. Y. and R. W. contributed equally to this project)

Disclosures: **T. Yan:** None. **R. Wang:** None. **R. Lin:** None. **M. Luo:** None.

Poster

675. Neuroinflammation: Neurophysiological Responses

Location: Hall A

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Program #/Poster #: 675.07/O40

Topic: F.05. Neuroimmunology

Support: BigData #1633164
Big Data #1633184
NIH P20 GM103642 06 to AG
#1707355 to JA
R25NS08068706

Title: Pumilio in hemocytes regulate sleep behavior

Authors: *N. M. DIAZ RODRIGUEZ[1], Y. ORTIZ-CASTELLANO[1], O. MENDEZ[1], M. R. FRANCIA[2], L. O. MARRERO RAMOS[1], A. GHEZZI[3], J. L. AGOSTO[4];
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Abstract: Sleep is a physiological state defined by periods of inactivity, low sensory response and homeostasis regulation. Despite mayor advantages in our knowledge of neural circuits, genes and biological processes that underlie sleep in *Drosophila melanogaster*, the specific molecular pathways that orchestrate this response remains unknown. Previous studies have shown that peptoglycan fragments from bacterial cell walls processed by macrophages such as muramyl peptides (MPs) can induce sleep behavior. This finding combined with other recent studies suggest that macrophages play a role on sleep regulation even in the absence of infection. We have previously shown that *pumilio* (*pum*), a translational repressor, produces an abnormal sleep pattern when is knocked down. In a screen to identify the specific tissues responsible for pumilio actions on sleep, we found that *pum* knockdown in hemocytes decreases sleep, while its

overexpression increases sleep. To dissect the mechanisms by which *pum* manipulations in hemocytes change sleep, we are currently investigating the expression of hemocytes products such as antimicrobial peptides and inflammation markers using Real-time PCR. Moreover, we are examining the impact of *pum* manipulations on hemocyte levels using GFP-labeled hemocytes and fluorescence microscopy. Our studies not only support the idea of a nobel role of hemocytes on sleep regulation but also provide further insights into the mechanisms by which *pum* regulate sleep behavior.

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Poster

675. Neuroinflammation: Neurophysiological Responses

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 675.08/O41

Topic: F.05. Neuroimmunology

Support: New Jersey Commission on Brain Injury Research
PNI Innovation Fund

Title: Adeno-associated virus (AAV) persistently alters cortical expression of immune genes that can regulate circuit structure and function

Authors: *C. M. SURIANO[1,2], J. VERPEUT[1,2], L. M. BOULANGER[1,2];
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Abstract: Recombinant viruses have revolutionized neuroscience research and hold promise for human gene therapy. Viruses allow researchers to alter endogenous gene expression or insert exogenous genetic material to visualize and manipulate neural circuits. Recombinant adeno-associated virus (AAV) is among the most commonly used viruses in neuroscience, in part because it has strong neuronal tropism, is non-replicative, persists in postmitotic cells, and is nonpathogenic. Immune responses to AAV administration in the periphery can reduce viral safety and efficacy, but AAV administration in the nervous system is not typically associated with significant inflammation, possibly due to the brain's immune privileged status. However, growing evidence suggests that several immune proteins also play critical roles in neural homeostasis. Therefore, we assessed changes in the expression of immune genes and protein levels 4 days and 21 days post-AAV injection, respectively, and compared AAV-injected samples to sham-injected and unoperated controls. Here we show that unilateral injection of a virus encoding only a fluorescent marker (AAV8-*mCherry*) into adult mouse motor and somatosensory cortex significantly alters levels of immune proteins that regulate synaptic

transmission and plasticity, including the classical MHCIs H2-K and H2-D, complement component C3, and the tyrosine kinase Fyn. AAV8-*mCherry* rapidly increases *H2-K, H2-D, C3* and *Fyn* mRNA levels in somatosensory but not motor cortex. Three weeks post-injection, H2-K, H2-D, C3, and Fyn protein levels are significantly elevated in somatosensory cortex, while only H2-K and C3 levels are elevated in motor cortex. In hippocampus, which was not directly injected and showed lower viral *mCherry* expression, AAV8-*mCherry* causes rapid increases in mRNA levels for most of the genes examined but no lasting increases in protein levels. In contrast, hippocampal immune protein levels are decreased three weeks after cortical sham injections. Our results demonstrate that a form of AAV commonly used as a negative control ("empty virus") in neuroscience research significantly and persistently disrupts the expression of immune genes that can regulate neuronal structure and function. These results suggest that sham-injected and/or unoperated controls may be necessary to isolate the effects of virally-delivered tools from the circuit impacts of the neuroimmune response to the virus itself.

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Poster

675. Neuroinflammation: Neurophysiological Responses

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Title: A circadian gated spinal reflex circuit regulates LPS sensing and subsequent inflammation

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Abstract: The autonomic nervous system (ANS) regulates the intensity of the inflammatory process in response to endotoxin, but how is the brain informed about the immune challenge has remained elusive. We hypothesized that the sensory afferent part of the ANS is responsible for sensing lipopolysaccharide (LPS) and allow the efferent ANS to modify its output towards immune organs. We show that sensory neurons located in the spinal cord become activated shortly after an LPS challenge by LPS-induced prostaglandin production. Denervation studies show that the inflammatory signal is transmitted by liver spinal and not vagal afferents. The

circadian system, which strongly influences the ANS output, imposes rhythmicity on the entrance of hepatic sensory input, establishing a differential sensitivity to LPS. This allows a high inflammatory response to happen during the active period of the animal, while attenuating its intensity during the resting phase of the animal. This study unravels the circuit used to transmit the peripheral LPS signal to the brain. Hereby, the hepatic spinal sensory nerves, strongly influenced by the circadian system, allow the immune organs to mount an efficient inflammatory response at the moment when it is most likely needed.

Disclosures: E. Soto-Tinoco: None. **E. Santacruz:** None. **R.M. Buijs:** None.

Poster

675. Neuroinflammation: Neurophysiological Responses

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 675.10/O43

Topic: F.05. Neuroimmunology

Support: P01HL046925-21A1

Title: Severe neonatal anemia in mice causes poor growth and neuroinflammation that are modulated by erythropoietin treatment

Authors: *G. SINGH, M. K. GEORGIEFF, T. GISSLEN;
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Abstract: Background: Premature infants are at risk for severe anemia particularly due to illness requiring frequent blood collection. Optimal treatment for phlebotomy-induced anemia (PIA) is unresolved, however recent evidence suggests that more severe anemia results in poorer neurodevelopmental outcomes. In our mouse model of PIA, we found significant neurodevelopmental deficits at adult ages and RNA-seq analysis of the hippocampal transcriptome showed an upregulation of pro-inflammatory pathways at postnatal (P) day 14. Erythropoietin (EPO) is an emerging treatment for PIA and has shown improved neurodevelopmental outcomes in neonates. EPO receptors are involved in downstream signaling of pro and anti-inflammatory pathways and therefore may play a role in modulating inflammation.
Objective: To determine the severity of neuroinflammation following severe PIA and whether erythropoietin treatment alters inflammatory phenotype.
Design/Methods: Neonatal mice were phlebotomized from P3 to P13 via facial venipuncture. Blood was drawn twice daily at 5.25 uL/g until goal hematocrit (hct) of 18% was reached and once thereafter (3.5 µL/g) to maintain Hct levels. A subset of these pups were treated with 5000 U/kg i.p. huEPO twice a day. Gene expression in the hippocampus was measured by qPCR and one hemisphere of each brain was used to obtain brain protein levels. Tissue from non-

phlebotomized pups was used as a control.
Results: PIA to hct of 18% caused significantly less growth in comparison to non-anemic controls, but growth normalized to control levels following EPO treatment. PIA increased signs of neuroinflammation resulting in a 33% increase in IL-6 concentration in the brain. Moreover, there was a 25% increase in hippocampal gene expression of the P65 NFκB subunit. After treatment with EPO, the increased IL-6 level in the brain persisted; gene expression of P50 and P65 NFκB subunits increased over non-EPO treated anemic levels. In contrast, EPO treatment caused increased concentration of the anti-inflammatory cytokines TGF-β and IL-10.
Conclusion(s): Severe anemia results in poor growth and neuroinflammation. EPO treatment of anemia improved growth and increased anti-inflammatory cytokine concentration. Activation of anti-inflammatory pathways may be one mechanism by which EPO is neuroprotective in the setting of neonatal anemia.

Disclosures: G. Singh: None. **M.K. Georgieff:** None. **T. Gisslen:** None.

Poster

675. Neuroinflammation: Neurophysiological Responses

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 675.11/O44

Topic: F.05. Neuroimmunology

Title: Effects of sensory denervation on the proliferation of testicular cells

Authors: *G. LEON[1], J. C. FLORES-ALONSO[2], U. QUIRÓZ-LÓPEZ[1], R. REYES-LUNA[1], J. R. LEON[1];
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Abstract: Uncontrolled cell proliferation can be generated in most organs of the body, causing the formation of tumors. The testicle can also present this type of anomalies among the cells that compose it, however it is not well understood what are the mechanisms that could be regulating this change in the cells. It has been reported that sensory innervation is involved in processes of metastasis and cell proliferation in some types of cancer, such as pancreatic ductal adenocarcinoma, basal cell cancer and breast cancer. However, it is unknown if this sensory innervation, also present in the testes, participates in cell proliferation and in the development of tumors of testicular origin. Therefore, the objective in this work was to evaluate the role of sensory innervation in the proliferation of testicular cells. Twenty-four mice of the CD1 strain of 35 days of age were used, which were divided into 4 groups; Two groups were induced to proliferate testicular cells by daily administration for 4 days of aqueous extract of *Echeveria gibbiflora* at a dose of 100mg / Kg of weight intraescrotally, later one of these groups (Ext +

Caps) was denervated with Capsaicin by the administration of 125mg / kg subcutaneously, while the other group induced only received Capsaicin vehicle (Ext + Vh); a third group only received vehicle extract (Vh); and finally the fourth group was not administered any substance and it was assigned as absolute control (TA). The animals were maintained for 35 days after the administration of Capsaicin and subsequently were sacrificed. The testicles and epididymis were dissected for further analysis. The weight of the testes, motility, vitality and sperm concentration, DNA fragmentation (comet test), cell proliferation by immunohistochemistry for Ki67 and immunoexpression of CGRP (sensory fiber neurotransmitter) were analyzed and compared. Our results showed that the weight of the testes did not change significantly in any of the experimental groups. The percentage of motility and vitality as well as the concentration of sperm decreased in the Ext + Vh group compared to the other experimental groups. The fragmentation of sperm DNA was not affected in any of the groups. In the Ext + Vh group, cellular conglomerates were observed in the testis with an intense Ki67 label, in the same way the Leydig cells were positive to the proliferation label with ki67. In addition, the expression of CGRP was found to be associated with cell conglomerates as well as with Leydig cells. We conclude that the sensory innervation inhibits sperm production and inhibits its motility, which could probably also inhibit the cellular proliferation mechanisms characteristic of testicular cancer.

Disclosures: G. Leon: None. **J.C. Flores-Alonso:** None. **U. Quiróz-López:** None. **R. Reyes-Luna:** None. **J.R. Leon:** None.

Poster

675. Neuroinflammation: Neurophysiological Responses

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 675.12/P1

Topic: F.05. Neuroimmunology

Title: New insight into the neuro-immune dialogue: A role for the α7 nicotinic acetylcholine receptor in mediating monocyte-derived macrophage migration

Authors: V. YAKUBENKO[1], K. CUI[1], M. M. ADDORISIO[2], D. L. WILLIAMS[1], ***V. A. PAVLOV**[2];
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Abstract: The α7 nicotinic acetylcholine receptor (α7nAChR) on macrophages has a key mediating role in the neuronal control of inflammation through the vagus nerve-based *cholinergic anti-inflammatory pathway*. Genetic α7nAChR deficiency has been associated with exacerbated pro-inflammatory responses in murine endotoxemia and other inflammatory

conditions. Activation of cholinergic signaling significantly decreases TNF and other pro-inflammatory cytokine production via α7nAChR-mediated mechanisms in endotoxin-stimulated macrophages. However, the role of α7nAChR in the regulation of other macrophage functions remains poorly understood. Here we tested the hypothesis that cholinergic signaling via α7nAChR alters macrophage migration and accumulation in organs during murine endotoxemia. We studied the migration of adoptively transferred α7nAChR knockout (KO) monocytes to the liver, lung and spleen of mice after LPS-administration. Briefly, monocyte progenitors were isolated from bone marrow of WT and α7nAChR-deficient (KO) mice using negative selection with antibodies conjugated to magnetic beads. Isolated monocytes were labeled with red PKH26 (WT) or green PKH67 (α7nAChR $^{-/-}$) fluorescent dyes, mixed in equal amounts and injected in tail vein of WT mice 20 min before the injection of LPS (12 μg/ml). The development of endotoxemia was manifested by the drop of body temperature (24-30 ^{0}C) in the experimental mice. After 48 hours, lungs, livers and spleens were isolated, digested and analyzed using multicolor flow cytometry (Fortessa-X20) and imaging flow cytometry (ImageStream X Mark II). Recruited fluorescently-labeled macrophages were detected as a red positive signal in Quadrant 4 (WT macrophages) and a green positive signal in Quadrant 1 (α7nAChR $^{-/-}$). α7nAChR deficiency resulted in significantly decreased accumulation of macrophages in liver (~10 folds), lung (~4 folds) and spleen (~3 folds) ($P<0.01$). The morphology of migrated macrophage was verified by imaging flow cytometry (ImageStream X Mark II). These results indicate a role for α7nAChR in the recruitment of monocytes to the site of acute inflammation that may be associated with α7nAChR regulation of adhesive receptors on macrophages. These findings present a new mechanism of cholinergic regulation during the neuro-immune dialogue in inflammation. Further studies are required to determine the adhesive receptors, which contribute to this process, and clarify the molecular mechanism of α7nAChR-dependent monocyte/macrophage migration.

Disclosures: V. Yakubenko: None. **K. Cui:** None. **M.M. Addorisio:** None. **D.L. Williams:** None. **V.A. Pavlov:** None.

Poster

675. Neuroinflammation: Neurophysiological Responses

Location: Hall A

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Program #/Poster #: 675.13/P2

Topic: F.05. Neuroimmunology

Support: NIH/NIGMS
NIH/NIAID

Title: Optogenetic stimulation of cholinergic neurons in the brainstem induces splenic nerve activity and attenuates systemic inflammation

Authors: A. M. KRESSEL, T. TSAAVA, E. H. CHANG, Q. CHANG, V. A. PAVLOV, K. J. TRACEY, ***S. S. CHAVAN**;
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Abstract: The inflammatory reflex is a well-defined neural circuit composed of afferent and efferent fibers that travel via the vagus nerve to regulate peripheral tumor necrosis factor (TNF) production. Electrical stimulation of the efferent fibers reduces splenic TNF output in an animal model of endotoxemia. However, the exact origin of these vagus nerve fibers in the brainstem and the means by which they innervate the spleen to modulate TNF levels is not yet understood. Using optogenetics, we selectively stimulated cholinergic neurons in the dorsal motor nucleus of the vagus nerve (DMN), the autonomic brainstem nucleus from which the efferent vagus nerve fibers originate. A fiber-optic cannula was inserted using stereotactic guidance into the DMN of transgenic mice expressing channelrhodopsin under the choline acetyltransferase promoter (ChAT-ChR2-EYFP mice). Mice were subjected to either optogenetic or sham stimulation (n=20 per group) for five minutes (473nm laser, 20Hz, 25% duty cycle). After 24 hours, animals were subjected to endotoxemia by intraperitoneal administration of lipopolysaccharide (0.25mg/kg), blood was collected after 90 minutes, and serum TNF were quantitated. Optogenetic stimulation of the cholinergic neurons in the DMN of ChAT-ChR2-EYFP mice significantly decreased endotoxin-induced serum TNF levels compared to sham controls (p=0.0004). Splenic nerve activity, recorded during DMN stimulation using a cuffed two-channel electrode, was significantly increased over baseline. Administration of bupivacaine in the cervical vagus nerve eliminated this effect, implicating a functional synapse between the vagus and splenic nerves. These studies provide the first direct evidence for the central origin of the efferent vagus nerve fibers regulating TNF production during endotoxemia, and suggest novel anti-inflammatory approaches based on targeting DMV cholinergic signaling. This study was funded by NIH/NIGMS/NIAID.

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Poster

675. Neuroinflammation: Neurophysiological Responses

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 675.14/P3

Topic: F.05. Neuroimmunology

Title: Trpv1 sensory nerves modulate antigen specific immune responses

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Abstract: We have previously demonstrated that local sensory neurons play a role in regulating antigen trafficking through the lymphatic system *in vivo*. However, the specific subsets of sensory neurons involved are unknown. To investigate this, we characterized antigen-specific immune responses in mice selectively lacking a specific neuronal population. Here we show that TRPV1 expressing neurons are required to develop an antigen specific immune response. To understand the role of TRPV1 expressing neurons, we generated TRPV1-Cre/Lox-diphtheria toxin A (DTA) mice to specifically ablate TRPV1 expressing neurons. Specific genetic ablation of TRPV1-lineage neurons results in a failure to generate a robust antigen-specific antibody response following immunization (Anti-KLH IgG levels Day 28, Wild type 8243.64 U/ml versus TRPV1 ablated 1068.60 U/ml). However, *in vitro* stimulated B-cells from TRPV1-ablated mice produce similar levels of IgG as wild type littermate controls suggesting that there is not a B-cell intrinsic defect in TRPV1-ablated mice. Co-culture of splenocytes with sensory neurons results in an increased level of antibody production. Direct activation of TRPV1+ signals by selective optogenetic stimulation (5 minutes, 473nm laser, 10Hz, 50% duty cycle) results in a significant decrease of antigen trafficking to the popliteal lymph node as compared to sham controls (sham 11012691 AFU versus photostimulated 5330646 AFU, $p<0.05$). These findings, together with our previous studies, reveal that TRPV1-expressing sensory neurons modulate antigen-specific immune responses. This implicates a neuro-immune crosstalk in both physiological and pathological conditions, and raises the exciting possibility that the nervous system collaborates with the immune system to regulate antigen-mediated responses.

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Poster

675. Neuroinflammation: Neurophysiological Responses

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Program #/Poster #: 675.15/P4

Topic: F.05. Neuroimmunology

Support: NIMH Grant F32MH115431
Stanford Innovator Grant

Title: Investigating subcortical regulation of systemic immunity with mass cytometry

Authors: *J. C. BORNIGER[1], E. GANIO[1], B. GAUDILLIERE[1], L. DE LECEA[2]; [1]Stanford Univ., Stanford, CA; [2]Psychiatry, Stanford Univ. Dept. of Psychiatry and Behavioral Sci., Stanford, CA

Abstract: How does the brain influence the immune system? Can we harness this connection to treat disease? A swath of studies have demonstrated that stress or fatigue can exacerbate sickness or promote disease development. Reciprocally, the placebo effect and the health benefits of meditation are real. These phenomena illustrate bi-directional control of the immune system by the brain. However, exactly how discrete parts of the brain modulate immunity remains largely unknown. Here, we use cell-type chemogenetics to activate (Gq) or inhibit (Gi) hypocretin neurons in the lateral hypothalamus and then collect blood for immunoprofiling using mass cytometry (CyTOF). Unlike flow cytometry, mass cytometry uses isotope-conjugated antibodies instead of fluorophores. This allows many more (>50) epitopes to be labeled with single cell resolution, and there is virtually no overlap between signals. We present an experimental protocol that can be used to test the role of discrete circuits in systemic immunity in an unbiased fashion. Using this protocol, we demonstrate dynamic changes in the immune system that occur in response to central neuromodulation. Future work will focus on additional subcortical circuits and investigate how deep brain stimulation in human subjects influences immune parameters.

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Poster

675. Neuroinflammation: Neurophysiological Responses

Location: Hall A

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Topic: F.05. Neuroimmunology

Support: KAKENHI 17H04766
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NIH 2R01MH090264-06
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Title: Individual differences in aggression mediated by temporal changes in cytokine signaling in the dorsal raphe nucleus

Authors: *A. TAKAHASHI[1], H. ALEYASIN[2], M. A. STAVARACHE[3], M. FLANIGAN[4], A. BRANCATO[4], C. MENARD[4], M. L. PFAU[4], V. KANA[4], J. WANG[4], G. E. HODES[4], S. OGAWA[1], B. S. MCEWEN[5], S. J. RUSSO[6];
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Abstract: Although several human studies have shown correlational relationships between peripheral cytokines and aggressive traits, causal links between cytokine action in the brain and aggressive behavior have not been established. Previously, we have shown that IL-1β in the dorsal raphe nucleus has suppressive effects on aggressive behavior. Male CD-1 mice with low levels of aggression (termed non-aggressors) showed higher level of IL-1β in the dorsal raphe nucleus compared to animals with higher aggressive behavior (termed aggressors). Also, both pharmacological antagonism and genetic deletion of IL-1 receptors in the dorsal raphe nucleus caused an increase of aggressive behavior in male mice. In this study, we aimed to understand temporal changes in the levels of IL-1β during aggressive behavior. We found that there was a phasic increase in IL-1β in the blood during aggressive encounter, but this change was observed similarly in both aggressors and non-aggressors. To examine temporal change of IL-1β level in the brain, we used in vivo microdialysis to collect dialysate from the dorsal raphe nucleus and then measured IL-1β via ELISA assay. We found a differential response pattern of IL-1β level during aggressive encounter in aggressors and non-aggressors. These data also supports an involvement of endogenous IL-1β in aggressive behaviors, however, the source of IL-1β in the dorsal raphe nucleus is still not clear and requires further investigation.

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Poster

675. Neuroinflammation: Neurophysiological Responses

Location: Hall A

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Topic: F.05. Neuroimmunology

Support: Office of Naval Research N00014-14-1-0787
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Title: The vagus nerve is critical for the rapid and widespread fos response in the brain following oral administration of a physiologically active bacteria

Authors: *A. BHARWANI[1], C. WEST[1], K. CHAMPAGNE-JORGENSEN[1], K.-A. MCVEY NEUFELD[1], J. RUBERTO[1], W. KUNZE[1], J. BIENENSTOCK[1], P. FORSYTHE[2];
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Abstract: While the literature is replete with evidence of gut-brain signalling, it is unknown which brain regions are recruited in response to bacterial signals, and how the neuronal response evolves following acute versus chronic exposure to such signals. Additionally, while several

pathways have been proposed to mediate such interactions, including neural, immune, and humoural signals, it is unclear whether bacteria recruit multiple pathways, and whether these transmit information to distinct regions of the brain.
Male Balb/c mice were orally administered a single dose of saline or a live or heat-killed preparation of a physiologically active bacterial strain, *Lactobacillus rhamnosus* (JB-1). 165 minutes later, depression-like behaviour was measured during the tail suspension test, mesenteric vagal afferent fibre firing was recorded, and c-Fos immunoreactivity in the brain was mapped. Mice also underwent sub-diaphragmatic vagotomy to investigate whether severing the vagus prevented JB-1-induced c-Fos expression. Finally, we examined the ΔFosB response and tail suspension test behaviour following acute versus chronic bacterial treatment.
Live, but not heat-killed bacteria significantly induced c-Fos expression in the basolateral and central amygdala, ventral hippocampus, periaqueductal grey, dorsal raphe nucleus, and locus coeruleus. Both live and heat-killed bacteria increased c-Fos expression in the paraventricular nucleus of the thalamus and facilitated firing of vagal fibres, absent behavioural changes. Severing the vagus prevented JB-1-induced c-Fos immunoreactivity in all regions except the ventral hippocampus and dorsal raphe nucleus. Only chronic, not acute treatment induced widespread ΔFosB in distributed brain regions, some of which previously exhibited no c-Fos response to a single dose.
These data identify regions that respond to bacteria-derived signals and highlight the differential response to acute versus chronic treatment. Moreover, the data suggest that the vagus nerve is critical for the widespread c-Fos response but also indicate the recruitment of additional signalling pathways. Future research will need to identify the gene targets of Fos proteins and their role in the observed behavioural changes.

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Poster

675. Neuroinflammation: Neurophysiological Responses

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Topic: F.05. Neuroimmunology

Support: MH048404
MH115027

Title: Sex differences in fibroblast growth factor 9 expression and function in dopamine neurons

Authors: *K. G. WALLIN-MILLER[1], M. L. KIELHOLD[1], D. R. KLIAMOVICH[2], B. MOGHADDAM[3];
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Abstract: Biological sex is a critical factor in the development and symptomology of most brain illnesses. Having a Y-chromosome is the single strongest risk factor for developing ADHD, autism, schizophrenia, Parkinson's disease, and substance use disorder. Notably, dopamine neurotransmission and function figure significantly in these disorders either as a primary measure of pathophysiology (e.g. Parkinson's disease) or target of effective treatments (e.g. ADHD). Recent studies have shown that organizational principals of dopamine neurons are not sexually dimorphic. The functional differences may, therefore, rely on secondary factors that are sex specific. Within the Y-chromosome, we hypothesized that a key culprit may be the SRY gene. SRY is expressed in dopamine (DA) cells and is involved in regulation of the DA system only in males. SRY is upstream of fibroblast growth factor 9 (FGF9), stimulating production of this protein, which has been implicated in male sex development. We find that FGF9 is expressed in dopamine neurons in the VTA and substantia nigra of both male and female adolescent and adults. The expression was significantly higher in males than females suggesting that this factor has important roles beyond sexual differentiation, influencing adolescent and adult brain function. Using a Cre-dependent viral knockdown of FGF9 in tyrosine hydroxylase-positive cells, we selectively inhibited expression of this protein in midbrain dopamine cells of both sexes. FGF9 infusion in adult VTA was not associated with measurable behavioral effects. FGF9 knockdown in dopamine cells of adolescents, however, causes behavioral changes in young adulthood that included increased anxiety-related behavior in both sexes and increased responsiveness to amphetamine selectively in females. FGF9 knockdown did not affect the size or number of dopamine cells present in the midbrain but led to activation of microglia supporting the notion that FGF9 has protective pro-inflammatory effects on dopamine neurons. We conclude that FGF9 contributes to dopamine-related sex differences and may be a critical factor for increased vulnerability to develop psychiatric disorders.

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Poster

675. Neuroinflammation: Neurophysiological Responses

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Topic: F.05. Neuroimmunology

Support: 1R01AA024798

Title: CCL2/CCR2 chemokine system in embryonic hypothalamus: Involvement in sexually dimorphic stimulatory effects of prenatal ethanol exposure on peptide-expressing neurons in embryo

Authors: G. Q. CHANG, O. KARATAYEV, D. S. S. K. BOORGU, ***S. F. LEIBOWITZ**; The Rockefeller Univ., New York, NY

Abstract: Maternal consumption of ethanol during pregnancy is known to increase the offspring's risk for developing alcohol use disorders and associated behavioral disturbances. Studies in adolescent and adult animals suggest the involvement of both neuroimmune and neurochemical systems in the brain that control these behaviors. To investigate how these systems interact to mediate these behavioral disturbances, we recently investigated in rats (Chang et al., 2015, 2018) a specific population of neurons in the lateral hypothalamus (LH), which express the inflammatory chemokine C-C motif ligand 2 (CCL2) and its main receptor CCR2 that are positively related to ethanol intake and also co-express the orexigenic neuropeptide, melanin-concentrating hormone (MCH), which similarly promotes ethanol drinking and related behaviors. In adolescent offspring, we demonstrated that maternal intraoral administration of ethanol at low-to-moderate doses (1-3 g/kg/day) from embryonic day 10 (E10) to E15 increases the expression and levels of CCL2 and CCR2 in the LH, their colocalization with MCH, and the consumption of ethanol. We also found that these neuronal and behavioral effects of ethanol are mimicked by maternal administration of CCL2 and blocked by a CCR2 antagonist administered during pregnancy, and that they are sexually dimorphic, consistently stronger in female adolescent offspring. To understand the developmental origin of these effects, we examined in this study the effects of maternal ethanol administration (2 g/kg/day, E10-E15) on the CCL2/CCR2 and MCH systems in the LH of the embryo. At E19, we obtained very similar results to those observed in adolescent rats, with prenatal ethanol exposure increasing the expression and density of CCL2 and CCR2 cells identified as neurons and also MCH neurons and their colocalization with CCL2. We also showed these effects in the embryo to be reversed by maternal administration of a CCL2 antibody (1 and 5 µg/day, i.p., E10-E15) that neutralizes endogenous CCL2 and the receptor antagonist INCB3344 (1 mg/day, i.p., E10-E15) that blocks CCR2. Notably, we discovered that these effects in the embryo are already sexually dimorphic, consistently stronger in female than male embryos, with endogenous CCL2 in males totally unresponsive to ethanol. These results, which link the CCL2/CCR2 system both anatomically and functionally to MCH neurons in the embryonic LH, suggest an important role for this neuroimmune system in mediating ethanol's sexually dimorphic, stimulatory effect on MCH neurons that may contribute to the higher levels of adolescent risk factors for alcohol use disorders described in females.

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Poster

675. Neuroinflammation: Neurophysiological Responses

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Topic: F.05. Neuroimmunology

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Title: Fractalkine signaling mediates postoperative neuroinflammation and cognitive dysfunction in tibial fracture-induced model

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Abstract: Post-operative pain is common complication after surgery and closely associated with development postoperative delirium (POD) and postoperative cognitive dysfunction (POCD). Orthopedic surgery can lead to persistent pain and remain a main cause of morbidity. The previous studies suggested regulation of neuro-immune interactions is important during neuropathic pain and fractalkine receptor, CX3C chemokine receptor 1 (CX3CR1) plays a key role in pain and inflammation. Therefore, we performed orthopedic surgery and confirmed CX3CR1 and inflammatory mediator levels in the spine and brain regions. In this study, we used a model of tibial fracture with intramedullary pinning in mice. After surgery, we assessed pain behavioral test, and cognitive/anxiety tests Also, we confirmed the levels of pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6 and Tumor necrosis factor alpha (TNF-α) in the lumbar spine, and brain regions. The level of CX3CR1 was also measured in same regions. Also, treatment of gabapentin and blocking fractalkine by neutralizing fractalkine after surgery, we evaluated cognitive ability and pain symptom**.** After tibial fracture surgery, mice showed mechanical allodynia. In addition, learning and memory impairment were induced after tibial fracture compared to the control. Also, the anxiety-related behavior was increased after tibial fracture in open field test and in elevated plus maze test. The level of inflammatory cytokines, such as IL-1β, IL-6 and TNF-α, were upregulated after tibial fracture and *Cx3cr1* transcrips were upregulated at 2 days after tibial fracture. Also, treatment of gabapentin and blocking fractalkine signaling after surgery, we observed that mice showed improved cognitive ability and pain symptom. Collectively, we proved that tibial fracture surgery triggered proinflammatory cytokines and CX3CR1expressoin in the lumbar spine and brain regions. Also, this surgery induced abnormal pain hypersensitivity and cognitive dysfunction. It is likely that inflammation and CX3CR1 is mainly involved in pathology of pain-mediated cognitive dysfunction after orthopedic surgery. Consolidating results, we suggest that blocking fractalkine signaling pathway may have potential as an effective therapeutic target or prevent the induction of POCD.

Disclosures: **B. Koo:** None. **I. Cho:** None. **E. Kam:** None.

Poster

675. Neuroinflammation: Neurophysiological Responses

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 675.21/P10

Topic: F.05. Neuroimmunology

Title: Regulation of plasma cell formation by splenic nerve-dependent neural activities

Authors: *X. ZHANG, B. LEI;
Tsinghua Univ., Beijing City, China

Abstract: It is increasingly clear that the immune system, traditionally thought as an autonomous system, is under regulation by the nervous system. However, it is not clear whether adaptive immune responses can be regulated by direct neural pathway instead of through the neuroendocrine route. We developed surgical splenic denervation for mouse and investigated its effect on B-cell immune responses. We verified the efficiency of our denervation by tyrosine hydroxylase staining on splenic tissue sections by immunohistochemistry. Following immunization with antigen, denervated mice produced fewer antibody-producing plasma cells than did sham-operated mice, whereas germinal center formation was not affected. These data suggest splenic nerve activities may regulate the developmental process of plasma cell formation. In probing the neurotransmitter involved, we found that acetylcholine could promote B cells to differentiate into plasma cells in vitro and in vivo, and that choline acetyltransferase-competent T cells may help relay sympathetic signals from the splenic nerve to acetylcholine-responsive B cells. We further found that expression of acetylcholine receptor, particularly the nicotinic subunit alpha9, is important for B cells to generate plasma cells of normal frequencies. Together, these results suggest neural activities propagated via the splenic nerve can regulate plasma cell formation during a T-dependent adaptive immune response. Work is ongoing to investigate brain regions that control this peripheral pathway and bodily behaviors that may invoke this neuro-immune connection to modulate immunity.

Disclosures: **X. Zhang:** None. **B. Lei:** None.

Poster

675. Neuroinflammation: Neurophysiological Responses

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 675.22/P11

Topic: F.05. Neuroimmunology

Support: NIH Grant MH105826

Title: Prenatal allergic inflammation affects striatal microglia, monoamine turnover, synaptic patterning, and behavioral inhibition

Authors: *K. M. LENZ, C. N. DYE, C. DODSON, R. GILFARB, A. JOSHI, A. I. SAULSBERY;
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Abstract: *In utero* exposure to maternal allergic or atopic conditions increase risk for neurodevelopmental disorders that are more common in males (e.g., autism, ADHD), yet little is known about how prenatal inflammation alters sex-specific brain development. We previously showed that prenatal allergen exposure programs hyperactivity and a loss of attentional flexibility in males and females, and decreased social behavior in males only. Here, we tested whether early life allergic inflammation impacts brain development via altering microglia function. Adult female rats were sensitized to ovalbumin (OVA), bred and challenged on gestational day (GD) 15. Fetal or neonatal brains were assessed for microglia number and phagocytic activity or cytokine and phagocytosis gene expression in developing medial prefrontal cortex (mPFC) or dorsal striatum. Other animals were grown to adulthood and dendritic spine density and gene expression for dopamine and histamine receptors were assessed. We found increased gene expression for interleukin 6 and the phagocytic marker CD68 in both males and females acutely post-OVA. OVA increased microglia number in the forebrain post-challenge. In the striatum, but not mPFC, on postnatal day (PD) 0, phagocytic microglia counts were increased in males, but not females. Adult striatum, but not mPFC, showed decreased dendritic spine density in both males and females after OVA exposure prenatally, but males only showed decreased striatal levels of histamine receptor 3 and dopamine receptor 2. These studies show that prenatal allergic inflammation alters microglia function and striatal development, particularly in males, and microglia may thus regulate sex-specific risk for neurodevelopmental disorders.

Disclosures: K.M. Lenz: None. **C.N. Dye:** None. **C. Dodson:** None. **R. Gilfarb:** None. **A. Joshi:** None. **A.I. Saulsbery:** None.

Poster

675. Neuroinflammation: Neurophysiological Responses

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 675.23/P12

Topic: F.05. Neuroimmunology

Support: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES/PROSUP) - Finance Code 001

Title: Stretching does not improve behavioral and immune responses during sickness behavior, after stress challenge, and in healthy rats

Authors: *M. C. GALVÃO, A. C. S. SAMPAIO, P. S. RODRIGUES, C. R. SALMON, N. MOREIRA, M. M. BERNARDI, T. B. KIRSTEN;
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Abstract: Yoga combines physical and respiratory techniques and meditation that stimulate well-being. It has been pointed out as a strategy against sedentarism because it not demands physical conditioning or complex infrastructure. Few studies correlate yoga practice in animal models. Stretching of the back of rats has revealed promising results after injury. However, there are no studies on behavior and well-being, which are the main focuses of yoga. The present study evaluated the use of stretching in different contexts, including in healthy rats, during sickness behavior, and after stress challenge. Adult male Wistar rats were submitted to stretching twice a day, for three consecutive days. Sickness behavior was induced by a single moderate dose of lipopolysaccharide (LPS). Psychological stress was induced by a single restraint session. Behavior of rats was evaluated in an open-field. Serum interleukin (IL-)1 beta (proinflammatory cytokine) was also evaluated. LPS decreased locomotion and rearing frequencies, increased immobility time, and increased IL-1 beta levels; i.e., LPS induced sickness behavior. Stress decreased rearing and immobility, and increased self-grooming, as well as decreased the time spent in central zone and increased the time spent in peripheral zone. LPS and stress factors presented interaction only by the decrease of the immobility of the rats. LPS and stretching factors presented interaction only by the increase of the self-grooming of the rats. There was no interaction between the other factors. In conclusion, LPS induced sickness behavior and stress induced stereotyped behavior and anxiety in rats. However, stretching seems not to have been able to ease the symptoms sickness behavior and of stress.

Disclosures: M.C. Galvão: None. **A.C.S. Sampaio:** None. **P.S. Rodrigues:** None. **C.R. Salmon:** None. **N. Moreira:** None. **M.M. Bernardi:** None. **T.B. Kirsten:** None.

Poster

675. Neuroinflammation: Neurophysiological Responses

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 675.24/P13

Topic: F.05. Neuroimmunology

Support: Grant-in-Aid of Research, University of Minnesota

Title: Sex differences in the association between temperament and immune response to antigen challenge in rats

Authors: *K. C. MICHAEL[1], K. KING[2];
[2]Psychology, Biol., [1]Univ. of Minnesota Morris, Morris, MN

Abstract: Animals differ in their exploratory behavior in novel environments; some set out immediately while others are slow to leave a familiar base and return frequently to it. Previous work has shown shorter lifespan in low-exploratory male rats, but also in high-locomotive female rats. These disparities in lifespan and behavior may be driven by immune function.
We conducted two experiments, one using lipopolysaccharide (LPS) to stimulate an innate response, and another using keyhole limpet hemocyanin (KLH) to stimulate antibody production. In both studies, we observed rat exploratory behavior in two open-field arenas: one with a novel social partner and one with novel objects. Both used a tube from the cage as a home base. Rats were thus classified as high- (HE) or low-exploratory (LE). LPS Study: 12 young adult Sprague-Dawley rats, 6 female and 6 male. Rats were administered 20ug/kg of LPS or saline IP. Blood was collected from tail vein at 0, 2, 4, 6, 10, and 24 hours post-injection. track blood levels of C-reactive protein (CRP), corticosterone (CORT), and TNF-α in order to analyze individual differences in dynamics of their immune responses.
LE rats had significantly higher CORT and TNF-α levels when compared to HE rats. (t_{Cort}= 2.997, $p<0.05$; t_{TNF}=3.559, $p<0.05$). TNF-α levels were higher for both LE and HE male rats compared to female rats. Within HE rats, however, males had significantly higher TNF-α levels than females (t_{TNF}=-3.055, $p<0.05$). Male rats had higher CORT, CRP, and TNF-α responses than female rats across exploratory groups and treatment groups (t_{Cort}= 3.866, $p<0.05$; t_{TNF}=5.454, $p<0.05$; t_{CRP}=4.493, $p<0.05$).
KLH Study: 12 young adult Sprague-Dawley rats, 8 female and 4 male. Rats were injected IP with KLH at age 4 months, then re-injected 30 days later. Blood was collected from tail vein at 0, 1, 2, 5, and 14 days post-second exposure to analyze IgM antibody production.
Dynamics varied greatly - males peaked at a moderate IgM level, while females had much greater variability in both peak IgM and decline over time. In males but not in females, IgM dynamics in response to KLH were predicted by exploratory behavior: LE males produced more total IgM over 14 days.

Rats in both studies are currently living out their natural lifespans. As of this writing, LE males are trending toward shorter lifespans than HE males. Within males, there was a correlation between total IgM production and lifespan. No relationships are yet apparent for females. While small, the results of these studies suggest a sex difference in the relationship between exploratory behavior, immune function, and lifespan. This could provide new angles from which to study individual differences in health outcomes.

Disclosures: K.C. Michael: None. **K. King:** None.

Poster

675. Neuroinflammation: Neurophysiological Responses

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 675.25/P14

Topic: F.05. Neuroimmunology

Support: The David Winston Turner Endowment
The Australian Govt Research Training Program Stipend
Victorian State Govt Operational Infrastructure Support
Australian Govt NHMRC IRIISS

Title: Pathogenic infection in male mice changes sperm small RNA profiles and transgenerationally alters offspring behaviour

Authors: *S. TYEBJI[1,2,4], A. J. HANNAN[4,3], C. J. TONKIN[1,2];
[1]The Walter and Eliza Hall Inst. of Med. Res., Melbourne, Australia; [2]Dept. of Med. Biol., [3]Dept. of Anat. and Neurosci., The Univ. of Melbourne, Melbourne, Australia; [4]Florey Inst. of Neurosci. and Mental Hlth., Melbourne, Australia

Abstract: Background: Perturbations in an animal's homeostasis can induce changes in the epigenetic blueprint that regulates normal neurodevelopment. Host organisms respond to pathogenic intrusions by initiating inflammatory and immune responses, while pathogens are known to actively manipulate the host in order to survive. Recent studies indicate that such host-pathogen interactions result in long-term changes in host epigenomes. When such epigenetic reprogramming occurs in the germline, its effects may become transgenerational. Here, we used mice infected with *Toxoplasma gondii* (*T. gondii*) parasites as a model to elucidate, for the first time, whether paternal infections can induce heritable behavioural changes and impairments in offspring learning and memory. Results: *T. gondii* cysts were detectable in infected mouse testis as early as 4 weeks post-infection (wpi), along with significantly reduced sperm count and altered sperm morphology. Offspring (F1) born to infected sires showed a pronounced anxiety and depression-like phenotype, along with impaired cognition in the male offspring, while the female offspring only displayed working memory impairments, when compared to littermates

conceived from an uninfected sire. Remarkably, the anxiety phenotype persisted in the male grand-offspring (F2, via the paternal line) of infected sires. In addition, both the male and female grand-offspring displayed changes in spatial and social recognition memory. To identify the biological mechanism of these transgenerational changes, we sequenced the small RNA obtained from the sperm of infected and uninfected mice. 26% of total small RNAs observed were dysregulated in sperm from infected mice compared to that from uninfected mice. In addition, we identified significant fold changes in a large proportion (23.7%) of detected microRNAs. Pathway analysis revealed that the validated targets of the differentially expressed genes were significantly enriched in several biochemical and cellular pathways, indicating an altered developmental trajectory of embryos conceived from infected fathers. Conclusions: Our results demonstrate for the first time a transgenerationally inherited link between paternal pathogenic infections and changes in offspring behaviour. One potential epigenetic mechanism may involve modification of sperm small RNA load in response to infection.

Disclosures: S. Tyebji: None. **A.J. Hannan:** None. **C.J. Tonkin:** None.

Poster

675. Neuroinflammation: Neurophysiological Responses

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 675.26/P15

Topic: F.05. Neuroimmunology

Support: NIMH ZIA MH001090

Title: Revealing repair roles for inflammatory leukocytes in neurovascular dysfunction caused by chronic social defeat

Authors: *M. L. LEHMANN, C. POFFENBERGER, S. KIGAR, M. HERKENHAM;
NIH, Bethesda, MD

Abstract: Psychosocial stressors, which contribute to the development of affective disorders in humans, induce central and peripheral immune pathway signaling that is increasingly thought to be relevant to the pathophysiology of depression. Previously, we showed that 14 days of chronic social defeat (CSD), a model of psychosocial stress, triggered a change in blood-brain barrier (BBB) permeability coupled with the leakage of intravascular substances into brain parenchyma, i.e., microhemorrhages. Peripheral monocyte subtypes that express chemokine receptor CCR2 have been implicated in the pathogenesis of several different disease processes. This pathology includes vascular permeability associated with inflammation and microhemorrhage. We wanted to understand how $CCR2^{+}$ cells contribute to the BBB pathologies that occur in response to CSD. We found that CSD induced significant declines in behavioral tests of sociability paired with scattered microhemorrhages in brain, but it had no effect on either the anatomical distribution or

density of $CCR2^+$ cells adhered to vasculature. However, a substantial elevation in numbers of adhered $CCR2^+$ cells was detected if mice were given seven days to recover from CSD stress in a homecage environment. We hypothesized that $CCR2^+$ cells have restorative functions and are involved with mediating vascular repair in previously stressed mice. We show that $CCR2^+$ cell trafficking to the BBB is dependent on the cessation of stress but not the duration of stress. We further determined that Corticosterone (CORT) secreted during stress inhibits cell trafficking to the BBB and found that chemical adrenalectomy increased the number of $CCR2^+$ cells adhered to the BBB after CSD. The effects were further interrogated using combinations of CCR2 functional knockouts and CORT administration to determine a causal role for $CCR2^+$ cells in the repair of vascular dysfunction after CSD stress.

Disclosures: M.L. Lehmann: None. **C. Poffenberger:** None. **S. Kigar:** None. **M. Herkenham:** None.

Poster

675. Neuroinflammation: Neurophysiological Responses

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 675.27/P16

Topic: F.05. Neuroimmunology

Title: Effects of estrogen on host gut microbial population and their metabolites in rats with chronic restraint stress

Authors: *M. XU[1], K. KROLICK[2], J. ZHU[4], H. SHI[3];
[1]Dept. of Biol., [2]Biol., [3]Miami Univ., Oxford, OH; [4]Dept. of Human Sci., Ohio State Univ., Columbus, OH

Abstract: The brain-gut axis bidirectionally communicates between the brain and the gut with diverse population of microorganisms, whose metabolites change constantly and feedback to the brain. Stress affects brain function and gut microbiome. Both female rodents and women display sex-specific stress responses dependent on estrogen status. It is unclear how the sex hormone estrogen affects gut microbial population and their metabolites when undergoing chronic stress. In this study, gut microbiota-metabolite relationship was characterized using integrated genomic analysis and MS-based metabolic profiling in rats with and without stress and estrogen. Female Sprague Dawley rats received either sham operation thus having intact ovaries and normal estrogen levels (Sham), or were ovariectomized (OVX) and received either oil (OVX+Oil) or estradiol (OVX+E2) replacement. Rats underwent either daily one-hour restraint stress or no-stress for 13 days. Gut and trunk blood were collected on the last day. Plasma corticosterone (CORT) levels from tail-bleed blood during stress were measured using ELISA. Cecum DNA was extracted for Illumina-based 16S rRNA gene sequencing to determine microbial population and LC-MS/MS-based metabolic profiling to determine microbial metabolites. Metabolic profile

was plotted using PLS-DA to show separation by using MetaboAnalyst 4.0. Stress significantly increased CORT levels of OVX+Oil rats during the entire stress period. In contrast, stress increased CORT levels of Sham and OVX+E2 rats at the beginning of the stress period comparing to their respective no-stress groups, but such increase disappeared at the end of the stress period. Microbial metabolic analysis indicated separation in major metabolic pathways between stress and no-stress rats of Sham group. Interestingly, some pathways were also separated between stress and no-stress OVX+E2 rats, but not OVX+Oil rats. Therefore, when estrogen level was reduced as seen in OVX-Oil rats, the hypothalamus-pituitary-adrenal (HPA) axis stress response persisted, as indicated by increased CORT levels throughout the stress period. However, a diminished stress response involving gut microbiota was observed, as indicated by overlapping patterns of microbial metabolites between no-stress and stress OVX-Oil rats. Normal levels of estrogen seen in Sham and OVX+E2 groups; however, relieved stress response involving the HPA axis but persisted the response involving gut microbiota. We conclude that estrogen may benefit brain-gut homeostasis, at least partially, via relieving prolonged stimulation of the HPA axis but maintaining microbial sensitivity to stress.

Disclosures: **M. Xu:** None. **K. Krolick:** None. **J. Zhu:** None. **H. Shi:** None.

Poster

675. Neuroinflammation: Neurophysiological Responses

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 675.28/P17

Topic: F.05. Neuroimmunology

Support: CONACYT Grant CB-2015-255317
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Title: Maternal overfeeding primes ghrelin sensitivity in the hypothalamus leading to hyperphagia in the offspring

Authors: *R. MALDONADO-RUIZ[1,3], M. CÁRDENAS-TUEME[2], L. MONTALVO-MARTÍNEZ[1,3], D. RESÉNDEZ-PEREZ[2], R. VIDAL-TAMAYO[4], L. GARZA-OCAÑAS[1], A. CAMACHO[1,3];
[1]Col. of Med., Univ. Autonoma De Nuevo Leon, Monterrey, Mexico; [2]Col. of Biol. Sci., Univ. Autonoma De Nuevo Leon, San Nicolas de los Garza, Mexico; [3]Ctr. for Res. and Develop. in Hlth. Sci., Univ. Autonoma de Nuevo Leon, Monterrey, Mexico; [4]Sch. of Hlth. Sci., Univ. de Monterrey, San Pedro Garza, Mexico

Abstract: Maternal overnutrition during pregnancy leads to metabolic disturbance including obesity, hyperphagia and inflammation in the offspring. It is still unknown the molecular effects of nutritional programing over inflammation and ghrelin sensitivity in the offspring. Here we aim to elucidate the role of hypercaloric diet-induced maternal programming on hypothalamic microglia activation and ghrelin-sensitive hyperphagia in the offspring. We used a nutritional programing model exposing female Wistar rats to Chow or Cafeteria diet from pre-pregnancy to weaning. We quantified daily basal and fasting-refeeding food intake, and food intake after central or subcutaneous ghrelin administration. Hypothalamic ghrelin sensitivity and microglia activation were evaluated by immunofluorescence against Iba-1 and c-Fos markers, and TBK1 pathway by western blot. Also, proinflammatory effects of palmitic acid (PAL), palmitoleic acid, stearic acid, linoleic acid or C6 ceramide incubation in microglia primary cell culture were determined by TNF-α, IL-6 and IL-1β production using ELISA assays. Finally, plasma glucose homeostasis and food intake sensitive to intracerebroventricular (i.c.v.) ghrelin (1μg/μl) administration were analyzed following PAL (40μg/μl), lipopolysaccharide (2μg/μl) or artificial cerebrospinal fluid (control) administration for 5 days. Here, we demonstrated that maternal nutritional programing by cafeteria diet exposure promotes hyperphagia in the offspring following 14h fasting and subcutaneous ghrelin injection, compared with matched controls. These effects corelate with an increased expression of microglia marker Iba-1 and neuronal activation marker c-Fos in the hypothalamus. Furthermore, we identified that 24h PAL stimulation promotes TNF-α, IL-6 and IL-1β secretion, and TBK1 activation in microglia primary cell culture. Of note, LPS and PAL i.c.v. injection for 5 days reproduces the hyperphagic effects of maternal cafeteria exposure following central ghrelin administration, which also correlates with microglia activation and neural c-Fos expression. Together, maternal nutritional programing primes hypothalamic ghrelin-sensitive hyperphagia and microglia activation in the offspring, which is replicated by palmitic central administration.

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Poster

676. Neuroinflammation: Cognition and Behavioral Responses

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 676.01/P18

Topic: F.05. Neuroimmunology

Support: SFI/15/JP-HDHL/3270
SFI/12/RC/2273

Title: Is the fountain of (brain) youth in the gut microbiome? Impact of fecal microbiota transplantation from young to aged mice on brain, behavior and immunity

Authors: *M. BOEHME[1], K. E. GUZZETTA[1], A. GUAL-GRAU[1], T. F. S. BASTIAANSSEN[1], M. VAN DE WOUW[1], L. OLAVARRÍA-RAMÍREZ[1], G. M. MOLONEY[2], E. MORILLAS[1], C. S. COWAN[1], N. RITZ[1], S. SPICHAK[1], O. O'LEARY[2], H. SCHELLEKENS[1], T. G. DINAN[1], J. F. CRYAN[1];
[1]APC Microbiome Ireland, [2]Dept. of Anat. and Neurosci., Univ. Col. Cork, Cork, Ireland

Abstract: Aging is defined as a slow deterioration process of various homeostatic functions throughout the lifespan. With the advance of aging, a low-grade inflammation commonly known as "inflamm-aging" occurs. This can impair various mechanisms crucial for maintaining homeostasis, particularly in the brain. A growing body of literature suggests an involvement of the gut microbiota in mediating inflamm-aging, but the effect on the aging brain remains understudied. Thus we sought to investigate the relationship between the aging brain and the microbiome. We hypothesized that transferring the microbiome of young (by fecal microbiota transplantation (FMT)) to aged mice may have a beneficial impact on inflamm-aging, and age-associated neuroimmune, neurobiological and behavioral changes. Male adult (3 months) and aged (22-23 months) C57BL/6 mice received bi-weekly FMT (young to aged, aged to aged, young to young) for 3 weeks (100 ul via oral gavage, 100 mg/ml) followed by behavioral investigations focusing on cognitive (novel object recognition, spontaneous alternation behavior, social recognition and memory, Morris Water Maze) and anxiety-like behaviour (open field and elevated-plus maze) while continuing bi-weekly FMT for additional 5 weeks. Systemic and gut-associated immunity was analyzed by flow cytometry. Neuroimmunity by immunohistochemistry to specifically investigate brain-region specific responses revealed by behavioral changes. Our data confirmed increased inflammation in aged mice in gut-associated immunity (mesenteric lymph nodes (mLNs)), the blood and the brain (hippocampus). This was distinctly alleviated by FMT from young to aged mice in mLNs targeting CD103+ dendritic cells and CD69+ T-killer cells. Ongoing analysis will investigate if FMT from young mice has also a beneficial impact on systemic and neuroimmunity in aged mice. Aged mice exhibited behavioral impairments that were ameliorated when aged mice received FMT from young mice. Further analysis will reveal if microbiota transplantation from young to aged mice is capable of modifying brain chemistry that will have implications for therapeutic interventions ameliorating age-associated functional decline. Collectively, our data contributes to a better understanding of the microbiota-gut-immune-brain axis in aging and the influence of specific microbiome manipulations in this interplay.

Disclosures: **M. Boehme:** None. **K.E. Guzzetta:** None. **A. Gual-Grau:** None. **T.F.S. Bastiaanssen:** None. **M. van de Wouw:** None. **L. Olavarría-Ramírez:** None. **G.M. Moloney:** None. **E. Morillas:** None. **C.S. Cowan:** None. **N. Ritz:** None. **S. Spichak:** None. **O. O'Leary:** None. **H. Schellekens:** None. **T.G. Dinan:** None. **J.F. Cryan:** None.

Poster

676. Neuroinflammation: Cognition and Behavioral Responses

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 676.02/P19

Topic: F.05. Neuroimmunology

Support: Enterprise Ireland Grant Number CC2008-001 and TC2013-0001
SFI (Grant Nos. SFI/12/RC/2273)

Title: The impact of the microbiota on acute stress induced monocyte trafficking

Authors: *G. M. MOLONEY[1], M. VAN DE WOUW[2], J. M. LYTE[3], M. BOEHME[4], T. DINAN[5], J. CRYAN[3], G. CLARKE[3];
[1]Anat. and Neurosci., [2]APC Microbiome Ireland, [4]APC Microbiome Institute, Lab. of Neurogastroenterology, [5]Dept. of Psychiatry and Neurobehavioural Sci., [3]Univ. Col. Cork, Cork, Ireland

Abstract: It is well-known that acute stress induces activation of the immune system, resulting in a mobilization of immune cells. These changes are largely due to stress-induced increases in glucocorticoids. In particular, monocytes are affected as their prevalence decreases in the peripheral circulation, indicating stress-induced trafficking into other tissues. This is important as repeated acute stressors result in an enhanced monocyte trafficking into the brain, which is often associated with neuroinflammation. As such, understanding how we can modulate stress-induced monocyte trafficking might provide novel insights into how we can attenuate chronic stress-associated neuroinflammation. The microbiota has been implicated as a promising therapeutic target for modulating immune responses, and even brain physiology and behaviour. As such, we wondered whether the microbiota could play a role in modulating acute stress-induced monocyte trafficking.Here we investigated stress-responses of male mice devoid of any bacteria (i.e., germ-free, GF), as well as GF mice colonized with a conventional microbiota (i.e., germ-free colonized, GFC). Mice were either sacrificed at baseline or underwent 15 minutes of restraint stress, after which they were sacrificed after 0, 45 or 240 minutes. Plasma corticosterone, adrenaline and noradrenaline was quantified using ELISAs. Blood and splenic monocyte subpopulations were quantified using flow cytometry. At baseline, GF mice showed elevated adrenaline, noradrenaline, and corticosterone levels, as well as decreased LY6Chigh and LY6Cmid monocytes, but not LY6Clow monocytes. Interestingly, all these changes were attenuated in GFC mice. Acute stress induced an increase in conventional, GF, as well as GFC mice. In response to acute stress, conventional mice showed an increase in circulating noradrenaline levels, which were absent in GF mice. Furthermore, stress-induced a decrease in circulating LY6Chigh and LY6Cmid monocytes, but not LY6Clow monocytes, which returned to baseline after 240 minutes in normal mice, but not GF and GFR mice. The same was observed

for splenic LY6Chigh monocytes, which are known to be continuously stored and subsequently utilized in response to an immune stimulation. These results reveal novel kinetics of monocyte subtype-specific trafficking induced by acute stress, which shows a decreased recovery when the microbiota is absent and even after subsequent recolonization. Overall, these data show a promising role for the microbiota in modulating acute stress-induced monocyte trafficking, which could have important implications in chronic stress-associated neuroinflammation.

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Poster

676. Neuroinflammation: Cognition and Behavioral Responses

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 676.03/P20

Topic: F.05. Neuroimmunology

Support: Ontario Brain Institute
Canadian Foundation for Innovation

Title: The impact of strain, sex, and early life stress on microbiota diversity, composition, and behaviour

Authors: C. FRANCELLA, J. LAI, K. RILETT, ***J. A. FOSTER**;
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Abstract: Microbiota-brain communication influences behaviour and brain function. Studies have shown that microbiota composition and diversity are influenced by host genetics, diet, and other environmental factors. Inbred (C57BL/6, Balb/C, FVB) and outbred (CD1) mice were bred in house or pregnant dams were ordered from outside supplier. Mice were exposed to immune challenge with lipopolysaccharide (LPS) at postnatal day (P) 3 and maternal separation at P9 (16 h overnight). Behavioural assessment of growth and development as well as behaviour (righting reflex, ultrasonic vocalizations in response to brief maternal separation, open field, sociability and grooming) was conducted. At P24, fecal samples were collected. Microbiota composition was determined by amplifying the 16S rRNA gene variable 3 (v3) region and then sequenced using the Illumina MiSeq platform data analyzed using DADA2, a Bioconductor pipeline. Alpha and Beta diversity analyses were conducted using the phyloseq package in the R software. Strain-, sex-, and early life stress-related differences in behaviour were observed. Strain was found to be significantly associated with microbial alpha diversity among the samples (PERMANOVA $p<0.001$ for all metrics). For beta diversity, strain, sex and treatment were significant with strain contributing the greatest amount of variation ($R^2=0.19$), followed by treatment ($R^2=0.004$) and sex ($R^2=0.003$). Alpha diversity was significantly associated with

ultrasonic vocalization, sociability, and self-grooming behaviour. Additional analysis of microbiota-behaviour associations related to strain, sex, and stress are ongoing. In parallel, the role of source (in house vs supplier), operator, and co-caging/litter effects will be presented. These findings are important to determining the influence of genetic and environmental factors on gut microbiota and will advance our understanding microbiome-brain signaling pathways on neurodevelopment and behaviour.

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Poster

676. Neuroinflammation: Cognition and Behavioral Responses

Location: Hall A

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Topic: F.05. Neuroimmunology

Support: SFI grant 15/JP-HDHL/3270
SFI grant SFI/12/RC/2273

Title: The impact of age-associated microbiota on neuroimmunity, physiology, and behavior in germ-free mice

Authors: *K. E. GUZZETTA[1], M. BOEHME[1], A. GUAL-GRAU[1], T. F. S. BASTIAANSSEN[1], E. MORILLAS[1], M. JAGGAR[1], J. PEREIRA[1], M. VAN DE WOUW[1], G. M. MOLONEY[2], N. RITZ[1], T. G. DINAN[3], O. O'LEARY[2], J. F. CRYAN[1];
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Abstract: There is increasing evidence for a role for the gut microbiota in regulating brain, behavior and immunity across the lifespan. Aging is associated with distinct deteriorations in cognition and increases in central and peripheral inflammation. Moreover, altered microbiota diversity and composition is also a hallmark of the ageing processes. Previous studies have shown that by targeting the microbiome it is possible to affect neuroimmune signaling in midlife and in ageing. However it is unclear if the age associated changes in microbiota composition is sufficient to alter neuroimmunity.
Thus, in this study we used microbiota deficient germ-free mice as a background to assess whether age-associated microbiota can differentially impact host neuroimmunity, physiology, and behavior by transferring microbiota from aged or young mice into young germ-free mice. After four weeks of bi-weekly fecal microbiota transplant mice underwent a cognition-related behavioral test (novel object recognition), then were immediately culled. RNA from the hippocampus was isolated, purified, and sequenced to determine how an aged vs. young

microbiota alters hippocampal gene expression. Flow cytometry was performed on blood and mesenteric lymph nodes to quantify differences in systemic and gut-associated immunity which may contribute to the inflammatory phenotype commonly observed in aging.
Germ-free mice who received microbiota from an aged donor displayed an increase in trafficking receptor expression on inflammatory monocytes accompanied with a trend towards elevated systemic proinflammatory markers suggesting that the microbiota of an aged individual may mimic some of the signs of systemic inflamm-aging. Our ongoing analysis will reveal whether the transplant of microbiota from aged donor mice to young germ-free recipient mice also alters brain chemistry and other aspects of neuroimmunity differently than microbiota transplanted from young donor mice. Interestingly no change in cognitive behavior between groups was identified using the novel object recognition behavioral test.
Taken together this research will illuminate the causal significance of changes in microbiota composition in exacerbating specific aspects of aging. Moreover, it opens up the opportunity of further targeting the microbiome for generating health brain ageing strategies.

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Poster

676. Neuroinflammation: Cognition and Behavioral Responses

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Topic: F.05. Neuroimmunology

Support: Science Foundation Ireland (SFI), grant (12/RC/2273)

Title: The influence of the gut microbiome on fundamental synaptic neurophysiology

Authors: *K. J. O'RIORDAN, H. DARCH, B. BUTLER, R. O'CONNOR, T. G. DINAN, J. CRYAN;
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Abstract: The microbiota (the trillions of microorganisms within and on our bodies) are key regulators of communication and function along the bidirectional gut-brain axis. This communication is facilitated via various routes including the immune system, the vagus nerve, and the enteric nervous system and involves direct or indirect effects of microbial metabolites such as short-chain fatty acids (SCFAs), branched chain amino acids and peptidoglycans. It is becoming increasingly evident that the microbiota are crucial in maintaining homeostasis, and that through targeting, novel therapeutic strategies could emerge.

The extent to which the microbiome can exact long-lasting neuroplastic changes in the host's brain is understudied, and currently unresolved. As a result, we examined the involvement of the microbiome in neuroplasticity from two different approaches. To start, we modelled the situation of microbial dysbiosis with altered brain concentrations of microbial metabolites. We focused on area CA1 of the murine dorsal hippocampus in a multichannel *ex-vivo* recording paradigm. Our initial findings suggest that a physiologically relevant, but high concentration of sodium acetate applied directly to slices, acutely affected LTP induction when present during the induction stimulation. Results from other microbially derived SCFAs are pending.
A powerful way to study the impact of microbiota on brain function has been via analyising the extreme situation of growing up germ-free (GF). Previous studies have shown that GF mice have alterations in arborisation, neurogenesis as well as changes in plasticity-related proteins such as brain derived neurotrophic factor in the hippocampus. In tandem with testing GF mice, GF littermates were transferred to conventional housing to re-introduce a microbiome during adulthood. Comparisons of hippocampal neuroplasticity between these groups and conventional internally-bred C57BL/6 mice highlight the impact of gross microbiome alterations during, and outside of, critical neurodevelopmental windows. Initial results indicate altered synaptic efficacy as measured by an input-output protocol, altered short-term plasticity as tested using a paired-pulse protocol, and impaired long-term potentiation (LTP) at 1 hour post theta-burst tetanus. We conclude that alterations seen in hippocampal neurophysiology must be as a result of the lack of a microbiome during critical neurodevelopmental periods, perhaps through altered synaptogenesis or axonal myelination.

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Poster

676. Neuroinflammation: Cognition and Behavioral Responses

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Support: MSCA EU Grant GutMIND
SFI Grant 12/RC/2273

Title: Sex- and timing-specific effects of antibiotic-induced microbiota depletion during murine early life: Are there critical windows in microbiota-gut-brain axis development?

Authors: *C. S. COWAN, A. VENTURA-SILVA, M. VAN DE WOUW, M. SCHVERER, E. TEICHMAN, M. G. CODAGNONE, T. DINAN, J. CRYAN;
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Abstract: Childhood psychiatric and neurodevelopmental disorders are alarmingly common, yet current gold-standard treatments fall short in creating lasting, meaningful improvements for many individuals. To improve outcomes, it is imperative to enhance our understanding of pathways to disordered neurodevelopment. The current study is based on two hypotheses regarding possible pathways. The first is that problems arise due to disruption of sensitive periods of neuroplasticity. The second is that psychiatric health is closely intertwined with gastrointestinal health and immunity, and more specifically, that the microorganisms resident in the gastrointestinal tract (the gut microbiota) can influence neural, immune and behavioral outcomes.
To identify critical windows of microbial influence on neurodevelopmental outcomes, an antibiotic cocktail (ABX) was administered during one of three developmental time windows (postnatal: postnatal days [P]2-9; pre-weaning: P12-18; post-weaning: P21-27). The ABX consisted of ampicillin, gentamicin, vancomycin and imipenem to provide broad-spectrum depletion of the microbiota. Following treatment in early life, behavioral outcomes were assessed in adulthood. In terms of learning and memory, the novel object recognition test showed that pre- or post-weaning ABX, but not postnatal ABX, enhanced recognition memory in males only. In the 3 chamber social interaction test, preference for a novel social partner was decreased by postnatal ABX only in males, but by pre- or post-weaning ABX in females.
Overall, these results provide evidence that disturbance of the microbiota during specific early-life windows has long-lasting effects on behavioral outcomes, in a sex-dependent manner. Ongoing research is focusing on the neurobiological and neuroimmune basis of such effects. This supports the hypothesis that there are sensitive periods in the microbiota-gut-brain axis and sets the stage for further research to explore the neural and psychological implications of these effects.

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Poster

676. Neuroinflammation: Cognition and Behavioral Responses

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Topic: F.05. Neuroimmunology

Support: Science Foundation Ireland (SFI), Ireland grant (12/RC/2273)

Title: Polyphenols reverse anxious and depressive-like behaviours in the maternal separation model: A role for the gut microbiome?

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Abstract: Stress related mental disorders, including depression and anxiety, are currently a major public health concern. In addition, accumulated evidence suggests that early life stress can exert long-lasting changes on the brain, and this early adversity is associated with increased risk for developing depression in adulthood. The maternal separation model in rats is a robust paradigm to study the effects of early life stress, which presents a consistent depressive and anxious phenotype in adult animals including microbiota imbalance. On the other hand, natural phytochemicals known as polyphenols have demonstrated therapeutic potential in treating stress related disorders and affecting microbiome composition. However, the underlying mechanisms are unclear. Therefore, we decided to investigate the potential antidepressant and anxiolytic effects of polyphenols in maternally separated male rats. Sprague Dawley rats were separated from their mothers (MS) 3 hours per day during postnatal day 2 through 12, and compared to a group of pups that were not separated (NS). At 8 weeks of age, MS and NS male rats underwent a dietary intervention with the naturally-derived polyphenols xanthohumol and quercetin, as well as with a phlorotannin extract (polyphenol-enriched fraction) and fluoxetine, for 8 weeks (n = 10 per group). MS rats showed increased immobility time and reduced swimming time in the forced swim test compared to NS rats, which is associated with depressive-like behaviour. In addition, MS rats showed increased anxiety in the open field test by spending less time in the centre of the arena compared to NS rats. Intriguingly, treatment with quercetin, xanthohumol and the phlorotannin extract prevented these MS-induced depressive and anxious-like behaviours. Maternal separation is also associated with alterations in the hypothalamic-pituitary-adrenal (HPA) axis and elevated concentrations of glucocorticoids. Therefore, we examined the effects of polyphenols on HPA axis regulation. As expected, MS rats showed increased release of corticosterone in plasma compared to NS following acute stress, which was inhibited with xanthohumol treatment. Thus, these results suggest that polyphenols have potential

antidepressant and anxiolytic effects in MS rats that could be partially mediated by modulation of the HPA axis. Current studies are investigating the effects of polyphenols in modulating neuroimmune pathways, the neurochemical balance of monoamines, and the potential implication of the gut-microbiota-brain axis in polyphenol mediated improvements in depressive and anxious behaviours in MS rats.

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Poster

676. Neuroinflammation: Cognition and Behavioral Responses

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Topic: F.05. Neuroimmunology

Support: NIH grant NS065926

Title: Inducible co-stimulatory molecule (ICOS) alleviates astrogliosis and attenuates chemotherapy induced-peripheral neuropathy in mice

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Abstract: Paclitaxel is a chemotherapy drug used to treat breast and ovarian cancer. The primary dose-limiting side effect of paclitaxel is a peripheral neuropathy that is caused by damage to peripheral nerves and the dorsal root ganglia (DRG). This neuropathy often results in neuropathic pain for which there are no effective treatments. Neuronal-immune interactions occur in chemotherapy-induced peripheral neuropathy (CIPN) and have been implicated both in the development and progression of disease as well as in disease resolution. Based on previous studies suggesting that T cells play an active role in CIPN resolution, we investigated the potential role of ICOS (Inducible co-stimulatory molecule), an immune checkpoint molecule that is expressed on the surface of activated T cells, as a costimulatory mechanism for the resolution of CIPN. First, we observed an increase in the number of T cells in paclitaxel treated mice in lumbar DRG when compared to control animals. We found that intrathecal administration of ICOS agonist antibody alleviates mechanical hypersensitivity caused by paclitaxel and advances the resolution of pain in female mice. Paclitaxel treatment caused a robust astrocytes gliosis in the spinal dorsal horn and a satellite glial cell gliosis in lumbar DRG. We did not observe signs of microgliosis in the spinal cord with paclitaxel treatment. Administration of ICOS agonist

antibody reduced astrocyte and satellite cell gliosis in mice that were treated with paclitaxel. Our findings support a model wherein ICOS agonist antibody, upon engagement with T cells, induces an expansion of anti-inflammatory cytokines such as IL10, IL4 that facilitate the resolution of paclitaxel-induced peripheral neuropathy.

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Poster

676. Neuroinflammation: Cognition and Behavioral Responses

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Topic: F.05. Neuroimmunology

Support: Capes
Cnpq
Fapergs

Title: Impact of zinc supplementation associated with cafeteria diet on recognition memory in rats

Authors: *S. D. OLIVEIRA[1], J. P. NETO[1], G. S. FEIJÓ[1], J. JANTSCH[1], R. M. ARENA[1], B. F. DENIZ[1], M. GIOVENARDI[1], M. PORAWSKI[2], R. P. GUEDES[2];
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Abstract: Introduction: Obesity triggers a systemic pro-inflammatory profile, which affects the central nervous system, predisposing the development of neurological diseases. Zinc is a mineral with potential anti-inflammatory action, thus it may play a role as a neuroprotective agent in obesity.
Objective: To evaluate the effects of zinc supplementation on metabolic parameters and memory of Wistar rats that received cafeteria diet.
Materials and Methods: This study was approved by the IACUC 570/18. Twenty-eight Wistar rats were divided into 4 groups: standard diet (SD); SD+ zinc; cafeteria diet (CAF); CAF+zinc; The diet was administered for 20 weeks and zinc treatment started from the 16th week until the end of the diet protocol. The memory was evaluated by the novel object recognition test and the recognition index was calculated. Weight gain and visceral fat were quantified. Insulin, glucose and triglycerides levels were evaluated in the plasma, as well as TNF-alpha levels in plasma and liver. Data were evaluated by two-way ANOVA followed by Bonferroni test considering $p<0.05$ as significant.
Results and Conclusion: Animals that received CAF showed higher weight gain and visceral fat than SD. CAF also caused an increase in insulin, glucose and triglycerides in the plasma. TNF-

alpha was also increased in the plasma and in the liver of obese rats. Zinc supplementation did not provide any beneficial effect on these parameters. However, in the object recognition test, obese animals presented a worse performance, and zinc treatment was able to reverse this deficit. Thus, our results demonstrate that zinc supplementation is not sufficient to avoid metabolic dysfunction caused by cafeteria diet, but it may be important to decrease memory deficits caused by obesity.

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Poster

676. Neuroinflammation: Cognition and Behavioral Responses

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Topic: F.05. Neuroimmunology

Support: FAPERGS 17/251-0001431-6
CNPq
CAPES

Title: Effects of BCAA or Zinc supplementation on neuroinflammatory parameters of obese rats

Authors: *R. P. GUEDES, G. S. FEIJÓ, S. DE OLIVEIRA, J. JANTSCH, L. F. DE CASTRO, B. FERRARY DENIZ, A. C. DE MOURA, M. GIOVENARDI, M. PORAWSKI;
Federal Univ. of Hlth. Sci. of Porto Alegre, Porto Alegre, Brazil

Abstract: Obesity is characterized by a production of pro-inflammatory mediators that leads to neuroinflammation. Among a range of commercial supplements which have known immune properties, we can highlight Zinc (Zn) and the branched chain amino acids (BCAA). Here, we aim to evaluate if 4 weeks of Zn or BCAA supplementation can affect memory and neuroinflammation in obese rats. Wistar rats were divided in the following groups: standard diet (SD); SD+Zn; SD+BCAA; high-fat diet (HFD); HFD+Zn; HFD+BCAA (n=6/group). The diet was administered for 20 weeks and the supplementation with BCAA (750mg/kg/day) or Zn (1,2 mg/kg) was performed by gavage from the 16th week. The study was approved by the local ethical committee (protocol #536/17). Object recognition memory (recognition index, IR); Immunohistochemistry for GFAP and gene expression (IL-6 and TNF-α) were evaluated. The results were analyzed by two-way ANOVA followed by Bonferroni ($p<0.05$). There was an interaction between diet and supplementation in the IR ($p=0.0069$), Zn supplementation reverted the memory impairment caused by HFD. No differences were found in IL-6 gene expression in cerebral cortex and hippocampus. TNF-α gene expression in hippocampus was increased

following HFD (p=0.0069). The number of astrocytes in cerebral cortex was reduced following HFD (p=0.0001) without an effect of Zn or BCAA supplementation. In hippocampus, dentate gyrus (DG) and CA1 areas showed a decrease in GFAP-positive cells in HFD-fed rats after Zn or BCAA supplementation (DG: p=0.0021; CA1: p=0.015). Sholl analysis showed that HFD decreased the number of primary ramifications (p<0.0001), total length of the longest ramifications (p<0.0001) and the total number of intersections of astrocytic processes (p<0.0001) in the cerebral cortex. Also, in the DG there was an interaction in the number of intersections (p=0.037), Zn prevented the increase in the number of intersections after HFD. In CA1, there was an interaction in the total length of the ramifications (p<0.0001), BCAA prevented the decrease in the length of ramifications after HFD. Zn supplementation is able revert the memory impairment caused by obesity. However, neither Zn nor BCAA supplementation were capable to dampen HFD-elicited neuroinflammation.

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Poster

676. Neuroinflammation: Cognition and Behavioral Responses

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Support: CAPES
CNPq
FAPERGS 17/2551-0001431-6

Title: Omega-3 supplementation decreases anxiety-like behavioral in obese rats

Authors: *J. JANTSCH, J. P. NETO, S. DE OLIVEIRA, G. FEIJÓ, M. F. BRAGA, B. F. DENIZ, M. GIOVENARDI, M. P. GARRIDO, R. P. GUEDES;
Federal Univ. of Hlth. Sci. of Porto Alegre, Porto Alegre, Brazil

Abstract: Introduction: Inflammatory mediators released by adipose tissue in obesity can trigger a neuroinflammatory profile that culminates in behavioral changes and neurological diseases. Evidence suggests that omega-3 (n3) plays an anti-inflammatory role by binding on its receptors GPR40 and GPR120. Activation of these receptors in the central nervous system may play a role in neuroprotection. **Objective:** To evaluate the effects of n3 supplementation associated with cafeteria diet in behavior and metabolic profile in Wistar rats.**Methodology:** 48 Wistar rats (IACUC/UFCSPA 117/13) were divided into 4 groups: CT (control diet); CT+n3; CAF (Cafeteria Diet); CAF+n3. The diet was administered for 20 weeks, with supplementation

starting at the 16th week. Weight gain and visceral fat were quantified; plasma levels of glucose, triglycerides and insulin were measured. Elevated plus maze and social recognition memory were conducted. Data were evaluated by two-way ANOVA followed by Bonferroni ($p<0.05$ considered significant), with exception of social recognition memory test that was analyzed by t-test. **Results:** CAF and CAF+n3 groups presented a significant increase in the weight gain and in the visceral fat depot ($p=0.0001$) compared to the control groups. CAF groups presented higher levels of glucose ($p=0.0001$) and triglycerides ($p=0.0001$) compared to the control groups. In behavioral tests, CAF group showed a lower permanency in the open arms in the elevated plus maze compared to the other groups, suggesting that untreated obese rats presented anxiety-like behavior. The percentage of the interaction between the 4th exposure of the juvenile rat 1 and the only exposure of the juvenile 2 in the social memory test did not present a statistically significant difference between CT groups (CT: $p=0.818$; CT+n3: $p=0.264$). The CAF and CAF+n3 groups interacted more with the juvenile 2 compared with the 4^{th} exposure of the juvenile rat 1 ($p=0.033$, $p=0.040$, respectively).**Conclusion**: Omega-3 supplementation does not provide a protection in metabolic parameters following cafeteria diet, but it exerts an interesting effect on the CNS by reverting the anxiety-like behavior in obese rats. In addition, cafeteria diet may increase social memory but n3 does not interfere in this type of behavioral response.

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Poster

676. Neuroinflammation: Cognition and Behavioral Responses

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Support: NIH R01CA194024

Title: Social enrichment attenuates chemotherapy induced neuroinflammation and affective behavior via oxytocin signaling

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Abstract: Patients receiving chemotherapy frequently display increases in anxiety and depression. However, the precise mechanism for chemotherapy-induced neuropsychological effects remains unknown. We hypothesized that chemotherapy increases neuroinflammation; thus, altering anxiety-like and depressive-like behavior. Adult (>8 weeks) female Balb/C mice received two injections, separated by two weeks, of vehicle (0.9% saline) or chemotherapeutic

cocktail (9 mg/kg doxorubicin (A) and 90 mg/kg cyclophosphamide (C)). Following the second injection tissue was collected at one of four timepoints (day 1, 3 ,5 or 7). Mice displayed increased peripheral inflammation one day following, and neuroinflammation seven days following, the completion of one cycle of dose-dense AC therapy. Because of the demonstrated beneficial effects of social enrichment on a multitude of diseases, we examined whether social enrichment could attenuate the increase in peripheral and central inflammation following chemotherapy administration. Singly housed mice receiving AC therapy display increased depressive-like (forced swim test) and anxiety-like (open field test) behavior with a concurrent increase in neuroinflammation and reduced neurogenesis. Pair housing mice throughout chemotherapy treatment lead to an attenuation in neuroinflammation, depressive-like behavior, and loss of neurogenesis. The beneficial effects of social enrichment have previously been associated with increased oxytocin signaling within the brain. Therefore, we sought to determine if ICV administration of oxytocin to singly housed animals could recapitulate the protective effects of pair housing. Indeed, administration of oxytocin to singly housed mice receiving chemotherapy mirrored the effects of pair housing. Additionally, administration of oxytocin antagonist to pair house mice receiving chemotherapy increased depressive-like behavior; thus, mirroring the effects of single housing and demonstrating a potential role for oxytocin. Together, these data add to the growing literature detailing the negative side effects of chemotherapy and provide further evidence that social enrichment may be beneficial in offsetting some of the adverse side effects.

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Poster

676. Neuroinflammation: Cognition and Behavioral Responses

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Title: Prenatal immune activation via TLR7 induces sex-dependent behavioral and neurophysiological alterations

Authors: *G. MISSIG[1], J. O. ROBBINS[1], E. L. MOKLER[1], N. MEHTA[1], C. J. MCDOUGLE[2], W. A. CARLEZON, Jr[1];
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Abstract: Epidemiological evidence indicates that immune activation during pregnancy via infection or autoimmune disease is a risk factor for neuropsychiatric illness. Work from our lab and others has demonstrated that prenatal immune can cause long-lasting behavioral and neurophysiological alterations in offspring. Previous prenatal immune activation protocols have primarily involved administration of agents to mimic infection that target subtypes of the toll-like receptor (TLR) family, a class of receptor proteins that regulate innate immune responses. As examples, TLR3 recognizes Poly I:C and TLR4 recognizes lipopolysaccharide (LPS). In this study we examined the role of TLR7 in prenatal immune activation, considering evidence that this receptor subtype is implicated in the etiology of autoimmune diseases. We administered subcutaneous injections of the selective TLR7 agonist imiquimod (IMQ, 5.0 mg/kg) or vehicle to timed-pregnant dams (C57BL/6J mice) on embryonic days (E) 12, 14, and 16. Mice exposed to prenatal IMQ exhibit a behavioral phenotype characterized by decreases in anxiety-like behavior, a fragmentation of social behavior, and alterations in ultrasonic vocalizations. This phenotype is readily distinguishable from those seen following prenatal activation of TLR3 and/or TLR4. Mice exposed to prenatal IMQ have normal baseline locomotor activity but are hyperactive in response to various types of stimuli including the presence of a social partner, circadian cues, or gonadal hormone fluctuations. Overall, underlying this phenotype is a propensity for "conditional hyperactivity", reflected by an exaggerated response to some types of internal and external stimuli. Additionally, prenatal IMQ exposure causes a decrease in microglia density and an increase in the number of microglia ramifications in numerous brain areas, with particularly strong effects in striatum. RNA-sequencing of the dorsal striatum revealed that prenatal IMQ exposure induces differential expression of hundreds of genes with virtually no overlap in differentially expressed genes between males and females. Considered with the existing literature, our findings suggest that early immune system activation can promote various—and sometimes even opposite—developmental trajectories, depending on the type and/or pattern of TLRs activated.

Disclosures: G. Missig: None. **J.O. Robbins:** None. **E.L. Mokler:** None. **N. Mehta:** None. **C.J. McDougle:** None. **W.A. Carlezon:** None.

Poster

676. Neuroinflammation: Cognition and Behavioral Responses

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 676.14/P31

Topic: F.05. Neuroimmunology

Support: NARSAD Young Investigator Award, BBRF

Title: The limited bedding and nesting paradigm as a naturalistic model of postpartum depression

Authors: *R. DELLA VALLE, J. M. SCHWARZ;
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Abstract: The Limited Bedding and Nesting (LBN) paradigm has been widely used to study the effect of adverse early experiences on brain development and behavior in the affected offspring, but very few studies have examined how limited resources in the peripartum period affect dams outside of documenting their disrupted maternal care. Postpartum depression affects around 15% of mothers, and suicide associated with postpartum depression is one of the leading causes of maternal death in first world countries. Key risk factors for postpartum depression include low social support, low socioeconomic status, unemployment, and negative life events during pregnancy. All of these risk factors have a common theme: psychological, social, or physical resource scarcity, suggesting that the LBN paradigm could provide a novel and naturalistic model for examining its effects on the risk of postpartum depression using rodents. Pre-clinical research on post-partum depression (PPD) has until now focused largely on the contributions of sex hormones and psychosocial stress, with very little focus on the impact of inflammation despite the growing body of evidence that inflammation may contribute to depression. Previous research in our lab has repeatedly demonstrated anhedonic behavior in unstressed dams at P1. This anhedonia is associated with elevation of the pro-inflammatory cytokine IL-6, and is rescued by pre-treatment with an IL-6 receptor antibody. We have also demonstrated postpartum changes in CNS inflammation and microglia density as well as changes in peripheral immune function. The current project aims to explore whether using chronic LBN as a stress paradigm during and following pregnancy provides more robust, chronic changes in anhedonic behavior, and whether these are associated with changes in inflammatory state caused by either the peripartum period itself, or LBN stress.

Disclosures: R. Della Valle: None. **J.M. Schwarz:** None.

Poster

676. Neuroinflammation: Cognition and Behavioral Responses

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 676.15/P32

Topic: F.05. Neuroimmunology

Support: National Research Foundation: NRF-CRP17-2017-04
National Medical Research Council: NMRC/OFIRG/0050/2017

Title: Behavioral changes associated with Zika infection in adult mouse

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Abstract: Congenital Zika virus (ZIKV) exposure is associated with fetal brain microcephaly and other serious birth defects. However, adult ZIKV infection and its consequences on brain function and behavioural change are largely unknown. Here, using the established type-I interferon receptor knockout (A129) mouse as well as wild-type B6 mice, we evaluated long-term neuropathological and behavioral consequences of adult ZIKV infection in mice. ZIKV infection in wild-type B6 mice did not trigger any behavioral deficits due to lack of viral replication in the brain. In contrast, ZIKV infection in A129 mice resulted in normal motor function and behaviors, except for increased stereotypy and repetitive behaviors. And this specific behavioral change observed in ZIKV-infected A129 mice could be rescued by small molecules that block viral replication. Taken together, adult ZIKV infection can result in specific behavioral changes in mice if ZIKV replication can be persisted, but did not result in neurological change Guillain-Barré Syndrome (GBS)-like manifestations.

Disclosures: A.T. Khoo: None. **S. Watanabe:** None. **M. Fukuda:** None. **S. Vasudevan:** None. **H.S. Je:** None. **K.W.K. Chan:** None.

Poster

676. Neuroinflammation: Cognition and Behavioral Responses

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 676.16/P33

Topic: F.05. Neuroimmunology

Title: Formation of pathogenic antibodies by immunization with *Toxoplasma gondii* induces behavioural impairments

Authors: *E. ROMERO NUÑEZ[1], K. SÓSTENES MARTÍNEZ[1], B. PINEDA OLVERA[2], D. F. GONZALEZ ESQUIVEL[1], A. JIMENEZ-ANGUIANO[4], M. MENDEZ ARMENTA[3], C. NAVA RUIZ[3], S. MUÑIZ HERNANDEZ[5], V. PEREZ DE LA CRUZ[1];
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Abstract: The activation of maternal immune system by a prenatal infection during pregnancy is a risk factor to develop psychiatric disorders in the offspring. One of the pathogens associated with considerable number of mental disorders, is the parasite *Toxoplasma gondii.* Epidemiological studies have shown the presence of high levels of IgG anti-*T. gondii* in neonates and young adults who later developed schizophrenia. The absence of the parasite and the high

levels of IgG's found in those patients suggest the transplacental transfer of anti-*T. gondii* IgG antibodies, which could bind fetal brain structures possibly due to molecular mimicry inducing alterations in neurodevelopment. The objective of this study was to determinate if the behavioral impairment observed in progeny of rats immunized with *Toxoplasma gondii* are related with the formation of pathogenic antibodies which can alter neuronal processes during the gestation. The female rats were immunized three times (one per week) with the *Toxoplasma gondii* lysate or PBS three weeks before gestation. At day 18 of gestation, fetus brains were obtained and fixed in 4% paraformaldehyde, dehydrated and embedded in paraffin to search for IgG joined to brain structures by means of immunofluorescence assay, using an anti-rat IgG-Cy5 antibody. Additionally, serum of the control female rats and immunized rats was obtained, in order to look for antibodies able to recognize brain proteins also by using immunofluorescence assay. Fetus brains from immunized mothers showed presence of antibodies joined to brain structures that were recognized by the anti-rat IgG-Cy5, while control group did not show any change. Serum of female immunized rats also reacted with normal fetus brains, but it was not found reactivity with the serum from control group. These results suggest the formation of pathogenic antibodies induced by *T. gondii* immunization, with ability to pass toward brain of fetus during gestation and this impacts behavioral profile of the progeny.

Disclosures: **E. Romero nuñez:** None. **K. Sóstenes Martínez:** None. **B. Pineda olvera:** None. **D.F. Gonzalez esquivel:** None. **A. Jimenez-Anguiano:** None. **M. Mendez Armenta:** None. **C. Nava Ruiz:** None. **S. Muñiz Hernandez:** None. **V. Perez De La Cruz:** None.

Poster

676. Neuroinflammation: Cognition and Behavioral Responses

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 676.17/P34

Topic: F.05. Neuroimmunology

Support: Ministry of Technology and Sciences (MOST 106-2314-B-532 -005 -MY3, 106-2314-B-532 -008 -MY2), Taiwan
Taipei City Hospital (TCH 10701-62-029), Taiwan

Title: Fkbp5 deficiency increases anxiety susceptibility involving inhibition of hippocampal GR and GAD65 upregulation in mice after transient peripheral inflammation

Authors: *Y.-L. GAN[1], C.-Y. WANG[1], R.-H. HE[1], P.-C. HSU[1], P.-H. SUNG[1], C.-J. JENG[2,3], M.-C. HUANG[4,5,6], Y.-H. LEE[1,3];
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Abstract: FK506-binding protein 51 (FKBP51) encoded by the *Fkbp5* gene is a negative feedback co-chaperone of glucocorticoid receptor (GR) and has been linked to many stress-related mental disorders involving dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. Peripheral inflammation has been suggested as a pathogenic inducer for anxiety disorder, but the role of FKBP51 in the inflammation-associated anxiety remained unknown. Here we used *Fkbp5*-deficient (*Fkbp5*-KO) mice treated with a single intraperitoneal injection of lipopolysaccharide (LPS) to study the behavioral and neurochemical changes after transient peripheral inflammation. We found that *Fkbp5* deletion did not affect LPS-induced transient sickness, whereas significantly increased anxiogenic response, not locomotor hypoactivity, in both open-field test and elevated plus maze test performed 7 days after the LPS injection. LPS injection induced a transient inflammation as well as glucocorticoid-mediated stress responses in both liver and hippocampus by increasing their *Tnfa* and *Fkbp5* gene expressions, respectively; and *Fkbp5* deletion attenuated the inflammatory response only in the hippocampus but not in the liver. The *Fkbp5*-dependent hippocampal inflammation is followed by a delayed upregulation of GR in the hippocampus, and this response was diminished in *Fkbp5*-KO. Neurochemical changes further revealed that LPS injection induced a *Fkbp5*-dependent elevation of hippocampal glutamic acid decarboxylase 65 (GAD65), the inhibitory GABA synthesizing enzyme, whereas $GABA_A$ receptor, serotoninergic $5HT_{1A}$ receptor or excitatory NMDA receptor subunits were not affected. In sum, these results suggest that FKBP51 may regulate immune-mediated hippocampal GR and GABAergic neurotransmission, thereby dampen the anxiety and stress susceptibility secondary to acute peripheral inflammation.

Disclosures: **Y. Gan:** None. **C. Wang:** None. **R. He:** None. **P. Hsu:** None. **P. Sung:** None. **C. Jeng:** None. **M. Huang:** None. **Y. Lee:** None.

Poster

676. Neuroinflammation: Cognition and Behavioral Responses

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 676.18/P35

Topic: F.05. Neuroimmunology

Support: Australian National University Institutional Funds
South Australian Health and Medical Research Institutional Funds
Flinders University Faculty of Medicine and Health Sciences Grant

Title: Behavior and gut microbiota changes in mice with simultaneous deficit in multiple pro-inflammatory pathways

Authors: *M.-L. WONG[1], J. LICINIO[1], A. INSERRA[2], J. CHOO[3], M. D. LEWIS[2], G. B. ROGERS[3];
[1]Psychiatry, SUNY Upstate Med. Univ., Syracuse, NY; [2]Mind & Brain, [3]Infection & Immunity

Theme and SAHMRI Microbiome Res. Lab., South Australian Hlth. and Med. Res. Inst., Adelaide SA, Australia

Abstract: Neuroinflammatory pathways have been implicated in major depressive disorder (MDD) development and antidepressant response. Decreasing pro-inflammatory signaling may be beneficial to MDD, and dysregulation in three major inflammatory systems has been described in this condition: i) low-grade chronic pro-inflammatory status with caspase 1 (CASP1) overproduction, ii) interferon gamma (INFG) over production driven by type 1 T helper (Th1) cells, and iii) increased oxidative stress with nitric oxide (NO) overproduction by NOS2 (NO synthase 2). We investigated the effect of simultaneous deficit in these 3 pro-inflammatory pathways in depressive-like behavior and the gut microbiome using a triple knockout mouse model lacking CASP1, INFG receptor, and NOS2 (Casp1, Ifngr, Nos2)-/-. At baseline, these animals showed decreased depressive- and anxiety-like behavior, and increased hedonic-like behavior and locomotor activity. They were resistance to developing anhedonic-like behavior and had a heightened emotional state following stress compared to wild-type (wt) mice. Plasma ACTH and CORT levels did not differ between the triple knockout and wt mice following chronic stress. Fecal microbiota differed in this mouse model in comparison to wt mice at baseline and showed reduced changes in response to chronic stress. Concomitant deficit in multiple pro-inflammatory pathways has antidepressant-like effects at baseline and confers resilience to stress-induced anhedonic-like behavior. Gut microbiome composition changes suggest that CASP1, IFNGR and NOS2 play a role in sustaining microbiome homeostasis.

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Poster

676. Neuroinflammation: Cognition and Behavioral Responses

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 676.19/P36

Topic: F.05. Neuroimmunology

Support: NIH Grant CA216920

Title: The role of gut microbiota in chemotherapy-induced anxiety-like behavior

Authors: A. LAHOUD[1], K. JORDAN[1], B. HAYNES[1], S. VICKERY[1], J. KAUR[1], K. A. SULLIVAN[2], ***L. M. PYTER**[1];
[1]Ohio State Univ., Columbus, OH; [2]Neurosci., The Ohio State Univ., Columbus, OH

Abstract: The gut microbiome influences neurobiology and anxiety-like behavior in rodents. Anxiety is a common behavioral symptom of cancer patients, often attributed to peripheral

inflammation after chemotherapy. Chemotherapy also has adverse effects on the intestines (e.g., diarrhea, shifts community structure of the gut microbiota). However, little is known about the potential role of the gut microbiome in chemotherapy-induced anxiety. This work assessed the causality of chemotherapy-induced shifts in the gut microbiota on anxiety-like behavior. Gut microbiotal alteration was induced by feeding C57Bl/6 mice broad-spectrum antibiotic-containing chow (or control) for one week prior to and during paclitaxel chemotherapy treatments (30 mg/kg; i.p.; every other day for 6 injections) or vehicle (n=10/group). Anxiety-like behavior was tested using the open field test immediately or one week after treatment; body mass and food intake were recorded throughout. Antibiotics modulated sickness behavior (not anxiety-like behavior) such that fatigue and hippocampal (CXCL10, CCL2) and peripheral (IL-1, CXCL1, IL-6) inflammation were exacerbated in chemotherapy+antibiotic-treated mice relative to chemotherapy controls, whereas antibiotics did not affect behavior/inflammation in vehicle-treated controls. These results suggest that the gut microbiota modulates inflammation and behavioral changes after chemotherapy.

Disclosures: **A. Lahoud:** None. **K. Jordan:** None. **B. Haynes:** None. **S. Vickery:** None. **J. Kaur:** None. **K.A. Sullivan:** None. **L.M. Pyter:** None.

Poster

676. Neuroinflammation: Cognition and Behavioral Responses

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 676.20/P37

Topic: F.05. Neuroimmunology

Support: Biobehavioral Health Department Seed Grant

Title: Chronic inhaled corticosteroids during development minimize allergic asthma symptoms but exacerbate comorbid anxiety symptoms

Authors: *S. A. CAVIGELLI, J. CAULFIELD, H. KAMENS;
Pennsylvania State Univ., University Park, PA

Abstract: Allergic asthma is the most common chronic condition for developing youth. The condition occurs during significant brain maturation, and is often comorbid with internalizing disorders, particularly anxiety. In a mouse model, we have found that experimentally-induced allergic asthma symptoms during development lead to adult anxiety-related behavior and serotonergic (5-HT) and corticotropin-releasing hormone (CRF)-related gene expression in emotion regulation brain areas. In the current study, we tested whether chronic inhaled corticosteroids (ICS), frequently used to control allergic asthma symptoms in youth, exacerbate or diminish developmental allergen-induced adult anxiety-related behavior and gene expression. We bred Balb/cJ mice and assigned same-sex littermates to one of 8 conditions in a 2x4 study

design (2: allergen vs. vehicle exposure 3 times/week during postnatal days 7-56; 4: vehicle vs. low- vs. mid- vs. high-dose ICS exposure 3 times/week during postnatal days 21-56). Results indicate that chronic low- and mid-dose ICS treatment during development attenuated allergen-induced lung inflammation ($p<.05$), and significantly increased anxiety-related behavior on the elevated plus maze ($p<.05$). We are analyzing 5-HT- and CRF-related gene expression in the prefrontal cortex and ventral hippocampus. ICS doses also led to decreased body weight, which is a well-documented side effect of ICS treatments in children, suggesting that the intranasal steroid treatment in a mouse model may mimic ICS treatment in children. Overall, results indicate that one of the most common maintenance regimens for allergic asthma in youth may exacerbate asthma-associated anxiety symptoms.

Disclosures: S.A. Cavigelli: None. **J. Caulfield:** None. **H. Kamens:** None.

Poster

676. Neuroinflammation: Cognition and Behavioral Responses

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 676.21/P38

Topic: F.05. Neuroimmunology

Support: NIH Grant T32GM108563

Title: The impact of developmental chronic variable social stress and asthma on anxiety-like brain gene expression, anxiety-like behavior, and stress response

Authors: *J. I. CAULFIELD, H. M. KAMENS, S. A. CAVIGELLI;
The Pennsylvania State Univ., University Park, PA

Abstract: Allergic asthma is the most common chronic condition diagnosed in children (9.5 percent of youth under 18yrs). Individuals with asthma have a significantly increased risk for developing an anxiety disorder compared to people without asthma, and this comorbidity can occur as early as adolescence. Asthma is highly prevalent in urban areas, and many aspects of urbanization impact the risk for developing/worsening of asthma. Social interactions are an important aspect of healthy living, and chronic social stressors (isolation and reorganization) that are part of urban environments negatively impact health. Minimal research has focused on how the social stress component of urban environments affects asthma and comorbid anxiety development. Here, we examine BALB/cJ mice as adults after developmental exposure to house dust mite (HDM; 3 exposures per week from postnatal day [P] 7-56) and chronic variable social stress (CVSS; 5 weeks of repeated cycling between isolation and social reorganization from P25-59). We examined general anxiety-like behavior using the elevated plus maze (EPM) and social anxiety-like behavior using the Social Approach-Avoidance Test (SAAT) on P66 and P71. Females exposed to HDM tended to spend more time on the open arms of the EPM compared to

vehicle females, whereas males exposed to HDM tended to spend less time on the open arms than vehicle males (p=0.07). In the SAAT, with the social target present, mice that experienced CVSS made fewer entries into the interaction zone compared to controls (p=0.035), but time spent interacting was not different between groups. At P76, we collected lung, prefrontal cortex, and hippocampus to examine immune and stress-related RNA gene expression and protein changes following these chronic developmental challenges. Corticosterone (CORT) was also measured from serum in response to a restraint stress challenge. Since preliminary results suggest that HDM exposure results in a lower baseline CORT level compared to vehicle, here we expect the CORT response to restraint stress to also be blunted vs. vehicle. The results from this study will provide important insight into a potential mechanism for how asthma is linked to anxiety in an at-risk population, which could inform future treatments for patients.

Disclosures: J.I. Caulfield: None. **H.M. Kamens:** None. **S.A. Cavigelli:** None.

Poster

676. Neuroinflammation: Cognition and Behavioral Responses

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 676.22/P39

Topic: F.05. Neuroimmunology

Support: Internal Grant from Purdue University Northwest

Title: Investigation of early exposure to clomipramine on central inflammatory markers in maternal and non-maternal Sprague-Dawley rats

Authors: *C. M. RAGAN, B. N. REGULA, L. M. GIELDA;
Purdue Univ. Northwest, Westville, IN

Abstract: Hormonal fluctuations that occur during the peripartum period can lead to alterations in brain chemistry that result in postpartum mood and anxiety disorders. Furthermore, these brain and behavioral differences observed during the postpartum period may be a result of early-life perturbations in development. Recent research has highlighted the role of the immune response in the pathogenesis of these mood and anxiety disorders in non-maternal populations. In non-maternal populations, inflammation in brain regions such as the orbitofrontal cortex (OFC) is 30% higher in people with obsessive-compulsive disorder (OCD) compared to healthy controls. Less is known about inflammation in the brain of postpartum females. Using a pharmacologically-induced model of OCD in Sprague Dawley rats, twice daily we exposed pups to the tricyclic antidepressant, clomipramine, during postnatal days 9-16 or a saline control. We observed that during the postpartum period, rat mothers previously-exposed to clomipramine during early development engaged in more passive nursing postures and more OCD-like behavior compared to control dams. The rat mothers that experienced early exposure to

clomipramine also expressed more pro-inflammatory IL-1 beta in the OFC compared to saline control dams. Our findings suggested that increased inflammation in the OFC may be a mechanism associated with OCD behavior in maternal and non-maternal populations.

Disclosures: C.M. Ragan: None. **B.N. Regula:** None. **L.M. Gielda:** None.

Poster

676. Neuroinflammation: Cognition and Behavioral Responses

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 676.23/P40

Topic: F.05. Neuroimmunology

Support: NIH Grant CA216290
OSU College of Medicine Funds

Title: Circadian dysregulation of behavior and physiology by tumor biology and chemotherapy in mice

Authors: *K. A. SULLIVAN[1,2], S. R. BEVER[2,5], L. D. STREHLE[1,2], K. L. G. RUSSART[2,3], K. JORDAN[1,2,6], A. PATEL[2], K. M. WENTWORTH[2], A. LAHOUD[2], J. KAUR[2], K. H. OBRIETAN[1], L. M. PYTER[1,2,3,4];
[1]Neurosci., [2]Inst. for Behavioral Med. Res., [3]Comprehensive Cancer Ctr., [4]Psychiatry and Behavioral Hlth., The Ohio State Univ., Columbus, OH; [5]Psychology, UC Berkeley, Berkeley, CA; [6]Knight Cardiovasc. Inst., Oregon Hlth. and Sci. Univ., Portland, OR

Abstract: Breast cancer survivors exhibit pervasive cognitive disruption for years post-treatment. In addition to memory and attention deficits, dysregulated sleep-wake activity cycles are frequently reported in this population, and flattened cortisol circadian (24-h) rhythms correlate with dysregulated cognition. Given that memory, activity, and cortisol all exhibit circadian rhythms in healthy humans, we hypothesized that both tumor biology and cancer treatments negatively impact physiological and behavioral circadian rhythms. Here, we use mouse models of non-metastatic breast cancer (tumor-bearing mice), breast cancer survivors (tumor-resected mice), and paclitaxel chemotherapy (30 mg/kg, 6 i.p. injections) to examine the extent to which tumors and cancer treatments independently attenuate cognition and circadian rhythmicity in behavior and physiology in female mice. Behavioral rhythms of wheel running were altered in tumor-bearing and tumor-resected mice compared to sham surgery control mice and running wheel activity was decreased in mice receiving chemotherapy. Blood was also collected at multiple points throughout a 24-hour period to analyze rhythms in corticosterone impacted by tumors and chemotherapy. Corticosterone rhythms were attenuated by the presence of a tumor, which was rescued by tumor resection. Chemotherapy decreased cognitive performance as assessed by memory recall for a contextual fear conditioning task, but paclitaxel

did not affect corticosterone rhythms. Overall, the implications of this work may lead to circadian-focused targets of resynchronizing physiology to ameliorate cancer- and chemotherapy-induced cognitive disruption.

Disclosures: **K.A. Sullivan:** None. **S.R. Bever:** None. **L.D. Strehle:** None. **K.L.G. Russart:** None. **K. Jordan:** None. **A. Patel:** None. **K.M. Wentworth:** None. **A. Lahoud:** None. **J. Kaur:** None. **K.H. Obrietan:** None. **L.M. Pyter:** None.

Poster

676. Neuroinflammation: Cognition and Behavioral Responses

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 676.24/P41

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Title: Lipopolysaccharide induces motivational deficits like behavior mediated by alteration of brain metabolites in mice

Authors: *K. ADACHI, M. MARUI, T. HAYASHI, M. NAGASAWA;
Meijo Univ., Nagoya-Shi, Japan

Abstract: Motivational deficits are one of initial symptoms of mental disorder induced by chronic stress (e.g. depression and anxiety). However, the underlying mechanism of motivational deficits is poorly understood, unraveling of that provides the preventive strategy of mental disorder. Recently, cytokine hypothesis in mental disorder has been proposed, since there are a lot of evidences about the relationships between chronic stress and brain inflammation. Thus, lipopolysaccharide (LPS) model has been paid attention to study the mechanisms for chronic stress. LPS injection induces the inflammatory response as well as chronic stress in animal body including the brain, resulting in the release of inflammatory cytokines. Therefore, we examined to evaluate motivated behavior in mice injected LPS, to verify the alteration of brain metabolites in the state of motivational deficits induced by chronic stress. Male eight-week old ICR mice were freely explored in the experimental arena (width: 60 cm × length: 60 cm × height: 40 cm) for 5 minutes, followed by the intraperitoneal injection of phosphate buffered saline (10 ml/kg) or LPS solution (400 μg/ 10 ml/kg). After 24 hours from an injection, every mice were re-explored the same experimental arena in which two novel objects were placed for 5 minutes. In this experiment, the total duration for exploring the objects was observed as an index for motivated behavior in mice. Immediately after each behavioral observation, the mouse was sacrificed under anesthesia, and the hippocampus was dissected from the whole brain. Biological metabolites extracted from the hippocampus were subjected to GC-MS. The total duration for exploring the objects was significantly decreased in LPS group, indicating the motivational decline. The metabolome analysis proposed the alterations of metabolic pathway in the hippocampus under the state of motivational deficits. To elucidate the mechanisms for the

motivational deficits, we focused on LPS model. The motivational deficits-like behavior was induced by LPS treatment. In accordance with that, various metabolic dysfunctions were observed in the hippocampus. Consequently, these results suggest that LPS model is an effective model to evaluate motivation, and the metabolic alterations in the brain play a key role in the onset of motivational deficits.

Disclosures: **K. Adachi:** None. **M. Marui:** None. **T. Hayashi:** None. **M. Nagasawa:** None.

Poster

677. Blood-Brain Barrier: Control and Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 677.01/P42

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: ERC Advanced Grant HOMEOSIGN n°339379

Title: The role of choroid plexus in health and disease

Authors: *V. OLIVEIRA MOREIRA[1], A. PLANQUES[2], K. ARNAUD[1], A. PROCHIANTZ[1], A. DI NARDO[1];
[1]Col. De France, Paris, France; [2]Inst. Jacques Monod, Paris, France

Abstract: The choroid plexus is a richly vascularized structure located in brain ventricles and is responsible for the production of CSF containing a large panel of molecules essential for various brain functions. We have shown that two proteins expressed by the choroid plexus are modulators of adult neurogenesis: the OTX2 homeoprotein transcription factorand the amyloid precursor protein (APP). OTX2 is highly expressed in the choroid plexus and is secreted into the CSF resulting in its transfer into astrocytes of the ventricular-subventricular zone (V-SVZ) and rostral migratory stream (RMS). When OTX2 is sequestered in the CSF of adult mice, we observed altered expression of astrocyte-specific extracellular matrix proteins, resulting in slowed neuroblast migration in RMS and decreased newborn neurons in the olfactory bulb. APP is also highly expressed in the choroid plexus and its soluble domain is released into the CSF. When APP levels were reduced in the adult mouse choroid plexus, we observed decreased proliferation in both neurogenic niches: V-SVZ and hippocampus dendate gyrus (DG). Increasing APP levels resulted in increased proliferation in both niches. To gage the impact on brain function of extracellular APP coming from choroid plexus, we expressed, specifically in choroid plexus of adult wild type mice, the human APP bearing SwInd mutations of familial Alzheimer disease. After 6 months, proliferation in V-SVZ and DG were significantly reduced. After 12 months, mice showed reversal learning deficits in open field behavior experiments and showed impaired plasticity in LTP measured by high frequency stimulation of hippocampus

slices. Our studies allowed us to highlight novel molecules from choroid plexus secretome involved in neurogenesis and brain functions.

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Poster

677. Blood-Brain Barrier: Control and Mechanisms

Location: Hall A

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Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

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Title: VEGF-C induced meningeal lymphangiogenesis in C57BL/6J mice enhances small molecular weight solute drainage from brain into lymphatics associated with the nasal conchae: A quantitative *in vivo* MRI study

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Abstract: Rationale: Cerebrospinal fluid (CSF) continuously exchanges with interstitial fluid (ISF) via the brain-wide glymphatic system (GS) to remove waste including Aβ and tau. Ultimate exit routes for waste solutes from the GS involves lymphatic vessels (LV) associated with meninges covering the brain and cranial nerves. Previous studies have shown that cranial meningeal LV are defective in neurodegenerative states and efforts to increase lymphangiogenesis with VEGF-C have therefore been proposed as a therapeutic strategy for maintaining efficient waste drainage across the lifespan to prevent neurodegeneration and cognitive decline. Currently, there is a gap in knowledge as to how efficient VEGF-C-induced meningeal lymphangiogenesis would be as a GS accelerator of waste drainage. Here we introduce a new, quantitative and time efficient magnetic resonance imaging (MRI) approach to quantify the effect of VEGF-C induced meningeal lymphangiogenesis on GS solute drainage. **Methods:** To induce meningeal lymphangiogenesis, adeno-associated virus (AAVs) encoding mouse VEGF-C (AAV-mVEGF-C) was administrated into CSF via the cisterna magna (CM) in 4-week old C57BL/6J (WT) mice, as previously reported (N = 6). Control WT mice were injected with AAVs encoding soluble mVEGFR3$_{4\text{-}7}$-Ig (VEGFR3 ectodomains that do not bind VEGF-C) (AAV-control) (N = 6). Four weeks later the mice underwent MRI for characterization of GS transport. The mice were anesthetized with ketamine/xylazine and received intra-CM

injection of Gd-DOTAREM (1:20; 1μl/min, 7 min). All MRI was done on a 9.4T MRI instrument. Fifty min after administration of Gd-DOTAREM, T1 maps were acquired at a spatial resolution of 100x100x100 μm. The volume of T1 voxels = 400-1600ms (representative of DOTAREM-solute tissue levels and GS transport) was extracted from whole brain and nasal conchae masks from each mouse and compared across groups.
Results and conclusions: GS transport in whole brain as represented by voxels with T1 values of 400-1600ms, was similar between control and AAV-mVEGF-C treated mice (AAV-control treated mice (N = 6): 262 ± 52 mm^3 vs AAV-mVEGF-C-treated mice (N = 5): 268 ± 42 mm^3, p = 0.78). In contrast, T1 values of Gd-DOTAREM associated with nasal conchae was found to be ≈20% higher in AAV-mVEGF-C treated mice (N = 5) when compared to AVV-control mice (N = 6): 11 ± 1 mm^3 vs 9 ± 2 mm^3, p = 0.035). AAV-mVEGF-C treated mice showed increased LV growth in cranial meninges and nasal conchae, compared to AAV-control treated mice. Therefore, increased CSF/ISF Gd-DOTAREM efflux correlates with LV growth in meninges and nasal conchae.

Disclosures: Y. Xue: None. **L.S.B. Boisserand:** None. **X. Liu:** None. **H. Lee:** None. **J. Thomas:** None. **H. Benveniste:** None.

Poster

677. Blood-Brain Barrier: Control and Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 677.03/Q2

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: NIH Grant NS034467

Title: Endothelial LRP1 controls cerebrovascular integrity and neuronal survival via the CycA-MMP9-NFkB pathway

Authors: *A. M. NIKOLAKOPOULOU[1], Y. WANG[1], Q. MA[2], A. SAGARE[1], A. MONTAGNE[1], M. HUUSKONEN[1], Z. ZHAO[1], B. ZLOKOVIC[1];
[1]USC, Los Angeles, CA; [2]The Lawrence D. Longo, MD Ctr. for Perinatal Biol., Loma Linda Univ., Loma Linda, CA

Abstract: The blood-brain barrier (BBB) is a major clearance site for Alzheimer's amyloid beta (Aβ) protein. This process is mediated by the receptor-mediated transport across the BBB into the peripheral circulation via the low-density lipoprotein receptor-related protein 1 (LRP1), which is a major receptor for both Aβ and apolipoprotein E. Whether LRP1 has other functions at the BBB remains, however, less clear. Here, we established a mouse model with endothelial specific deletion of LRP1, and found that endothelial LRP1 is required for the maintenance of BBB integrity, as identified by increased deposition of extravascular blood-derived IgG and

fibrin accumulates, and neuronal accumulation of systemically injected exogenous cadaverine molecule. Moreover, BBB breakdown that develops at 2 months of age in these mice, leads at 4 months of age to neuronal loss and behavioral deficits. Mechanistically, LRP1 loss from endothelium led to upregulation of cyclophilin A, a pro-inflammatory cytokine, which transcriptionally activated metalloproteinase-9 (MMP9) causing degradation of the capillary basement membrane and tight junction BBB proteins. These data point to a new role of endothelial LRP1 in vascular and neuronal protection.

Disclosures: **A.M. Nikolakopoulou:** None. **Y. Wang:** None. **Q. Ma:** None. **A. Sagare:** None. **A. Montagne:** None. **M. Huuskonen:** None. **Z. Zhao:** None. **B. Zlokovic:** None.

Poster

677. Blood-Brain Barrier: Control and Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 677.04/Q3

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: NRF-2018R1C1B6001055

Title: NMDA receptor signaling regulates function and integrity of the blood brain barrier

Authors: C. LEE, ***D.-G. KIM**;
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Abstract: The brain is the center of the cognitive function and it receives tremendous oxygen and glucose from peripheral system in a very selective manner through its vascular system called the blood brain barrier (BBB). Several *in vitro* and *in vivo* studies have shown that signaling systems can control the permeability of the BBB and suggests that it may be the key to control the sophisticated molecular delivery system to the brain from periphery. In this study, we have focused on the glutamate, which is one of the most abundant neurotransmitter in the brain, may be able to control the permeability of the BBB as an important signaling pathway to control the permeability of the BBB to enhance the molecular delivery to the brain. And we have hypothesized that this may occur through the N-Methyl-D-aspartate (NMDA) receptor signaling which is one of most well characterized neurotransmitter receptors mediating long term potentiation. To test this, we have used *in vitro* BBB model and tested the effect of the NMDA receptor signaling. We have observed rapid and reversible significant changes in the permeability of the *in vitro* BBB by NMDA receptor activation mediated by its calcium influx. Further, *in vivo* study showed that the NMDA receptor activation can transiently induce changes in the BBB permeability suggesting its potent and reversible permeabilization of the BBB. Lastly, we generated vascular specific NMDA receptor knock out mouse and we have found that the permeability of the BBB is also affected from these mice indicating that the NMDA receptor

signaling pathway is one of the core component controlling the permeability of the BBB. Overall, NMDA receptor signaling in the brain endothelial cell affects the permeability of the BBB and possibly neuronal or astrocytic glutamate may be the major signal to control the molecular delivery to the brain in a need base manner.

Disclosures: C. Lee: None. **D. Kim:** None.

Poster

677. Blood-Brain Barrier: Control and Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 677.05/Q4

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Title: Magnetic resonance-guided focused ultrasound-mediated gene therapy delivery to brain tissue post-surgical resection

Authors: *M. A. STAVARACHE, G. M. WINSTON, M. YUAN, A. ZANELLO, E. M. JURGENS, M. G. KAPLITT;
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Abstract: The standard treatment of malignant gliomas (GBM), the most common subtype of primary brain tumors, consists of surgery, followed by radiotherapy and chemotherapy. In recent years, advancements in molecular virology led to development of oncolytic viral therapy using genetically engineered oncolytic viruses designed to selectively replicate and kill cancer cells without harming normal tissue. The GBM's highly invasive, infiltrative nature, relative resistance to radiation and chemotherapy, and physiological isolation due to the blood-brain-barrier (BBB) contribute to a poor prognosis. T[MS1] he promising results of viral therapy suggests the need [MS2] for an update in the standard of care [MS3] for GBM therapy. We have previously reported our results using magnetic resonance-guided focused ultrasound (MRgFUS), a novel technique that temporarily and safely disrupts the BBB, to deliver Oncolytic Herpes Simplex Virus-1 (oHSV-1) to specific areas in the brain. Here, we focused on its efficiency in delivering oncolytic viral therapy to the residual tissue following the resection of a portion of brain parenchyma. Sprague-Dawley rats (200-250g) underwent unilateral brain parenchyma resection at the cortical level. Forty [MS4] days later, the rats underwent simultaneous sonication in resection area under MRI control with intravenous administration of dsRed tagged-oHSV-1 at a titer 5*10^8 pfu and albumin-coated gas-filled microbubbles[MS5] . Intravenously administered Gd-DTPA contrast agent confirmed the BBB disruption in T1-weighed images collected post-sonication. A separate group underwent a second sonication session, one week later, following the same protocol. The animals were sacrificed at 2-, 8-days and one-month later, with the brain, liver, heart, and lungs processed for histological analysis. Immunostaining of dsRed, our gene reporter, showed a strong expression in the parenchyma delimiting the

resection area. Immunostaining for neuronal marker NeuN showed no neuronal death in the sonicated area, while GFAP (astrocytic marker) and Iba-1 (microglial marker) staining revealed a transitory local inflammatory response detected only in the animals perfused 2- and 8-days post-FUS. No off-target dsRed staining was detected. Gross observation revealed no behavioral abnormalities in the days post-sonication. These results suggest that MRgFUS can be utilized for non-invasive delivery of larger sized viruses such as oHSV-1 to targeted areas post-surgical resection, which can increase the effectiveness of oncolytic virus therapy in GBM patients.

Disclosures: M.A. Stavarache: None. **G.M. Winston:** None. **M. Yuan:** None. **A. Zanello:** None. **E.M. Jurgens:** None. **M.G. Kaplitt:** None.

Poster

677. Blood-Brain Barrier: Control and Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 677.06/Q5

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: NIH R01 NS099595
AARGD 16-440893
NIH R25 GM072643

Title: Hyperinsulinemia induced brain microvessel insulin resistance correlates with reduced insulin transport

Authors: *L. S. WATSON[1], C. J. SMITH[2], A. S. WILLIAMS[1], C. SIMS-ROBINSON[1]; [1]Neurol., [2]Neurosci., Med. Univ. of South Carolina, Charleston, SC

Abstract: During Alzheimer's disease and stroke, two of the most common age related neurodegenerative disorders, patients present with systemic hyperinsulinemia. Systemic hyperinsulinemia is associated with reduced CNS insulin levels, however the mechanisms underlying this are not well understood. Insulin is fundamental in the brain for neuroplasticity, and has anti-apoptotic, -inflammatory, -thrombotic, and -vasodilatory properties. Insulin must be transported across the blood brain barrier (BBB). Some have suggested this occurs via insulin receptor-mediated transcytosis. Thus, the purpose of the following studies are to determine the impact of hyperinsulinemia on insulin transport across the BBB. In the current study, at four weeks of age, B6 mice were placed on either a standard diet (STD) or a high-fat diet (HFD) for 6 and 24 weeks. Hippocampal microvessels were extracted and the levels of serine-phosphorylated insulin receptor substrate, a docking protein that can inhibit insulin receptor function, were measured. Furthermore, these microvessels were stimulated with insulin to determine the ability to activate downstream insulin signaling. We observed evidence of insulin resistance in HFD microvessels and impaired insulin signaling. To explore whether these alterations impacts insulin

transport, we utilized primary brain endothelial cells, a key component of the BBB, and exposed the cells to hyperinsulinemic conditions to evaluate insulin resistance, signaling, and transport. Our data demonstrates that insulin resistance and impaired insulin signaling correlates with reduced transport. Future studies will seek to validate these findings in more complex BBB systems.

Disclosures: L.S. Watson: None. **C.J. Smith:** None. **A.S. Williams:** None. **C. Sims-Robinson:** None.

Poster

677. Blood-Brain Barrier: Control and Mechanisms

Location: Hall A

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Program #/Poster #: 677.07/Q6

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: NIH grant NS100459
NIH grant AG039452

Title: Pericyte loss leads to circulatory failure and pleiotrophin depletion causing neuron loss

Authors: *B. V. ZLOKOVIC, A. M. NIKOLAKOPOULOU, A. MONTAGNE, K. KISLER, Z. DAI, Y. WANG, M. HUUSKONEN, A. P. SAGARE, D. LAZIC, M. D. SWEENEY, Z. ZHAO; Keck Sch. of Med. of the Univ. of Southern California, Los Angeles, CA

Abstract: Brain pericytes are the vascular mural cells located within the basement membrane of blood microvessels between brain endothelial cells, astrocytes and neurons. Pericytes maintain blood-brain barrier integrity, regulate cerebral blood flow (CBF) and participate in the clearance of brain toxic byproducts and degenerate in multiple neurological disorders. Understanding the role of pericytes in the brain has been challenging due to the lack of pericyte-specific models; studies so far have used mouse models. where pericyte deficiency is caused by aberrant signaling between endothelial-derived platelet-derived-growth factor B (PDGF-B) and PDGF-receptor β (PDGFRβ) in pericytes Here, we report the development of an inducible pericyte-specific Cre line utilizing a double-promoter approach with the platelet-derived growth factor receptor-β (Pdgfrβ) and chondroitin sulfate proteoglycan-4 (Cspg4) promoters, and show Cre-dependent expression of a dtTomato reporter only in brain pericytes, but not in oligodendrocytes, oligodendrocyte progenitor cells, vascular smooth muscle cells, brain endothelial cells, astrocytes or microglia. To specifically ablate pericytes, we crossed pericyte-specific Cre mice with the iDTR mice carrying a Cre-dependent human diphtheria toxin receptor (DTR). After acute pericyte ablation with diphtheria toxin, mice developed a severe loss of cerebral blood flow, blood-brain barrier breakdown, rapid loss of neurons and behavioral deficits. Pericyte loss led to depletion of pleiotrophin (PTN), a neurotrophic growth factor, which is highly enriched in

pericytes compared to other brain cell types. Replacing depleted PTN in pericyte-ablated mice prevented neurodegeneration and improved performance in behavioral tests regardless of the continuous blood-brain barrier dysfunction triggered by pericyte loss. These data suggest a rapid neurodegeneration cascade connecting pericyte loss to acute circulatory failure and loss of neurotrophic PTN, both required to cause neurodegeneration. Thus, replenishment of pericytes or pericyte-related neurotrophic factors may play a crucial role in developing therapies for brain diseases associated with pericyte loss.

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Poster

677. Blood-Brain Barrier: Control and Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 677.08/Q7

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: NMSS RG-1803-30494
NJCSCR CSCR13IRG012

Title: Regulation of blood-brain/spinal cord barrier integrity by Hedgehog-responsive astrocytes in the adult mouse CNS

Authors: H. WANG, Z. XU, Z. XIA, M. RALLO, ***M. P. MATISE**;
Neurosci. & Cell Biol., Rutgers-RWJMS, Piscataway, NJ

Abstract: The blood-brain/spinal cord barrier (BBB) plays a central role in maintaining CNS homeostasis. Disruption of the BBB commonly occurs following CNS injury, and is recognized as critical in the etiology of many diseases affecting the CNS, including MS, ALS and AD. Restoration of the BBB is also crucial for functional recovery following injury or disease. BBB permeability is regulated by several distinct cell types that together form the Neurovascular Unit (NVU), including blood vessel endothelial cells, pericytes, and astrocytes. Prior studies have shown that astrocytes are critically involved in maintaining the BBB, although their specific role in controlling permeability is not fully defined. One signaling pathway implicated in BBB homeostasis involves the Sonic Hedgehog (Shh) protein. However, recent evidence indicates that the pathway plays an unexpected and distinct role in regulating the BBB than has been previously suggested.
Our current work, and data from other labs, has revealed that the canonical Hedgehog (Hh) pathway is selectively active in a sub-population of resident astrocytes located in the gray matter (GM) of the adult mammalian CNS, as shown by the expression of *Gli1*, a Shh target gene and

pathway effector. These cells are distributed widely in the GM of the brain and spinal cord, but not the white matter, and extend endfoot processes to blood vessels. Transcriptome analysis of FACS isolated Gli1+ spinal cord cells shows specific enrichment of canonical Hh pathway transduction components including *Gli1*, *Gli2*, *Gli3*, and *Ptch1*, the receptor for Hh proteins. These observations indicate that Gli1+ cells possess a distinct molecular genetic identity that distinguishes them from other glial cell populations in this tissue, and also suggest that they have a unique function. Consistent with this, targeted genetic inactivation or pharmacologic inhibition of the Hh pathway in Gli1+ astrocytes in adult mice results in rapid but transient breakdown of the BBB, as indicated by extravasation of intravenously-injected tracers and other vascular proteins. Notably, this disruption appears to specifically affect transcytosis but not paracellular diffusion barriers. Together, these findings reveal a critical role for Hh signaling in a unique subset of protoplasmic, perivascular reactive astrocytes in the normal maintenance of the BBB. Furthermore, our studies clarify the role of the Hh pathway in regulating the BBB by demonstrating that signaling in astrocytes, but not other cells of the NVU, is primarily involved.

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Poster

677. Blood-Brain Barrier: Control and Mechanisms

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Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: University of Wisconsin- Madison School of Pharmacy
NIH National Centre for Advancing Translational Sciences (NIH UL1TR000427 and KL2TR00428)
NSF GRFP DGE-1256259
NIH fellowships (NRSA T32 EBO11434)

Title: Transport of macromolecules from CSF-to-brain: Biodistribution of endogenous IgG and intrathecal antibodies or oligonucleotides reveals the importance of perivascular pathways

Authors: B. WILKEN-RESMAN[1], *M. E. PIZZO[2], R. THORNE[2];
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Abstract: The specific mechanisms governing CSF-to-brain transport of large endogenous or exogenous macromolecules (e.g., 150 kDa antibodies and ~7-8 kDa antisense oligonucleotides (ASOs)) are currently not well understood, despite their importance for interpretation of ongoing clinical trials, understanding of approved therapeutics, and insight into physiological processes such as immune surveillance. Studies suggest that diffusion primarily governs transport in the

ISF-filled 40-60 nm wide brain extracellular spaces, but convective flow may occur in CSF compartments and perivascular spaces surrounding blood vessels. However, the anatomical boundaries of the PVS and its role in CSF/ISF exchange are only just beginning to emerge (Pizzo et al. J Physiol. 2018; Abbot et al. Acta Neuropath. 2018). Additional factors yet to be investigated may significantly alter the CSF-to-brain distribution of macromolecules, e.g., physicochemical characteristics, CSF protein binding, and binding to leptomeningeal fibroblast-like cells. Here, we intracisternally infused labeled macromolecules into the CSF of rats at a physiological flow rate and investigated the CNS distribution. *Ex vivo* fluorescence imaging of brain sections revealed: (i) striking perivascular transport throughout the brain indicating bulk flow and (ii) a gradient at the brain surface consistent with Fickian diffusion. ASOs with different chemical modification and sequences revealed unique differences in perivascular and diffusive signal for i) a fully phosphorothioated oligonucleotide, ii) a partially phosphorothioated ASO containing a 2'MOE modification, and iii) an ASO with neutral phosphorodiamidate morpholino (PMO) modifications. Thorough understanding of the mechanisms underlying antibody and ASO distribution in the brain and impact of molecular weight, sequence, binding, and electrostatic interactions are needed. Intrathecal antibodies and endogenous IgG were predominantly localized within the meninges and perivascular spaces around vessels of all calibre, with somewhat limited penetration into the brain parenchyma. Endogenous IgG distribution within the CNS closely resembled the distribution resulting from intrathecal application of labeled IgG, suggesting tracer biodistribution from the CSF to brain has additional relevance for understanding CSF:ISF exchange of endogenous proteins within the central compartment. Our results provide critical guidance for understanding and improving drug delivery of macromolecules as well as interpreting the results of clinical trials utilizing CSF injection and/or infusion paradigms.

Disclosures: B. Wilken-Resman: None. **M.E. Pizzo:** A. Employment/Salary (full or part-time):; Denali Therapeutics. **R. Thorne:** A. Employment/Salary (full or part-time):; Denali Therapeutics.

Poster

677. Blood-Brain Barrier: Control and Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 677.10/Q9

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: NIH R01DA040619
NIH T32DA007237

Title: Chronic exposure to electronic cigarettes or cigarette smoke causes BBB compromise and neuroinflammation in mice

Authors: *N. A. HELDT[1,2], S. GAJGHATE[1], A. SELIGA[1], M. WINFIELD[1], N. REICHENBACH[1], S. ROM[1,2], Y. PERSIDSKY[1,2];
[1]Dept. of Pathology and Lab. Med., [2]Ctr. for Substance Abuse Res., Lewis Katz Sch. of Med. At Temple Univ., Philadelphia, PA

Abstract: Electronic cigarette (EC) use has grown substantially since entry into the US market, particularly among adolescents and combustible tobacco users. Despite growing popularity and claims of harm reduction, the health effects of these products outside the lung is poorly understood. Several constituents of cigarette smoke (CS) with known neurovascular and inflammatory effects are present in EC liquids or formed during the generation of vapor. The present study characterizes the impact of EC exposure on neuroinflammation and blood-brain barrier (BBB) function, and provides comparison of outcomes with reference cigarette exposure normalized to comparable levels of nicotine delivery. Additionally, the contribution of nicotine to observed effects is elucidated through comparison with EC liquids which are verified to be nicotine-free. C57BL/6 mice are exposed to 2 hrs of daily EC vapor or CS, beginning at 8 wks of age. Changes in BBB gene expression are first characterized by whole exome sequencing of isolated brain microvessels following chronic (2 month) EC exposure. Several pro-inflammatory genes are upregulated following exposure including chemokines (Cxcl10, Ccl2), adhesion molecules (Icam1, Pecam1, E-Sel, P-Sel) and transcription factors (Nfatc3, Irf1). EC exposure increases BBB permeability to sodium fluorescein (by 30%) and alters localization of tight junction proteins occludin and claudin 5. Leukocyte - brain endothelia interactions are also impacted. Following intracerebroventricular administration of TNFalpha (mimicking encephalitis), leukocyte recruitment and adhesion to cerebral vasculature is 1.5-fold greater in mice exposed to EC compared with room air control. Lastly, we assess the impact on cognition and anxiety through several measures (novel object recognition, open field, plus-maze, Y-maze). No deficits in cognition or change in affective state are evident following EC exposure based on the outcomes measured, though novel object recognition is impaired following comparable CS exposure. The effects of EC are noted to be partly independent of nicotine content, suggesting that additional compounds within e-liquid or generated during vapor production are contributing to the observed BBB effect of EC. Based on our findings, long-term EC exposure compromises BBB function and induces neuroinflammation, although there is reduced neuroimmune impact when compared with a comparable dose of CS.

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Poster

677. Blood-Brain Barrier: Control and Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 677.11/Q10

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: F31 Grant 1F31NS110403-01

Title: What are the mechanisms of blood-brain barrier dysfunction in disease?

Authors: *C. P. PROFACI, K. BAJC, J. P. MILLER, T. Z. ZHANG, R. DANEMAN;
Univ. of California San Diego, La Jolla, CA

Abstract: The blood-brain barrier (BBB) is a set of properties unique to central nervous system (CNS) endothelial cells (ECs) that comprise the inner walls of blood vessels. In contrast to peripheral vessels, which allow extensive exchange of molecules and ions between the blood and tissue, CNS ECs exert tight control over what can enter the parenchyma. BBB dysfunction is a key component of many neurological conditions, including multiple sclerosis (MS), stroke, epilepsy, and traumatic brain injury (TBI). Despite the vastly different triggers of these diseases, in each case vascular permeability causes an influx of blood-borne molecules, disruption of ionic homeostasis, and an increase in immune cell extravasation. These events contribute to the dysfunction, damage, and even degeneration of neurons, ultimately worsening clinical outcomes. Identifying common molecular changes in ECs during disease could point towards a therapeutic target for reducing BBB dysfunction in wide range of neurological diseases.
To investigate the molecular changes occurring in CNS ECs during disease, we isolated ECs from four disease models during BBB dysfunction and performed RNA sequencing. A set of 198 genes was upregulated across multiple conditions, suggesting a common pathway for BBB dysfunction regardless of the trigger of disease. To further probe this BBB dysfunction pathway, I focused on Pdlim1, a cytoplasmic protein previously unexplored in the context of the BBB. Pdlim1 is not expressed in healthy CNS ECs, but its expression is upregulated in ECs across all four disease models, exclusively in regions of BBB permeability. To manipulate Pdlim1 expression *in vivo*, I created a mouse line that overexpresses Pdlim1 in ECs. I found that overexpressing endothelial Pdlim1 is protective in a model of multiple sclerosis. To further probe the mechanistic role of Pdlim1, I isolated endothelial cells from control and transgenic mice and performed RNA sequencing to determine how overexpression of Pdlim1 affects the transcriptional profile of CNS ECs.

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Poster

677. Blood-Brain Barrier: Control and Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 677.12/Q11

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: NIH R01 NR-015038

Title: Blood brain barrier contributing to brain changes in patients with obstructive sleep apnea

Authors: *L. EHLERT[1], B. ROY[1], E. DANIEL[1], M. LAI[1], D. KANG[2], R. AYSOLA[2], E. WEN[2], M. WOO[3], R. M. HARPER[4], R. KUMAR[1];
[1]Anesthesiol., [2]Med., [3]Sch. of Nursing, [4]Neurobio., Univ. of California at Los Angeles, Los Angeles, CA

Abstract: Obstructive sleep apnea (OSA) patients show brain damage in sites that control autonomic, cognitive, and mood functions, as well as compromised blood brain barrier (BBB) function in global gray and white matter areas. However, it is unclear whether altered BBB function in OSA subjects contributes to brain changes in the condition. Our aim was to examine relationships between regional brain changes and BBB integrity in OSA subjects. We acquired diffusion tensor imaging (DTI) and diffusion-weighted pseudo-continuous arterial spin labeling (DW-pCASL) data from 14 treatment-naïve OSA subjects (age 43.75±9.11 years; AHI 36.2±20.6 events/hour; 8 males) using a 3.0-Tesla MRI scanner. Using DTI data, whole-brain mean diffusivity (MD, indicative of brain changes) maps were calculated, normalized to a common space, and smoothed. Using DW-pCASL data, whole-brain BBB indices were calculated. The smoothed MD maps were used to examine relationships between regional brain changes and BBB integrity in OSA subjects with partial correlation procedures (SPM12; covariates, age and sex; uncorrected $p<0.005$). Significant positive correlations emerged between brain changes and BBB indices in the cerebellum, medulla, pons, vermis, temporal gyrus, frontal gyrus, prefrontal gyrus, lingual gyrus, insula, para-hippocampus, and anterior, mid, and posterior cingulate, and negative correlations in selective cerebellar, temporal, and frontal areas. Newly-diagnosed, treatment-naïve OSA subjects show significant correlations between regional brain changes and BBB integrity in various sites involved in autonomic, mood, and cognition functions. The findings indicate that alterations in the BBB function may play a crucial role in the development of brain injury in the condition.

Disclosures: L. Ehlert: 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 R01 NR-015038. **B. Roy:** None. **E. Daniel:** None. **M. Lai:** None. **D. Kang:** None. **R. Aysola:** None. **E. Wen:** None. **M. Woo:** None. **R.M. Harper:** None. **R. Kumar:** None.

Poster

677. Blood-Brain Barrier: Control and Mechanisms

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Topic: I.06. Computation/ Modeling/ and Simulation

Support: The Beijing Brain Initiative of Beijing Municipal Science & Technology Commission (Z181100001518004)
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National Major Scientific Research Instrument Development Project (No. 61827808)
Peking University Clinical Scientist Program （BMU2019LCKXJ007）

Title: Research of brain extracellular space in China

Authors: *H. HAN[1,2];
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Abstract: Brain extracellular space (ECS) provides the immediate living environment for neural cells and accounts for approximately 15%-20% of the total volume of living brain. 25 years ago, as an interventional radiologist, the author was engaged in studying the early diagnosis and treatment of cerebral ischemic stroke, the parameter of brain ECS was firstly derived from the raw data of calculating the BBB permeability in the cerebral ischemic region in 2004. Since then, the author and his team have been working on developing novel measuring method of ECS: tracer-based MRI, which can measure brain ECS parameters in the whole brain scale and make the dynamic drainage process of the brain interstitial fluid (ISF) drainage visualized. By using the new method, the team discovered a new division system in the brain, named regionalized ISF drainage system. The ISF in the caudate nucleus can drain to ipsilateral cortex and finally into the subarachnoid space, which maintained the pathway of ISF- cerebrospinal fluid (CSF) exchange. However, the ISF in the thalamus was eliminated locally in its anatomical division. After verifying the nature of the barrier structure between different drainage divisions, the author proposed the hypothesis of "regionalized brain homeostasis". Thus, we demonstrate that the brain is protected not only by the BBB, which avoids potential exogenous damage through the vascular system, but is also protected by an internal ISF drainage barrier to avoid potentially harmful interference from other ECS divisions in the deep brain. Together with findings on the drainage route of ISF-cerebrospinal fluid (CSF) and the CSF-lymph system by the other research groups, a more detailed picture of ISF drainage pathways in the whole brain can be built. With the new findings and the proposed hypothesis, an innovative therapeutic method for the treatment of encephalopathy with local drug delivery via the brain ECS pathway has been established. In present, the above new method and the findings have been applied in the field of neuroscience, new drug development, development, aging, aerospace medicine and new artificial neural network modeling.

Disclosures: H. Han: None.

Poster

678. Sleep Mechanisms and Function

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 678.01/Q13

Topic: F.08. Biological Rhythms and Sleep

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Title: Identification of vigilance states in freely behaving animals using thalamocortical activity and Deep Belief networks

Authors: *J. HARROD[1], P. L. PURDON[2], E. N. BROWN[4], F. J. FLORES[3];
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Abstract: Identifying the relationships between behavioral and neural activity lies at the core of neuroscience research. In controlled experiments, the behavior can be constrained without ambiguity by the experimental setup. However, there are situations where this relationship must be inferred in freely behaving animals. This is particularly true in studies that require the identification of vigilance states, such as active wakefulness or non-REM sleep. This task is often carried out by experimenters, based on protocols and guidelines developed to reduce bias and variability. However, the variability between the states identified by different experimenters for the same dataset can be as high as 80 %. Therefore, it is highly desirable to have a method that can aid the researchers to discover patterns on the electrophysiological activity and assign them to vigilance states. While many procedures have been proposed in this direction, the recent developments in artificial neural networks offer a new and powerful methodology to address this problem. Here we aim to develop a robust deep learning classifier/labeling system for raw thalamocortical data. We implanted male Sprague-Dawley rats, weighing between 500-700 g, with depth electrodes aiming at prefrontal cortex and anterior thalamus, and recorded neural activity while allowing the animals to freely behave in a home cage. The raw traces were segmented into two-second windows, and each window was labeled visually by three researchers to build the training set. In order to perform sleep classification, we trained a supervised DBN (Deep Belief Network) based on binary Restricted Boltzmann Machines (RBMs) with a top-layer linear classifier. The RBMs were trained for 20 epochs with a 100x100 hidden layer structure and a learning rate of 1. The top-layer linear classifier was then trained for 150 epochs with a learning rate of $1x10^{-3}$and 20% dropout. Training and test data was divided using an 80/20 split, for a total of 170 epochs with a batch size of 16. This model achieved a 5-fold cross-validation

accuracy greater than 90% on the dataset. Training the model took less than 300 seconds on average across the 5-fold cross-validation. Based on this performance, we have demonstrated that it is possible to implement and train a deep learning model to high accuracies on rodent thalamocortical data for the identification of vigilance states. Also, the training time required to achieve this high performance suggests that this model might be easily trained to similar performance levels on other rodent datasets.

Disclosures: **J. Harrod:** None. **P.L. Purdon:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inventor on patents pending on brain monitoring technologies assigned to Massachusetts General Hospital, Inventor on a patent assigned to Massachusetts General Hospital and licensed non-exclusively to Masimo Corporation, Co-Founder of PASCALL Systems, Inc., a start-up company developing closed-loop physiological control systems. **E.N. Brown:** A. Employment/Salary (full or part-time):; MGH and MIT. 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 R01 GM104948, NIH P01GM118269, the Department of Anesthesia, Critical Care and Pain Medicine,Massachusetts General Hospital, Boston, MA, The Picower Institute for Learning and Memory, Massachusetts Institute of Technology, Cambridge, MA.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Massachusetts General Hospital has licensed intellectual property for EEG monitoring developed by Drs. Brown and Purdon to Masimo. Drs. Brown and Purdon hold interests in PASCALL, a start-up company., Drs. Brown and Purdon hold interests in PASCALL, a start-up company developing EEG-based anesthetic state control systems for anesthesiology. **F.J. Flores:** A. Employment/Salary (full or part-time):; Massachusetts General Hospital.

Poster

678. Sleep Mechanisms and Function

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Title: Interhemispheric connectivity during sleep arousals measured by scalp EEG

Authors: *J. V. LIU, H. K. YAGGI;
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Abstract: Introduction: During sleep, arousals occur spontaneously and are identified by the transient increases of high-frequency (8-45 Hz) signals in the scalp EEG. It is clinically important to identify and score arousals in sleep studies (polysomnographies), because frequent arousals are associated with sleep fragmentation and poor sleep quality. Here we investigated the transient changes of interhemispheric connectivity during sleep arousals to provide new insights into the neural mechanisms of sleep arousals.
Methods: We analyzed polysomnography data from the MrOS study on 1000 community-dwelling elderly men (http://sleepdata.org). This dataset was chosen because EEG signals from both hemispheres (C3-A1 and C4-A2) were measured. The EEG signals were decomposed into five frequency bands (delta: 1-4; theta: 4-8; alpha: 8-13; beta: 13-25; gamma: 25-45 Hz), and the EEG power (amplitude) as well as the interhemispheric EEG coherence were computed for each frequency band, at a high temporal resolution by using a 10-second sliding time window.
Results: During arousals, EEG powers in high-frequency bands (8-45 Hz) showed transient increases, maximizing to 1.5-2.0 times the baselines at around 10 seconds after arousal onset. In contrast, the interhemispheric EEG coherence in alpha and beta bands did not significantly change during arousals. The interhemispheric EEG coherence in delta, theta and gamma bands all had significant transient decreases during arousals, and the decreases were larger during rapid eye movement (REM) sleep than during non-REM sleep. Remarkably, the transient increases in EEG powers in the gamma band (highest frequency) were strongly correlated with the transient decreases in the interhemispheric EEG coherence in the delta band (lowest frequency) across subjects. **Conclusions:** During sleep arousals, there are transient decreases in the interhemispheric connectivity that are most significant in the delta band (slow wave frequency) of EEG, and are strongly associated with the transient increases in high-frequency EEG powers. We hypothesize that both the interhemispheric connectivity decrease and the high-frequency EEG power increase are driven by disruptions to the thalamocortical oscillations during sleep arousals.

Disclosures: J.V. Liu: None. **H.K. Yaggi:** None.

Poster

678. Sleep Mechanisms and Function

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Title: Competing roles of slow waves and delta waves on memory consolidation

Authors: *K. GANGULY[1], T. GULATI[2], J. K. KIM[3];
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Abstract: Sleep has been implicated in both selective memory consolidation as well as forgetting of memories after prolonged awake periods. However, it is unclear what physiological process governs the fundamental balance between memory strengthening and weakening. Here we specifically tested how activity-dependent processing during sleep might differentially regulate these two likely competing processes. We specifically examined how neural reactivations during NREM sleep are causally linked to strengthening versus forgetting of the "motor memory" of novel skills gained through practice. We specifically recorded populations of neurons in the primary motor cortex of rats while they were trained on a brain machine interface (BMI) task and subsequent sleep. Strikingly, we found that high amplitude slow-waves (SW; <4 Hz) and delta-waves (δ; 1-4 Hz) have dissociable and competing roles in memory consolidation during sleep. By modulating cortical spiking linked exclusively to SW or δ using closed-loop optogenetic methods, we could respectively weaken or strengthen memory reactivations and thereby bidirectionally modulate sleep-dependent performance gains. We further found that changes in the precise temporal coupling of spindles (10-14 Hz) to SW could account for such effects. Thus, our results indicate that neural activity driven by SW and δ may have competing roles during sleep-dependent memory processing.

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Poster

678. Sleep Mechanisms and Function

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Title: Sleep attenuates late neuronal auditory responses in rat perirhinal cortex

Authors: *Y. SELA[1], A. J. KROM[2,3], L. BERGMAN[2], N. REGEV[2], Y. NIR[1,2];
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Abstract: How behavioral states affect sensory processing remains unclear. Sleep entails reduced behavioral responsiveness to external stimuli, but its effects on sensory pathways remain elusive. Previous work established that, contrary to the classical "thalamic gating" notion, responses in primary auditory cortex (PAC) are comparable across wakefulness and sleep. We hypothesized that robust differences emerge downstream in higher-order regions, and tested this by comparing auditory responses across wakefulness and sleep in PAC (n=7) and rhinal cortex (RC, n=9). To monitor PAC and RC activity, 16/32-channel microwire arrays were implanted into the temporal lobe of ten adult rats. Epidural EEG, EMG, and video were used for sleep scoring. After recovery, sleep stabilization, and habituation to stimulation, acoustic stimuli (pure tones, band-limited noise, click-trains, and ultrasonic vocalizations) were presented in a soundproofed environment to freely-moving rats. Sleep scoring (4s epochs) and spike sorting were performed offline. We isolated 485 neuronal clusters (203 in PAC, 282 in RC, 79% were auditory responsive), and divided them according to response latency to 'early responders' (<20ms, prominent in PAC) vs. 'late responders' (with typical latencies around 40-80ms, prominent in RC). Early-responding units responded similarly across wakefulness, NREM sleep, and REM sleep (5-12% attenuation), replicating previous reports. In contrast, late-responding units exhibited robust attenuation during NREM sleep (median: 44% reduction) and a significant - albeit more modest - attenuation during REM sleep (median: 33% reduction). Late auditory responses beyond PAC are significantly attenuated during sleep, possibly reflecting a disruption in inter-cortical signaling and/or 'fading out' of response fidelity with accumulating propagation. Differential RC responses during sleep pave the way to dissecting the underlying mechanisms.

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Poster

678. Sleep Mechanisms and Function

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Support: NIAAA IRP (Y01AA3009)
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Title: Chronic sleep deprivation and circadian disruptions differently affect the brain's resting state functional connectivity, impulsivity and attentional performance

Authors: *R. ZHANG[1], D. TOMASI[1], E. SHOKRI-KOJORI[1], C. E. WIERS[1], G.-J. WANG[1], N. D. VOLKOW[1,2];
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Abstract: Chronic sleep deprivation and disruption of circadian rhythms can impair brain function and cognitive performance. But limited studies have investigated the effect of chronic sleep deprivation and mild circadian disruptions associated with daily work life. In this study, we examined the effect of work-related chronic sleep restrictions and circadian alterations on attention and impulsivity and how it relates to changes in resting-state functional connectivity (RSFC).
Fifty-six (43.9 ± 13.6 years, 26 male) healthy subjects participated in this study. The work-related sleep deprivation and the circadian rhythm were assessed by the differences between weekdays and weekend days in terms of sleep duration and sleep midpoint using one-week actigraphy data. All subjects underwent 3Tesla BOLD-fMRI in resting-state conditions (eyes open; 15 min). We examined the correlation between weekday-weekend variation in RSFC, as well as impulsiveness and attentional performances assessed by Barratt Impulsiveness Scale (BIS), and the accuracy and reaction time during a visual attention task (VAT).
We found that weekday-weekend variation in sleep duration and sleep midpoint were independent of each other and differently affected RSFC and behavior. Regarding sleep duration, larger differences between weekdays and weekend were associated with lower cognitive complexity, a BIS subscale. Subjects with larger variation had lower RSFC within the default mode network (DMN), higher RSFC between the salience network (SN) and the DMN, and lower RSFC between the frontoparietal network (FPN) and the inferior frontal gyrus (IFG). In contrast, referring to sleep midpoint higher weekday-weekend variation was associated with worse attentional performance in VAT and lower RSFC between SN and occipital cortex, and with overall lower thalamocortical RSFC especially between thalamus and frontal cortex. Our findings suggest that sleep deprivation and circadian disruptions differently affect functional networks (DMN, SN FPN) modulated by dopamine. As sleep deprivation and changes of circadian rhythms are often confounded with each other, it's essential for future studies to identify their specific contributions to RSFC and its relation to performance.

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Poster

678. Sleep Mechanisms and Function

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Title: Interlinked electrophysiological, hemodynamic, and cerebrospinal fluid oscillations appear in the human brain during sleep

Authors: N. FULTZ[1], G. BONMASSAR[2], K. SETSOMPOP[3], R. STICKGOLD[4], B. R. ROSEN[5], J. R. POLIMENI[6], ***L. D. LEWIS**[1];
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Abstract: Sleep is essential for both cognition and physiological maintenance of healthy brain function. During sleep, slow waves in neural activity contribute to memory consolidation, and cerebrospinal fluid (CSF) clearance of metabolic waste products from the brain is increased. Whether these two processes are related is not known. We exploited recently developed techniques for accelerated multimodal neuroimaging to simultaneously measure CSF flow, blood-oxygenation-level-dependent (BOLD) signals, and neural dynamics in the human brain. We studied thirteen subjects at 3 Tesla using fast fMRI (TR<400 ms) and EEG as they fell asleep in the scanner. We discovered a large oscillation in CSF flow that appears during non-rapid eye movement (NREM) sleep. This CSF oscillation was tightly locked to a coherent pattern of oscillating electrophysiological and hemodynamic signals: neural slow waves were followed by oscillations in the vasculature, respiration, and CSF flow. We next hypothesized a potential mechanism: as broadly coherent low-frequency neural signals increase in NREM sleep, they induce cerebral blood volume changes locked to neural activity, throughout the cortical gray matter. This large-scale contraction and expansion of total brain tissue volume in turn draws CSF into and out of the head, due to constant intracranial volume. Using a biophysical model, we found that the coupled timing of these oscillations was consistent with a model in which increased slow waves of coherent neural activity drive blood volume decreases, which then induces pulsatile CSF inflow on a macroscopic scale. These findings suggest that the low-frequency neural activity that defines NREM may also enhance clearance of metabolic waste products from the brain, due to increased mixing and clearance of solutes generated by these CSF waves. Our results therefore suggest that the cognitive and physiological effects of sleep are linked through coupled oscillatory neural, vascular, and mechanical processes.

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Poster

678. Sleep Mechanisms and Function

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Title: Ancestral neural signatures of sleep

Authors: *L. C. LEUNG[1], G. X. WANG[1], R. MADELAINE[1], G. SKARIAH[1], K. KAWAKAMI[4], K. DEISSEROTH[2], A. E. URBAN[3], P. MOURRAIN[1];
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Abstract: While slow wave sleep (SWS) and paradoxical/rapid eye movement sleep (PS/REM) have been found in mammals, birds and lizards, it is unclear whether these neuronal signatures are found in the non-amniotic animals that comprise about half of all vertebrate species. Although a bona-fide sleep state has been well established in adult and larval zebrafish through behavioral criteria, it is unknown whether the lack of an expanded neocortex precludes the expression of these signatures and whether a common functional significance of such sleep patterns exists across vertebrates. To delve into such questions, we developed a non-invasive fluorescence-based polysomnography (fPSG) for the teleost vertebrate zebrafish, leveraging its optical clarity, compact size, linear rostrocaudal brain organization as well as the conservation of sleep neurochemistry. Through unbiased, brain-wide Ca^{2+} imaging coupled with assessment of eye movement, muscle dynamics and heart rate, we report two major sleep signatures: Slow Bursting Sleep (SBS) and Propagating Wave Sleep (PWS) which share commonalities with SWS and PS/REM states, respectively. In contrast to desynchronous activity during wake, SBS is characterized by oscillating synchronous dorsal pallium activity coupled with reduced muscle, eye and heart activity, while PWS features brain-wide travelling waves leading to muscle atonia, loss of eye movement and heart arrhythmia. Our live imaging data also identifies for the first time a potential role for ependymal cell activation as an initial event in the transition to sleep dynamics. We also found that fish ependymal cells are activated by melanin-concentrating hormone (MCH), a neuropeptide implicated in mammalian PS/REM, but whose sleep role in fishes has been debated since its 1983 discovery in salmon when its eponymous pigmentation

role was revealed. We show that MCH signalling bears both pigmentation and sleep regulatory roles consistent with our previous finding that zebrafish MCH2 is the true orthologue of the mammalian MCH gene. As such, MCH signal disruption in the fish leads to a dramatic reduction in behavioural sleep quantity and perturbs the generation of PWS signatures. Together, the observations of SWS- and PS-like neural and muscular activities in a teleost suggest that common neural signatures of sleep may have emerged in the vertebrate brain over 450 million years ago.

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Poster

678. Sleep Mechanisms and Function

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Topic: F.08. Biological Rhythms and Sleep

Title: Dynamic alterations in spontaneous neural activity at the sleep onset period: A simultaneous EEG-fMRI study

Authors: *T. ISHII[1], T. KOIKE[2], E. NAKAGAWA[2], M. SUMIYA[2], T. ASO[1], N. SADATO[2]; [1]Human Brain Res. Center, Kyoto Univ. Grad. Sch. of Med., Kyoto, Japan; [2]Natl. Inst. for Physiological Sci., Okazaki, Japan

Abstract: The sleep onset period, involving so-called stage N1 sleep largely, is characterized by a reduction in the amount of alpha activity and the appearance of slower theta waves compared to wakefulness. Various kinds of physiological and psychological changes are also apparent, such as slow eye movements, changes in muscle tonus and the hypnagogic dream-like mentation. Because of these diverse changes, the definition of the sleep onset period itself has still been the object of much discussion. These phenomena are thought to be the reflection of dynamic alterations in the brain during the transition period, however, details of these changes have still been uncovered. Here, we aimed to investigate a dynamic shift in the brain activity at sleep onset using the method of EEG-fMRI simultaneous recording. Seventeen healthy subjects (9 females, 21.8±2.5 years) participated in the study. Simultaneous EEG/fMRI recording was performed during an hour's nap in a 3T-MRI scanner. An MR-compatible EEG system placed according to the international 10/20 electrode system was used for polysomnographic recordings. Real-time online monitoring of EEG was performed by experimenters outside a scanner room. To record the transition period between awake and sleep multiple times during a session, an experimenter inside a scanner room touched a subject's foot for inducing arousal when a shift to NREM sleep stage 1 was observed. After corrections for gradient-induced and cardioballistic artifacts, EEG data were scored according to the AASM criteria in 30s epochs. Based on sleep stages defined

by polysomnographic findings, we examined changes in brain activation patterns between stages and performed functional connectivity analyses of fMRI data. The activation of the thalamus and basal ganglia significantly reduced during NREM sleep stage 1 compared with stage W ($\alpha <$ 0.05, corrected). Functional connectivity analyses revealed that connectivity between the thalamus and cortical regions reduced sharply in the descent to sleep stage. Meanwhile, cortico-cortical connectivity including the default mode network maintained at the sleep onset period. Our data support the hypothesis that reduced thalamocortical connectivity which leads to limit the capacity of the brain to integrate information is associated with the transition of consciousness at sleep onset. The present findings also suggest that intrinsic BOLD fluctuations do not necessarily reflect conscious mentation.

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Poster

678. Sleep Mechanisms and Function

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Title: Firing dynamics of identified parietal cortical pyramidal cells and interneurons in nonREM sleep

Authors: *S. BORDÉ, R. G. AVERKIN, J. HORVÁTH, V. DASHKOVSKYI, B. BOZSÓ, V. SZEMENYEI, G. TAMAS;
Univ. of Szeged, Szeged, Hungary

Abstract: The nonREM sleep is characterized by interchanging periods of up (active) and down (silent) states which appear in packets separated by short microarousals or by REM sleep episodes. Temporal progression of nonREM packets is characterized by an increase in the power of spindle band oscillations in the cortex together with a surge in the activity of low-firing putative pyramidal neurons, while high-firing putative pyramidal cells and fast-firing putative interneurons decrease their activity (Watson et al., 2016). However, the high-firing and fast-firing neurons might include several cell classes with unknown contribution to sleep packets. To reveal the firing dynamics of anatomically identified pyramidal cells (PCs), fast spiking interneurons (FSIs) and regular spiking interneurons (RSIs) during nonREM sleep, we applied juxtacellular recording and labelling of parietal cortical neurons during natural sleep in Wistar rats (Averkin et al., 2016). Deep layer PCs and layer 3 PCs were more active compared to layer 2

PCs with sporadic firing encompassing nonREM packets. The firing of deep and superficial layer FSIs had the highest frequency which gradually increased as nonREM packets progressed and this was in correlation with an increasing power of spindle frequency band network oscillations. Cell to cell variability was found in the firing of RSIs with increasing, decreasing or stable firing rates during nonREM packets. Contribution to successive spindles during the timecourse of nonREM packets was cell class dependent, with only a subpopulation of FSIs with spindle trough related firing showing a change by increasing firing. Firing around the end of the delta waves (down-to-up state transitions) started with a peak of FSI activity followed by different classes of PCs and RSIs and the order of peak firing latencies for cell classes remained stable during of nonREM packets. In conclusion, cell class specific shifts in relative firing contribution might characterize nonREM sleep packets and ongoing spindle oscillations.

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Poster

678. Sleep Mechanisms and Function

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Title: Functionally related brain areas exhibit a higher proportion of simultaneous sleep spindles

Authors: *F. KATSUKI, J. T. MCKENNA, Y. BOLORTUYA, J. M. MCNALLY, R. E. BROWN;
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Abstract: Abnormalities in sleep spindles, 10-15 Hz waxing-and-waning cortical electrical oscillations observed in non-rapid-eye-movement (NREM) sleep, have been reported in patients with various neuropathological conditions, most notably schizophrenia, and may contribute to deficits in memory consolidation. However, much remains to be learned about the functional role of spindles in memory formation. Sleep spindles are known to be distributed heterogeneously among cortical and subcortical regions both in humans and rodents. Here, we hypothesized that

anatomically and functionally related brain areas would exhibit more common spindle events, providing a possible substrate for associative synaptic plasticity. To test this hypothesis, we recorded local field potentials (LFP) simultaneously from different regions and assessed what proportion of the spindles detected in different areas were common events.
LFP recordings were performed in wild-type mice (C57BL6J). Two LFP electrodes were implanted in each mouse with a different combinations of brain regions: 1) Secondary motor cortex (M2) bilaterally (N=4), 2) Prelimbic cortex (PrL) and Dorsomedial striatum (DMS) ipsilaterally (N=4), a corticostriatal circuit involved in goal-directed behavior and cognitive flexibility; and two cortical areas with less robust connectivity, 3) M2 and PrL ipsilaterally (N=4), and 4) M2 and Infralimbic cortex (IL) ipsilaterally (N=4). Eight hours of data during the light phase was analyzed. A MATLAB-based offline automated sleep spindle detection algorithm was used to detect NREM sleep spindles in each electrode (Uygun et al., 2018). Detected spindles in each electrode were then compared between electrodes within each animal to identify spindle events that occurred simultaneously in both areas ("common" spindles with >90% duration overlap).
Average percentages of common spindle events between areas were: 58±13% between bilateral M2, 42±5% between PrL and DMS, 21±1% between M2 and PrL, and 23±4% between M2 and IL. Thus, consistent with our hypothesis, anatomically and functionally-related brain areas showed a higher proportion of common spindles (bilateral M2 recordings and PrL-DMS) than those areas with less strong connectivity (M2-PrL and M2-IL). However, even functionally and anatomically separated pairs exhibited ~20% common spindles, possibly representing "global" spindles.
Further investigation of the proportion of common/uncommon spindles in functionally-related brain areas following training on behavioral tasks may provide mechanistic insights into how and whether sleep spindles facilitate synaptic plasticity and memory consolidation.

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Poster

678. Sleep Mechanisms and Function

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Program #/Poster #: 678.11/R5

Topic: F.08. Biological Rhythms and Sleep

Support: Veterans Health Administration, Rehabilitation Research and Development Service 1I01RX001640

National Institute of Neurological Disorders and Stroke 5K02NS093014
American Heart & Stroke Association Predoctoral Fellowship 17PRE33410530

Title: Cortical sleep rhythms drive coordinated corticostriatal activity during motor skill learning

Authors: *S. M. LEMKE[1], D. RAMANATHAN[2], K. GANGULY[1];
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Abstract: Specific rhythms of neural activity in motor cortex during sleep are known to play a role in motor skill learning. These rhythms, including sleep spindles and slow oscillations, are believed to drive plasticity critical for the increased speed, consistency, and efficiency of movements that characterize skill learning. While we also know that inter-area plasticity is required to learn motor skills, whether such plasticity is driven by sleep rhythms remains unknown.
Plasticity in the projections from primary motor cortex (M1) to the dorsolateral striatum (DLS) is central to motor skill learning. Here, we recorded neural activity across M1 and DLS in rats to investigate whether activity patterns during sleep play a role in motor skill learning. We hypothesized that during sleep after training, sleep spindles and slow oscillations in M1 drive coordinated activity across M1 and DLS and that this activity plays a role in shaping the corticostriatal projections critical for skill learning.
To test this, we classified sleep spindles and slow oscillations in M1 during slow wave sleep after training and show that, in fact, M1 sleep rhythms drive coordinated activity across M1 and DLS. We show that M1 and DLS modulation during spindles is increased when spindles are nested in slow oscillations and that these nested spindle events are uniquely related to offline improvements in performance. This work aims to establish a role of sleep in driving interarea plasticity during motor skill learning.

Disclosures: S.M. Lemke: None. **D. Ramanathan:** None. **K. Ganguly:** None.

Poster

678. Sleep Mechanisms and Function

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 678.12/R6

Topic: F.08. Biological Rhythms and Sleep

Support: NIH Grant R00MH111748

Title: Decoding electrophysiological arousal state from fast fMRI data

Authors: *S. D. WILLIAMS[1], U. AGRAWAL[3], J. CHEN[4], B. SETZER[2], N. FULTZ[4,2], L. D. LEWIS[2];

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Abstract: During changes in arousal, the brain undergoes shifts in dynamics that can be either global or confined to local cortical regions. For example, slow wave oscillations can appear in one cortical area but not in another, termed local sleep. Tracking these local changes in arousal with high spatial and temporal resolution could clarify how arousal-related changes in dynamics affect neural computation and cognitive function. Here we estimate arousal levels from fMRI signals alone, suggesting that fMRI dynamics in local brain regions contain information about arousal. We leveraged technological advances in fMRI that have enabled subsecond whole brain imaging with concurrent EEG. The fast image acquisition allowed us to directly measure and localize low-frequency oscillations (0.1-1 Hz) in the fMRI signals. We imaged 12 subjects as they transitioned between wakefulness and sleep inside the scanner. We collected simultaneous EEG-fMRI (TR=367 milliseconds) data from the subjects in two sessions, a sleep-restricted (4 hours of sleep) session and a well-rested (at least 6 hours of sleep) session. We estimated arousal state from the spectral dynamics of the EEG signals, and then built a Random Forest (RF) model that predicts EEG arousal from the fMRI data alone. We extracted several features from the fMRI data, including percent signal change, 0.1-1 Hz power, and temporally-lagged versions of the features. We used our RF model to (1) characterize the minimal features necessary to extract from fMRI data in order to accurately predict arousal state, and (2) estimate the individual contribution of each feature using the importance scores generated by the RF model. We find that (1) an RF model trained on dynamics extracted from a local cortical region (volume: 5% of cortical grey matter) generates above-chance predictions of EEG arousal in novel subjects, and (2) both the amplitude and frequency content of fMRI signals contribute to this prediction, rather than only a single feature type. Our findings are consistent with previous work showing that arousal can be decoded from information contained in fMRI, and further show unique contributions of time-varying fMRI dynamics. In addition, our results demonstrate the feasibility of predicting arousal state using a model trained only on data from a single cortical region. This work suggests that temporally-varying fMRI dynamics in local brain regions can be used to track fluctuations in arousal state.

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Poster

678. Sleep Mechanisms and Function

Location: Hall A

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Program #/Poster #: 678.13/R7

Topic: F.08. Biological Rhythms and Sleep

Support: Universidad Nacional Autónoma de México, PAPIIT: IA208018

Title: Temporal organization of brain electrical activity in obstructive sleep apnea: Sex differences

Authors: *Z. MUNOZ-TORRES[1,2], U. JIMÉNEZ-CORREA[3];
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Abstract: Obstructive sleep apnea (OSA) is a syndrome characterized by repetitive cessation (apnea) or reductions (hypopnea) of breathing during sleep. OSA is associated with snoring, sleep fragmentation, nocturnal hypoxemia, excessive daytime sleepiness, cognitive difficulties and depressive and anxiety symptoms. Epidemiologic studies have consistently shown a male predominance of OSA. Hormonal differences, breathing control, upper airway anatomy and fat distribution have been described as causes of the sexual differences in OSA. Additionally, clinic manifestations are more accentuated in men than in women, but white matter structural integrity is more affected in women than men. To our knowledge, there has been no previous studies exploring gender differences in electrical brain activity features of OSA. To determine differences in temporal organization of brain activity between genders across sleep and wakefulness in two different severity levels of OSA, polysomnography was performed in 45 patients with untreated OSA (22 women and 23 men) and power spectral density (1-50 Hz) was compared between groups. OSA men during sleep showed lower power spectral density of fast frequencies than women. Men with severe OSA in comparison to moderate, showed lower Sigma power during Non-REM, and higher Delta frequencies during REM sleep. In contrast, women groups (severe/moderate) did not show significant differences in power. The group of severe apnea was characterized by lower power during wakefulness of Beta and higher power of Delta during REM sleep. These findings contribute to providing alternative explanations for some of the gender differences in OSA. While the diagnosis is the same for men and women, the evolution of the syndrome induces substantial differences in the oscillatory brain activity. This study emphasizes the importance of understanding the differential effects on men and women of sleep disorders, and thereby achieve better knowledge of the underlying neural mechanisms in order to improve therapeutic outcomes.

Disclosures: Z. Munoz-Torres: None. **U. Jiménez-Correa:** None.

Poster

678. Sleep Mechanisms and Function

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 678.14/R8

Topic: F.08. Biological Rhythms and Sleep

Support: NSERC Discovery Grant to BLM and MT
AHFMR Polaris Award to BLM

Title: Strong cortical activation of task related neural activity during REM and SWS sleep precedes rapid learning of a motor skill

Authors: M. J. ECKERT[1], B. L. MCNAUGHTON[1,2], ***M. TATSUNO**[1];
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Abstract: Neural activity during rest is hypothesized to participate in the consolidation of memory traces. Many studies have demonstrated that neural activity recorded during performance on a behavioral task is replayed during subsequent rest and sleep. Approximately 1 hour (or less) of rest following training is typically recorded in such studies, and these data often show reactivation during SWS that is initially strong but decays within 1/2 to 1 hour. Pre-play of neural activity prior to a task or experience has also been demonstrated, although support for pre-play is not consistent. To date there is little evidence for replay or pre-play during REM sleep, with the exception of one study, which showed pre-play (Louie and Wilson, 2001). This is surprising given that behavioral studies support a role for REM sleep in the consolidation of motor skill learning in particular. We provide evidence that activation of task related neural activity patterns occurs during pre-task REM sleep as well as post-task SWS in rats learning a novel motor skill. We implanted 5 rats with tetrode arrays in the forelimb region of primary motor cortex and recorded single-unit activity on a single pellet reaching task. Daily recordings included a 3 hr pre-task sleep period, 30 min training on the reaching task, and 3 hr post-task sleep. Rats were naive to the task at the start of recording (except a brief test of paw preference) and daily recordings continued until they reached asymptotic levels of performance. Two of the rats showed rapid learning on the task, becoming very skilled within 5-6 days. The other three rats exhibited a slower and more variable gain in proficiency across 2 weeks, although they ultimately achieved success rates similar to the rapid learners. The first principal component of reach related activity (Peyrache et al., 2009) exhibited activation during both SWS and REM sleep. SWS activation was strongest immediately following the training session and was associated with spindle oscillations. REM activation was strongest in pre-task sleep and was accompanied by an increase in the amount of pre-task REM sleep. In the rapid learning rats, the strongest REM and SWS activation co-occurred on days just prior to large performance gains, whereas strong REM and SWS activation was more distributed across training days in gradual learning rats. Pre-task REM activation and post-task SWS activation were both significantly associated with neck EMG activity. Our data suggest that coordinated REM and SWS activation facilitates rapid skill learning, and further suggest a possible evolution of sleep activation of task activity that is initially stronger in SWS and later becomes stronger in REM sleep.

Disclosures: M.J. Eckert: None. **B.L. McNaughton:** None. **M. Tatsuno:** None.

Poster

678. Sleep Mechanisms and Function

Location: Hall A

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Program #/Poster #: 678.15/R9

Topic: F.08. Biological Rhythms and Sleep

Title: Modulation of the cortical population dynamics by phasic activation of the locus coeruleus

Authors: *E. DURÁN, M. YANG, R. NEVES, N. K. LOGOTHETIS, O. ESCHENKO;
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Abstract: Synchronized population activity in cortex is a hallmark of slow-wave sleep, quiet wakefulness, or anesthesia. Rhythmic fluctuations of neuronal membrane excitability are reflected in extracellular field potentials as delta (1-4 Hz) or large-amplitude slow (~ 1Hz) oscillations (SO); the latter are indicative for Up-to-Down-states transitions. The Up-states comprise periods of neuronal membrane depolarization accompanied by sustained spiking activity; the Down-states are associated with membrane hyperpolarization and neuronal silence. The level of cortical synchronization depends on the input from a number of subcortical neuromodulatory centers, including the brainstem nucleus Locus Coeruleus (LC). The LC regulates cortical excitability via its direct or indirect ascending projections and norepinephrine (NE) release in the target regions. We have previously demonstrated that phasic LC activation causes transient cortical desynchronization. Here, we sought to characterize the effect of transient NE release on the cortical population dynamics at a fine temporal scale. To this end, we quantified the effects of the direct electrical stimulation of LC (LC-DES) on the Up/Down-state transition in the medial prefrontal cortex (mPFC) in urethane-anesthetized rats. Biphasic electric pulses (0.4 ms, 0.02-0.05 mA) were applied to the LC unilaterally at 50 Hz for 200 ms while mPFC activity was monitored ipsilateral to the simulation site. The effect of LC-DES on cortical population activity depended on the phase SO. The LC-DES presented within an Up-state prolonged the ongoing Up-state for 94.3 ± 21.3 ms and caused ~20% increase of the firing rate in the mPFC. In addition, Down-states coincided with LC-DES were followed by a rapid transition to Up-state in ~20% of trials. Our results suggest that the effect of NE release on cortical population dynamics strongly depends on the cortical state preceding LC activation.

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Poster

678. Sleep Mechanisms and Function

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Topic: F.08. Biological Rhythms and Sleep

Support: Wellcome Trust Grant 109059/Z/15/A
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Title: Sleep spindle quality reflects spatio-temporal dynamics of oscillatory activity within cortical networks in mice

Authors: *C. BLANCO DUQUE[1], L. KRONE[1], M. C. KAHN[1], P. ACHERMANN[3], D. M. BANNERMAN[2], E. OLBRICH[4], V. V. VYAZOVSKIY[1];
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Abstract: Sleep spindles (SS) are field potentials that occur at 10-15 Hz during NREM sleep. SS are thought to play a role in sensory processing and memory consolidation; however, their origin and biological function remains uncertain. In part, this results from a limitation of traditional SS detection methods, which treat SS as all-or-none phenomena, and often do not take into account their complex spatio-temporal dynamics. To address this limitation, we used a novel methodological framework, which treats brain signals as a superposition of stochastic harmonic oscillators whose frequency and damping vary in time. To detect SS, we fit autoregressive models to EEG and LFP signals -recorded in adult male C57BL6 mice- from the primary somatosensory cortex using 16-ch microwire arrays (n=6) and 16-ch laminar probes (n=7). SS events are detected based on the damping of the signal within a 10-15Hz frequency band. SS events display significant diversity in their spatial extent (e.g. in how many LFP channels they manifest simultaneously) and their strength of damping, which we refer to as “spindle quality index” (SQI 1-5 = strong-to-weak damping). Low quality SS (i.e. weak oscillations) occur at a higher rate (SQI1: 3.6/min ± 0.2) than high quality SS (SQI5: 0.1/min ± 0.01). Furthermore, we find that SQI is strongly associated with the duration and spatial synchronisation of SS. Specifically, SS with low SQI are predominantly local (37% ± 0.2 of all LFP channels) and transient (1.2s ± 0.06), whereas SS with high SQI last longer (2.3s ± 0.3) and encompass larger cortical regions (77%, ± 0.07 of all LFP channels; low vs high SQI: $p<0.001$). In addition, there is a strong positive correlation between SQI, or spatial synchrony of local LFP SS events, and the power density in the SS frequency range in the frontal EEG ($r=0.99$, $p=0.0001$). Finally, we investigated the relationship between SQI and the occurrence of recently reported infra-slow oscillation in SS activity. Our preliminary results confirm that SS occur in bursts, lasting on

average 14.4s ± 0.2 and comprised of 1 spindle every ~2.38s ± 0.005. These SS bursts exhibit a 0.02Hz oscillation (i.e. with a ~50s period) and 0.36/min ± 0.01 incidence during NREM. During the last quartile of NREM sleep episodes there was a 15% ± 0.07 increase in SQI within a given burst, which was not apparent in first three quartiles. In summary, we demonstrate that SS are not all-or-none phenomena, but show a continuum in their properties, which until now remained underappreciated. We conclude that considering the quality dimension of SS is necessary for providing a complete understanding of their underlying network dynamics and biological function in health and disease.

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Poster

678. Sleep Mechanisms and Function

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 678.17/R11

Topic: F.08. Biological Rhythms and Sleep

Support: NIH grant NS027881

Title: Optogenetic activation of medial prefrontal cortex fibers in the dorsal raphe (DR) increases dark phase sleep-like behavior and requires hypocretin/orexin (OX) neuropeptides

Authors: *N. E. MOLINA[1], E. A. BERRY[2], K. THOMPSON[3], M. ISHIBASHI[4], C. S. LEONARD[5];
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Abstract: The neural circuit changes resulting from the loss of OX signaling, which underlie the sleep disorder narcolepsy, are not well understood. Evidence indicates that OX signaling at serotonin (5-HT) DR neurons and their connections to the amygdala are important in suppressing cataplexy, a key symptom of narcolepsy that is characterized by abrupt behavioral arrests during waking that are enhanced by positive emotions. Since suppressing activity in mPFC reduces cataplexy, and mPFC projects to both amygdala and DR, we used excitatory optogenetics to investigate the ability of mPFC->DR projections to modulate cataplexy in narcoleptic (OX-null) mice. Bilateral mPFC microinjections of AAV1-CAG-Chronos-GFP delivered > 4w prior to beginning experiments resulted in robust Chronos-GFP expression in mPFC and DR terminals. Optical stimulation of PFC terminals in brain slices produced monosynaptic EPSCs and disynaptic IPSCs in 5HT and putative GABA DR neurons in slices from WT and OX-null mice, and these PSCs faithfully followed light pulses up to 40Hz. For behavioral experiments, we

implanted a fiber optic near the midline in the DR of both WT and OX-null mice. We found that 20Hz optical stimulation (5ms pulses, for 10s every 20s) did not alter open field locomotion in either genotype but was aversive for both genotypes in a real-time place preference test. Cataplexy- and sleep-like events (CLEs and SLEs) were scored blindly during the 1st 4h of the active period in the home cage under four experimental conditions: baseline, optical stimulation, emotional arousal (given chocolate m&ms), arousal + stimulation). CLEs were significantly increased in arousal conditions in OX-null mice, but were not altered under stimulation conditions, suggesting that mPFC afferents may not target neurons regulating cataplexy. In contrast, SLEs were decreased in arousal conditions in both WT and OX-null mice. Unexpectedly, SLE number & total duration increased considerably (> 3x) in stimulation conditions for WT, but not OX-null mice. During SLEs, mice typically assumed a head-down, resting posture in the nest, but these events were not tightly linked to each stimulation epoch. This suggests that mPFC afferents do not gate SLEs but increase sleep drive. The absence of this effect in OX-null mice suggests mPFC afferents may induce SLEs by suppressing wake-promoting OX neuron output, perhaps via direct 5-HT mediated inhibition. Collectively, our findings suggest a novel pathway for top-down control of sleep-wake circuits which may relate to reduced NREM slow-wave activity and cognitive decline observed in age-related PFC atrophy.

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Poster

678. Sleep Mechanisms and Function

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Topic: F.08. Biological Rhythms and Sleep

Support: Human Frontiers Science Program N023241-00_RG105
NSF BCS-1749430
NIH DP2 MH104119

Title: Effects of learning and sleep on ribosome phosphorylation and ribosome-associated mRNAs in different hippocampal neuronal populations

Authors: *J. DELORME[1], V. K. KODOTH[2], S. J. ATON[2];
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Abstract: Sleep plays a critical role in hippocampus-dependent memory consolidation. Research has found substantial sleep-associated alterations to hippocampal circuit connectivity and

network activity patterns. It remains unclear whether and how sleep-associated activity alterations affect intracellular pathways critical for synaptic plasticity in the hippocampus. Recent data have suggested that sleep may regulate protein synthesis. To characterize the influence of sleep and prior learning on protein synthesis, we have characterized activity-associated phosphorylation of ribosomal subunit S6 (pS6) in the hippocampus using immunohistochemistry. Surprisingly we have found that both sleep and prior learning alter ribosome phosphorylation across both excitatory (CaMKIIa-expressing) and inhibitory (somatostatin- and parvalbumin-expressing) neurons of the rodent hippocampus (DG, CA1, & CA3). To further characterize which mRNAs might be translated into protein during post-learning sleep, we employed the translating ribosome affinity purification (TRAP) technique to isolate mRNA associated with ribosomes from excitatory neurons (CaMKIIa-CRE×Rpl22-HA) and those associated with phosphorylated ribosomes (pS6) from the hippocampus, under different experimental conditions. Our data show that not only does sleep differentially affect ribosome-associated mRNA species in different hippocampal neuron populations, but a learning task (contextual fear memory - CFM) also leads to subsequent changes in ribosome-associated mRNA profiles, in a sleep-dependent manner.

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Poster

678. Sleep Mechanisms and Function

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 678.19/R13

Topic: F.08. Biological Rhythms and Sleep

Title: Sleep spindles and gamma brain connectivity during NREM sleep: An insight from intracranial electrodes

Authors: V. ZAPATA[1], D. HENAO[1], L. MAYOR[1], M. NAVARRETE[2], M. LE VAN QUYEN[3], ***M. VALDERRAMA**[1];
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Abstract: Sleep is highly necessary for several functional and cognitive processes. Specifically, it is thought that during non-REM (NREM) sleep an active memory consolidation process takes place, where recently acquired information is distributed between different brain areas for its long-term storage. This communication is mediated by the action of slow oscillations that modulate the coordinated occurrence of thalamocortical spindles and cortical and hippocampal gamma and ripples events. In particular, it is believed that the precise occurrence of spindles and gamma/ripples oscillations facilitates the transfer of information between hippocampal and cortical regions during sleep. In order to study the dynamic interaction among these areas,

different studies have reported the evolution of brain connectivity over different sleep stages leading to the identification of functional most connected areas. However, most of these analyzes have been based on fMRI or scalp EEG techniques that do not allow the mapping of brain activity at specific intracerebral locations with high temporal resolution. Here, we studied the brain connectivity during NREM sleep through complex networks constructed from intracranial electrodes. We aim at identifying most connected areas for spindles (8-18Hz) and gamma (30-100Hz) activities due to their relevance in cognitive processes. For this, brain graphs where constructed from intracranial recordings of 13 epileptic patients that were implanted for the treatment of their epilepsy. In particular, we investigated how the connectivity strength changed across the night for each of the recorded regions. In total, we analyzed 159 sleep hours during seizure-free nights and 1052 intracranial electrodes located over 32 brain regions, mainly in temporal and frontal cortices and parahippocampal areas. Results were focused on NREM sleep stages N2 and N3, and Wake periods. We report a statistically significant (p-value < 0.05) increase of global brain connectivity in spindles and gamma for most of the patients (>60%) during NREM than wake. Most connected regions during NREM and wake periods were consistent between the two ranges of gamma activity (30 to 49Hz, and 51 to 99Hz), but not between slow (8 to 12Hz) and fast (12 to 18Hz) spindles. Most connected electrodes were found in the precental gyrus and the insula during NREM sleep for slow spindles and gamma activity. During fast spindles, connectivity was moved towards the caudate region, the inferior parietal and paracentral lobules, and the inferior temporal gyrus. Taking together, our results provide new evidences of functional brain connectivity during sleep.

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Poster

678. Sleep Mechanisms and Function

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Topic: F.08. Biological Rhythms and Sleep

Support: NIH Grant R01EB019804
Pennsylvania State University Academic Computing Fellowship

Title: Simultaneous measurements of the brainstem sleep-wake neuronal activity indicates non-discrete state transitions

Authors: *F. BAHARI, M. W. BILLARD, C. CURAY, J. KIMBUGWE, K. D. ALLOWAY, B. J. GLUCKMAN;
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Abstract: Sleep-wake states are thought to be driven by brainstem and hypothalamic circuits. The states are predominantly characterized from EEG and EMG and have been described as discrete states with fast-switching mechanisms. Models of underlying mechanisms of sleep-wake regulation attempt to reproduce these quantized transitions. To do so, these models often invoke discrete co-inhibitory dynamics analogous to electrical flip-flops.
Observations of switching mechanisms behind states transitions are derived predominantly from experiments with head-fixed or lightly anesthetized animals, or short recordings in sensory deprived novel environments. These conditions are abnormal and inherently dysregulate sleep-wake patterns.
To study sleep-wake transitions in normal conditions, we have obtained long-term continuous experimental single- and multi-unit measurements simultaneously from multiple of the hypothalamic and brainstem sleep-wake regulatory nuclei, along with cortical and hippocampal, activity and head acceleration, from freely behaving rats in their home-cages.
We categorized three main SOVs of REM, NREM, and Wake based on EEG rhythms, and head acceleration (Sunderam 2007): REM is characterized by a sharp spectral peak in the theta band of hippocampal activity and an absence of accelerometer activity except for brief muscle twitches. NREM is characterized by high amplitude, slow oscillations resulting in high delta band power in cortical activity and an absence of accelerometer activity. Wake is characterized by either low or high-power accelerometer activity indicating small or large head-movement respectively.
We found that transitions between these states are not discrete. We characterized a significantly long intermediate state between NREM and REM with no accelerometer activity and no clear spectral peak at delta or theta frequencies. The coarse-grained activity of the cell groups match the patterns of discrete state transitions. But on finer scale the firing rates of the REM-ON neurons did not reflect and/or predict occurrence of the intermediate state.
We report the first network analysis of the sleep-wake regulatory system derived from simultaneous measurements across multiple cell groups involved in sleep-wake regulation, in freely behaving rats. Our findings suggest that state transitions are governed by fluid interactions across multiple mechanisms rather than discrete on-or-off switches. This questions the conventional discrete definition of sleep-wake states used to investigate sleep-wake regulation in normal or diseased brain.
Sunderam S. et al. J Neurosci Meth, 2007

Disclosures: F. Bahari: None. **M.W. Billard:** None. **C. Curay:** None. **J. Kimbugwe:** None. **K.D. Alloway:** None. **B.J. Gluckman:** None.

Poster

678. Sleep Mechanisms and Function

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Program #/Poster #: 678.21/R15

Topic: F.08. Biological Rhythms and Sleep

Title: Aberrant homeostatic sleep processes following exposure to chronic social defeat stress

Authors: *B. M. RADWAN[1], G. JANSEN[2], A. YANEZ[1], S. HAMMAMI[1], S. DEMAS[3], R. KHALIL[3], D. CHAUDHURY[1];
[1]Biol. Dept., New York Univ. Abu Dhabi, Abu Dhabi, United Arab Emirates; [2]Dept. of Physiology, Develop. and Neurosci., Univ. of Cambridge, Cambridge, United Kingdom; [3]Dept. of Biology, Chem. and Envrn. Sci., American Univ. of Sharjah, Sharjah, United Arab Emirates

Abstract: Increased stress of modern life negatively impacts sleep in the global population. Sleep and mood are closely related as sleep loss was shown to negatively affect mood. However, how chronic stress affects sleep regulation and sleep homeostasis is still poorly understood. Here, we hypothesize that the homeostatic mechanisms of sleep that signal sleep need, and restore brain stability, are aberrant in individuals exposed to chronic social defeat stress (CSD). Adult C57BL/6 mice were implanted for electroencephalogram recordings (EEG) and then exposed to a 15-day CSD protocol. They were classified as either susceptible or resilient to stress based on their social interaction and sucrose preference scores following CSD. Subsequently, the EEG was measured across a 24-h post-stress baseline, followed by a 4-h sleep deprivation (SD), and then a 8-h sleep recovery period. To further investigate how the brains of stress-naïve versus stress-exposed individuals respond to prolonged wake experience/SD, and how it recovers during sleep, we profiled gene expression by performing RNA sequencing analysis. Additionally, the differences in synaptic density and morphology via Golgi staining following SD and recovery sleep were assessed in the stress-susceptible and stress-resilient mice in order to investigate "synaptic renormalization" or downscaling during recovery sleep. Moreover, the change in the frequency and the amplitude of the miniature EPSCs (mEPSCs) recorded from the mPFC slices was examined in the stress-exposed and stress-naïve mice to explore the homeostatic depotentiation of synapses due to sleep compared to SD. We report that mice susceptible to stress exhibited increased and lasting rapid eye movement (REM) sleep rebound response following 4-h SD, whereas REM sleep occurrence in mice resilient to stress returned to the control value at a faster rate. Furthermore, stress-exposed mice display deficient non-rapid eye movement (NREM) sleep response compared to stress-naïve individuals. Our preliminary data showed that the spine density in the cortical neurons in the medial prefrontal cortex (mPFC) in stress-naïve mice was lower after 4-h recovery period compared to the stress-susceptible mice. The amplitude of mEPSCs in the stress-suceptible mice is higher than in the stress-resilient and stress-naïve mice following both SD and sleep demonstrating a deficient depotentiation mechanism of the synapses. Our data provide evidence that the homeostatic sleep processes are altered in stress-susceptible mice and that the synaptic downscaling during sleep might be deficient due to stress.

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Poster

678. Sleep Mechanisms and Function

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Topic: F.08. Biological Rhythms and Sleep

Support: NS052287
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Title: Deep-brain imaging of lateral hypothalamic vGAT neurons during sleep

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Abstract: An important goal in neuroscience is to map the circuits in the brain that are activated in response to specific behaviors, including sleep. We use microendoscopy to monitor activity in neurons that contain the vesicular GABA transporter (vGAT) and considered to be GABAergic. The vGAT neurons are a distinct population juxtapositioned with the neurons that contain orexin or melanin-concentrating hormone (MCH) in the lateral hypothalamus (LH). The activity of the LH vGAT neurons in sleep is unknown. Here, we find that they are maximally active in active waking and REM sleep. In vGAT-cre mice, rAAV-DIO-GCaMP6m was delivered stereotaxially to the LH (isofluorane anesthesia) and a GRIN lens, together with EEG and EMG electrodes were implanted. Three weeks later a baseplate was inserted (isofluorane) that allowed a miniscope (INSCOPIX) to be attached. After adaptation to the miniscope, sleep was recorded and vGAT fluorescent neurons were imaged. Thirty-eight neurons were extracted (PCA-ICA analysis; Mosaic software) from vGAT-cre mice (n=3; female; GCaMP6M). The average Ca2+ fluorescence was significantly higher during both active waking and REM sleep compared to quiet waking (QW), NREM or REM transition [$F(4,175)=14.05$; $P=0.001$; Mixed Model SPSS25]. The fluorescence in NREM was the lowest compared to the other states [$P=0.001$]. In REM sleep, the fluorescence was event-dependent and synchronized between neurons. During active waking, fluorescence was elevated during walking or grooming behavior. We found that vGAT neurons were very active during purposeful behaviors such as walking and grooming, and during REM sleep when there is muscle atonia. We contrast the activity of vGAT neurons with

the MCH neurons (Blanco etal, J Neuroscience, 2019) which were preferentially active during REM sleep. Mapping activity of neurons and glia during active waking and sleep will yield a sleep connectome.

Disclosures: C. Blanco-Centurion: None. **S. Luo:** None. **A. Vidal-Ortiz:** None. **Y. Sun:** None. **M. Liu:** None. **P.J. Shiromani:** None.

Poster

678. Sleep Mechanisms and Function

Location: Hall A

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Program #/Poster #: 678.23/R17

Topic: F.08. Biological Rhythms and Sleep

Support: Swiss National Science Foundation #168567
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Title: High-density EEG investigation of sleep in REM sleep behavior disorder

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Abstract: Patients with rapid eye movement (REM) sleep behavior disorder (RBD) display dream enactment during REM sleep. It has been recently suggested that, in addition to REM sleep alterations, NREM sleep and wake functions may also be impaired. We thus investigated topographical differences in neuronal activity between RBD patients and controls using high density electroencephalography (hdEEG) recordings in both REM and NREM sleep.
9 RBD patients underwent a regular sleep polysomnography coupled with 256 channel hdEEG. They were matched (sex and age) to 9 non-medicated controls and 9 controls with similar psychiatric conditions and medications. EEG data from N2-3 NREM and REM sleep were 1-40 Hz filtered and average-referenced. Independent component analysis was applied to remove physiological noise. Power densities of each classical EEG frequency band, absolute and subject-normalized EEG topographies, and overnight decline in delta and theta power were compared between groups. Tests were thresholded at corrected $p<.05$ (using nonparametric threshold-free cluster enhancement).
Non-medicated controls had relatively less N1 and tonic REM sleep, a shorter REM sleep latency and a faster alpha peak frequency than both patients and medicated controls (ANOVA $p<.05$). No difference in sleep architecture was found between patients and medicated controls. All three groups had similar sleep efficiency and periodic leg movement- and apnea-related

measures. Topographical analyses for REM sleep revealed marginal differences between groups. Compared to both control groups, however, patients displayed less reduction in beta power in centro-occipital regions in phasic compared to tonic REM sleep. During NREM sleep, patients showed a smaller overnight decrease in delta and theta power compared to both control groups. They also showed decreased occipital normalized alpha power compared to both control groups. Differences in sleep architecture between patients and non-medicated controls are likely related to medication effects, given they do not survive analysis with medicated controls. Compared to both control groups, patients display a reproducible decrease in attenuation of fast frequency brain activity in phasic compared to tonic REM sleep. This suggests a decreased depth of phasic REM sleep, which may be related to the occurrence of dream enactment. In addition, patients display impaired NREM sleep homeostasis compared to both control groups. This may reflect decreased cortical plasticity, possibly related to an impairment of the noradrenergic locus coeruleus, and may contribute to the non-motor symptoms of RBD and associated neurodegenerative diseases.

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Poster

678. Sleep Mechanisms and Function

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Topic: F.08. Biological Rhythms and Sleep

Support: NIH Grant MH111276

Title: Daily rhythm of orexin immunoreactivity and release in a diurnal rodent model of seasonal affective disorder

Authors: *A. MOODY[1], K. GEORGE[1], K. LINNING-DUFFY[1], J. LONSTEIN[2], L. YAN[2]; [1]Psychology, [2]Psychology and Neurosci. Program, Michigan State Univ., East Lansing, MI

Abstract: Orexin/hypocretin is a neuropeptide that has been implicated in many functions including sleep/wakefulness, energy expenditure, reward, mood and cognitive functions. Our previous work using diurnal Nile grass rats (*Arvicanthis niloticus*) has shown that there are fewer hypothalamic orexin-immunoreactivity (ir) cells in animals housed in a 12:12 hr light:dark (LD) cycle involving dim daylight intensity (50 lux, dimLD), in comparison to animals housed in bright daylight (1000 lux, brLD). Grass rats housed in dimLD also showed higher depression-like behaviors and spatial memory impairments compared to the animals in brLD, suggesting that the orexin system may serve as a link between daylight intensity and the behavioral changes. It has been reported in humans and nonhuman primates that orexin peptide is high during the day

and low at night in brain tissue or cerebrospinal fluid (CSF), suggesting a diurnal rhythm in peptide release. In the present study, we examined day/night fluctuation in the number, soma size, and optical intensity of orexin-ir cells in the hypothalamus of grass rats housed in dimLD or brLD for four weeks. Male and female grass rats were perfused at zeitgeber time (ZT, lights on is defined as ZT0) 2 and 14. Brains were processed to examine orexin-ir in the hypothalamus (n = 6-8/condition/sex/time point). The results revealed a significant day/night difference in the number, soma size and optical density of orexin-ir neurons, with more neurons, bigger soma size and greater density observed at ZT14 in both brLD and dimLD conditions. The higher orexin-ir at night is consistent with the high release of peptide during the day in diurnal species. Although a day/night fluctuation was observed in both brLD and dimLD groups, the amplitude was higher in brLD group, suggesting more peptide released during the day in brLD animals than in the dimLD group. To confirm this, the next experiment collected cisternal CSF in the late afternoon at ZT10 and measured orexin peptide A content using ELISA. Consistent with the higher amplitude of orexin-ir in the hypothalamus, CSF orexin A was also higher in brLD group compared to the dimLD group. The results suggest that in diurnal rodents, orexin peptides accumulate within the cell body at night, before being released during the day. Daylight intensity modulates the degree of orexin change in the hypothalamus and in CSF across a day.

Disclosures: **A. Moody:** None. **K. George:** None. **K. Linning-Duffy:** None. **J. Lonstein:** None. **L. Yan:** None.

Poster

678. Sleep Mechanisms and Function

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Topic: F.08. Biological Rhythms and Sleep

Support: NIH Grant MH111276

Title: Too sad to sleep? Sleep patterns in a rodent SAD model analyzed by the piezoelectric system

Authors: *S. D. PHILLIPS[1], H. XIONG[1], K. DONOHUE[3], B. F. O'HARA[3], J. S. LONSTEIN[2], L. YAN[2];
[1]Psychology, [2]Psychology and Neurosci. Program, Michigan State Univ., East Lansing, MI; [3]Univ. of Kentucky, Lexington, KY

Abstract: Seasonal Affective disorder (SAD) is a major depressive disorder that occurs in the fall and winter months followed by remission in the spring and summer. The major symptoms include depressed mood, anxiety, cognitive impairments and sleep disturbance. To explore the underlying neuropathology, our lab has developed an animal model of SAD using the diurnal

Nile grass rat, *Arvicanthis niloticus.* Previous research from our lab has found that grass rats housed in a winter-like dim daylight condition show increased depressive-like behaviors and impaired spatial learning/memory compared to those housed in a summer-like bright daylight condition. These behavioral changes are accompanied by changes in the neuropeptide orexin, which has been implicated in regulating sleep/wakefulness and mood. Given the effects in behaviors and orexin, the present study investigated the extent to which sleep is affected in our SAD model, and the association between sleep disturbance and depressive behaviors. Male and female grass rats were housed in a 12 hr bright light (1,000 lux):12 hr dark (brLD) or 12 hr dim light (50 lux):12hr dark (dimLD) conditions (n=7-8/condition/sex). Sleep pattern were recorded and analyzed over four weeks using a piezoelectric motion sensor system. Following sleep recording, animals were tested for anxiety and depression-like behavior using the open field and forced swim test (FST). Analysis of sleep recording revealed a significant effect of daytime light intensity in male grass rats. Males housed in dimLD had a lower diurnal wake ratio and shorter sleep bout lengths at night compared to those in brLD. The peak wake time also appeared to be delayed, occurring toward the end of the day, in some of the dimLD animal in contrast to early morning peaks in all of brLD males. In females, the difference between brLD and dimLD group was not statistically significant. This may be due to a higher intergroup variability and/or limited sensitivity of the motion sensor because of a lighter body weight compared to males. We also confirmed again that animals housed in dimLD condition showed increased depression-like behaviors revealed by a shorter latency and longer duration of immobility during FST ($p<0.05$) in both males and females. Interestingly, males that showed a shorter sleep bout at night tend to have a shorter latency ($R=0.89$, $p = 0.001$) and longer duration ($R=-0.44$, $p = 0.23$), while females that showed a shorter sleep bout during the day tend to have a shorter latency ($R=0.77$, $p < 0.01$) and longer duration ($R=-0.7$, $p = 0.02$) of immobility during FST. These results will contribute to a better understanding of the interplay among depressed mood, sleep disturbance, and sex in SAD.

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Poster

678. Sleep Mechanisms and Function

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 678.26/R20

Topic: F.08. Biological Rhythms and Sleep

Support: ERC

Title: Effect of closed-loop auditory stimulations on sleep homeostasis and delta waves dynamics

Authors: *K. EL KANBI[1], K. BENCHENANE[2];
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Abstract: Slow-wave-sleep is a critical phase for recovery. More precisely, slow oscillations coming from the rhythmic occurrence of delta waves - broad oscillations (~1Hz) observed in mammals - seem to be linked to the amount of time spent awake and are a widely used marker for sleep pressure. Studies have shown possible to manipulate these slow waves with auditory stimulations: enhancing slow waves would result in an improvement in sleep dependent memory task, whereas perturbing them impairs would have an negative effect on a sleep dependent visuo-motor task. After assessing the short-term effect of auditory stimulations on the cortical multi-unit activity during sleep in mice, we study the effect of impairing or enhancing delta waves with sounds on sleep homoeostasis and delta waves dynamics at a larger time scale

Disclosures: K. El Kanbi: None. **K. Benchenane:** None.

Poster

679. Circadian Clocks

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Topic: F.08. Biological Rhythms and Sleep

Support: SC1GM12567
US54NS083932

Title: *In vivo* cell specific characterization of AVP neurons in the mouse suprachiasmatic nucleus

Authors: *A. C. STOWIE[1], I. ELLIS[1], D. CAMACHO[1], M. BENVENISTE[2], A. J. DAVIDSON[1];
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Abstract: Previous work has identified an important role for VIP expressing neurons in maintaining and resetting the phase of the mammalian master clock, the SCN *in vivo*. Conversely, though it is known that AVP expressing neurons in the mammalian SCN are important in determining the circadian network period, little is known about how these neurons behave in an intact neuronal network. In the present work, we have utilized miniaturized one-photon microscopy to characterize the calcium dynamics in AVP neurons of awake, behaving mice in constant darkness, a light/dark schedule, and during acute light exposure. In contrast with global SCN electrical activity measured by MUA, we found that only a relatively small proportion of SCN AVP neurons seem to display daily rhythms in both baseline fluorescence as well as spontaneous calcium events and with a subjective nighttime peak. Interestingly, when

present, these calcium events were high amplitude and last as long as 30 seconds. Further, we have not observed changes in baseline fluorescence or induction of calcium events in response to acute light exposure. Taken together, these data provide unexpected characteristics of neurons within the murine master clock which are thought to have an important role in synchronizing extra-SCN oscillators throughout the body.

Disclosures: A.C. Stowie: None. **I. Ellis:** None. **D. Camacho:** None. **M. Benveniste:** None. **A.J. Davidson:** None.

Poster

679. Circadian Clocks

Location: Hall A

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Program #/Poster #: 679.02/S2

Topic: F.08. Biological Rhythms and Sleep

Title: Implantable microimaging CMOS sensor for deep brain gene expression analysis in freely behaving mice

Authors: *J. OLOROCISIMO, J. BRIONES, R. REBUSI, Y. OHTA, M. HARUTA, K. SASAGAWA, Y. NAKAHATA, Y. BESSHO, J. OHTA;
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Abstract: The suprachiasmatic nucleus (SCN) is the main regulator of our circadian rhythm, and is dubbed as the body's "central clock". It controls the timing of numerous physiological processes in an organism such as the sleep-wake cycle, hormonal secretion, digestion, metabolism and even mood. The dysfunction of circadian rhythm has been implicated in a wide variety of diseases such as obesity, cancer, and depression. However, the causal mechanism has yet to be established.
In order to do this, there must be a method to observe and manipulate the SCN most especially *in vivo*. However, due to its deep brain location and small size, it has been difficult to observe and much more manipulate the SCN. Recent technology employed the use of implanted optical fibers to visualize luciferase reporter-based gene expression in the SCN, but this involves the use of huge photomultiplier tubes which are very expensive and difficult to handle.
In our study, we present a very lightweight and ultrasmall microimaging CMOS sensor that is safe to implant and inexpensive to manufacture. We tested the sensitivity and signal-noise ratio of our device compared to previous models, and found a remarkably improved performance. Furthermore, we added an alternating array of optical absorption filter on the device to reduce background noise. The new device showed: a higher sensitivity to small changes in light intensity; a better signal-noise ratio, as exhibited by a larger difference between signal and noise readings; and finally, a low fluctuation of temporal noise despite long exposure times. The improvement of these parameters was important because of the weak intensity of bioluminescent

reporters like luciferase.
The device can enable us to observe circadian gene expression in freely behaving *Bmal1-Luc* and *Per1-Luc* mice. This will allow for the analysis of both deep brain gene expression and organismal behavior at the same time and in the same individual. Furthermore, the device can be coupled with uLEDs for optogenetic manipulation. This can potentially be used to elucidate the relationship between neural activity, gene expression and behavior, and see how the interplay of these might lead to circadian dysfunction and its numerous implicated diseases.

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Poster

679. Circadian Clocks

Location: Hall A

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Program #/Poster #: 679.03/S3

Topic: F.08. Biological Rhythms and Sleep

Title: Characterization of SynGAP circadian expression within the murine suprachiasmatic nucleus

Authors: *S. ATEN[1], K. R. HOYT[2], K. OBRIETAN[3];
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Abstract: Mammalian physiology is modulated by a complex, distributed, network of circadian timing systems. At the center of this organism-wide web of oscillators is the suprachiasmatic nucleus (SCN) of the hypothalamus. As the master clock, the SCN modulates the phasing of peripheral oscillator networks. In addition, the SCN serves as the sole conduit by which the 24 hr light cycle sets the phasing of the circadian timing system. One key effector of SCN timekeeping and light entrainment is the p44/42 mitogen-activated protein kinase (ERK/MAPK) cellular signaling pathway. Notably, the ERK/MAPK cascade is activated by a number of small-molecule GTPases—including Ras and Rap. Here, we analyzed the expression of SynGAP—a GTPase-activating protein that functions as a negative regulator of Ras and Rap signaling—within the murine SCN. Of note, SynGAP is known to be expressed mainly in the postsynaptic density of excitatory, glutamatergic, neuronal populations, where it couples NMDA-receptor activation to the suppression of Ras/ERK/MAPK signaling. Using a combination of immunohistochemical, cell culture, and Western blotting approaches, we show that SynGAP is highly expressed within the SCN. Specifically, double fluorescence-based immunolabeling revealed that SynGAP is expressed in GABAergic SCN neurons. Further, we show that SynGAP is enriched within the arginine vasopressin-positive neurons that form the shell region of the SCN—with lower levels of expression detected within the retinoreceptive SCN core region. In

addition, a significant circadian oscillatory expression pattern of SynGAP was detected in both the SCN shell and core regions—a finding that was not observed in animals with germline deletion of the core circadian-clock gene *BMAL1*, which renders animals arrhythmic. Finally, we found that a light pulse (15 min; 100 lux) during the early subjective night triggered an increase in SynGAP phosphorylation at Serine 1138—an event that has been shown to disrupt SynGAP signaling by triggering its dispersion from the synapse. These findings raise the prospect that, via its effects on MAPK signaling, SynGAP could function as a potent modulator of SCN clock timing and entrainment. Currently, we are in the process of characterizing the circadian and light entrainment phenotypes of *SYNGAP1* null and heterozygous animals.

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Poster

679. Circadian Clocks

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Topic: F.08. Biological Rhythms and Sleep

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Title: Somatostatin contributes to light-driven plasticity of circadian behavior and master clock function

Authors: *D. A. JOYE, M. ARZBECKER, T. INDA, A. WUORINEN, N. O'NEILL, A. TELEGA, E. HERFF, J. A. EVANS;
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Abstract: Daily rhythms in behavior and physiology are programmed by a master clock in the anterior hypothalamus known as the suprachiasmatic nucleus (SCN)—a neural network containing different types of neurons distinguished by peptide expression. Somatostatin (SST) is an inhibitory neuropeptide produced by a subclass of SCN neurons that form extensive connections with many different types of SCN neurons. Although this suggests that SST may influence SCN function, the specific role of SST signaling in the master clock remains unclear. Previous research has found that seasonal lighting conditions influence SST expression in the hypothalamus, but whether this likewise occurs in the SCN has not been examined. Here we test that long days increase the number of SCN somatostatin (SST) neurons and that SST signaling regulates circadian clock function. Using a genetic labeling approach, we find evidence that long days activate *de novo* somatostatin transcription in a reserve pool of SCN neurons. Further, loss of somatostatin alters circadian behavioral responses to long day photoperiods and other environmental lighting conditions. In line with these results, the SCN expresses receptors for

SST, with spatiotemporal variation in the pattern of SSTR expression that is distinct from that found for other SCN neuropeptides. Lastly, loss of somatostatin signaling markedly attenuates the ability of SCN neurons to resynchronize and return a synchronous state after exposure to long day photoperiods. Collectively, these results suggest that somatostatin signaling is an important SCN signal that contributes to light-driven plasticity of circadian behavior and master clock function. More broadly, this work identifies a novel peptidergic subclass that forms a critical circuit node required for clock network function, expanding our understanding of SCN circuitry.

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Poster

679. Circadian Clocks

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R01GM131403
U01EB02195601

Title: Circadian circuits underlying daily rhythms in corticosterone release

Authors: *J. R. JONES, E. D. HERZOG;
Washington Univ. in St. Louis, St. Louis, MO

Abstract: The circadian release of hormones at the optimal time of day is essential for normal behavior and physiology. Disruption of these rhythms due to disease or lifestyle is associated with numerous pathologies including affective and metabolic disorders. Understanding the neural circuits regulating the daily pattern of hormone production is therefore a fundamental problem in neuroscience. The timing of hormone release is controlled by the master circadian pacemaker, the suprachiasmatic nucleus (SCN). However, fundamentally, we do not know how the SCN regulates daily rhythms in different hormones that each peak at different times of day. Here, we address this problem by investigating the mechanisms underlying the circadian production of corticosterone. Specifically, we examined the interaction between vasoactive intestinal peptide (VIP)-producing neurons in the SCN and corticotropin-releasing hormone (CRH)-producing neurons in the paraventricular nucleus of the hypothalamus (PVN). We postulated that circadian signals from SCN VIP neurons to PVN CRH neurons influence rhythmic corticosterone production in the hypothalamic-pituitary-adrenal axis. We found that ex vivo, CRH neurons exhibit daily rhythms in intracellular calcium levels as measured by

GCaMP6s and core clock gene expression as measured by PER2::LUC. We also found that the majority of CRH neurons express the VIP receptor VPAC2R. Both PER2 expression and calcium transients in CRH neurons were induced after applying VIP to the ex vivo PVN slice. In vivo, we found that CRH neurons exhibited daily rhythms in calcium transients peaking either around midday or dusk. These results suggest the existence of subpopulations of circadian CRH neurons with distinct times of daily activity in the PVN. Finally, we found that in vivo optogenetic stimulation of SCN VIP neurons reduced the peak amplitude of circadian corticosterone release measured every 4 hours over 3 days. Together, these preliminary results indicate that the circadian regulation of corticosterone release depends on a daily inhibitory signal from SCN VIP neurons to circadian subpopulations of PVN CRH neurons. This work is supported by F32HL133772 to J.R.J. and R01GM131403 and UO1EB02195601 to E.D.H.

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Poster

679. Circadian Clocks

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Topic: F.08. Biological Rhythms and Sleep

Support: NIH Grants NS036607 and NS103842

Title: Tonic and synaptic $GABA_A$ receptor-mediated currents in suprachiasmatic nucleus neurons

Authors: M. MOLDAVAN, O. CRAVETCHI, *C. N. ALLEN;
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Abstract: $GABA_A$ receptor ($GABA_AR$)-mediated neurotransmission plays an important role in the function of suprachiasmatic nucleus (SCN). Despite the fact that $GABA_A$ receptor-mediated synaptic currents (GPSC) are well studied, the origin and parameters of the $GABA_AR$-mediated tonic current (Itonic) remain unexplored. Whole-cell patch clamp recordings from SCN neurons in rat brain slices were performed using a high $CsCl^-$ intracellular recording solution. Picrotoxin (50 µM) and the $GABA_AR$ inhibitors gabazine (10 µM) and bicuculline (20 µM), induced an outward shift of holding current (6.2 ± 1.4 pA, 9.1 ± 2.6 pA, and 9.5 ± 2.0 pA, respectively), which defined the magnitude of the Itonic. The Itonic amplitude increased proportionally to the spontaneous GPSC (sGPSC) frequency and the magnitude of synaptic charge transfer. TTX (1 µM) inhibited action potential dependent synaptic GABA release and reduced the Itonic 82.0 ± 4.0 %, which demonstrates the importance of GABA diffusing out of GABAergic synapses for Itonic activation. Circadian regulation of the tonic and $GABA_A$-mediated synaptic currents were analyzed. The root mean square noise (RMS) reflects the sum of the currents flowing through

individual extrasynaptic $GABA_A$ receptors ($GABA_ARs$). RMS increased during activation of extrasynaptic $GABA_ARs$ and decreased during their inhibition by bicuculline, gabazine and picrotoxin. Activation of presynaptic $GABA_B$ receptors inhibited the GABA release from synaptic terminals, decreased the sGPSC amplitude and frequency, and decreased the Itonic. The baseline current was not altered by activation of postsynaptic $GABA_B$ receptors nor the glycine receptor antagonist strychnine (1 μM). The equilibrium potential for Itonic was close to 0 mV, which was similar to the calculated Cl^- equilibrium potential, under our experimental conditions, and was the same as the equilibrium potential for the currents induced by GABA (50, 100 μM). The Itonic amplitude showed noticeable outward rectification at membrane potentials over the range of -70 mV to -10 mV then was linear at voltages greater than -10 mV. Expression of α4-, α5- and δ- $GABA_AR$ subunits in the SCN was shown using fluorescent microscopy and their contribution to Itonic was confirmed by application of the $GABA_AR$ agonist THIP and $GABA_AR$ inverse agonist L655,708. Thus, Itonic was mediated by extrasynaptic $GABA_ARs$, and was primarily activated by GABA diffusing out of GABAergic synapses.

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Poster

679. Circadian Clocks

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Topic: F.08. Biological Rhythms and Sleep

Support: Chang Gung Medical Foundation (CMRPD1H0071;CMRPD1H0072)
Taiwan Ministry of Science and Technology (MOST107-2320-B-182-040-MY2)

Title: Colocalization of Na^+/Ca^{2+} exchanger NCX1 and L-type Ca^{2+} channel $Ca_V1.2$ with neuropeptides in the rat suprachiasmatic nucleus

Authors: Y.-S. CHEN, *R.-C. HUANG;
Dept. of Physiol. and Pharmacol., Chang Gung Univ. Col. of Med., Tao-Yuan, Taiwan

Abstract: The central clock in the suprachiasmatic nucleus (SCN) is composed of two oscillators with asymmetric mutual interaction. Light information entrains the gastrin-releasing peptide (GRP)- and vasoactive intestinal peptide (VIP)-containing neurons in the core or ventrolateral SCN oscillator, which in turn entrains the arginine vasopressin (AVP)-containing shell or dorsomedial SCN oscillator. In the rodent SCN, high K^+ solution produces Ca^{2+}-dependent release of dense-core vesicles as well as all three major neuropeptides, VIP, GRP, and AVP. In the rat SCN neurons, the Ca^{2+} response to high K^+-evoked depolarization is shaped by Ca^{2+} entering both L-type and non L-type Ca^{2+} channels and by Ca^{2+} clearance through the plasmalemmal Na^+/Ca^{2+} changer (NCX). The rat SCN expresses NCX1 and NCX2, but not

NCX3, with NCX1 distributed in the whole SCN and NCX2 restricted to the ventral SCN. The immunostaining results also indicated colocalization of NCX2 with VIP, GRP and VIP/GRP in the ventral SCN, but not with AVP in the dorsal SCN. In this study we used double and triple immunofluorescence staining to investigate the colocalization of NCX1 and CaV1.2 with neuropeptides (VIP, GRP, and AVP) and markers for major input pathways (vesicular glutamate transporter type 2 (vGluT2), serotonin transporter (SERT), and neuropeptide Y (NPY)) in the SCN prepared from Sprague-Dawley rats (23-25 days old; n = 12). Our results indicated high levels of colocalization of NCX1 with AVP and VIP, but not GRP, in particular, in puncta surrounding the soma and in varicosity-like swelling along the process. NCX1 is also found to colocalize with SERT and NPY, but not vGluT2. The colocalization pattern of NCX1 is consistent with our previous observation that NCX1 is distributed in the whole SCN, but with more intense NCX1 immunoreactivity in the ventral region that receives major inputs. Furthermore, triple staining of NCX1, CaV1.2 and VIP can be observed as puncta opposing the soma, and there is also triple staining of NCX1, CaV1.2 and SERT scattered as puncta in the ventral SCN, suggesting the involvement of NCX1 and CaV1.2 in the regulation of VIP and serotonin release. Together with our previous observation of more restricted localization of NCX2 with VIP, GRP, and VIP/GRP, the results suggest a differential role of NCX1 and NCX2 in the regulation of neuropeptide release in the SCN.

Disclosures: Y. Chen: None. **R. Huang:** None.

Poster

679. Circadian Clocks

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 679.08/S8

Topic: F.08. Biological Rhythms and Sleep

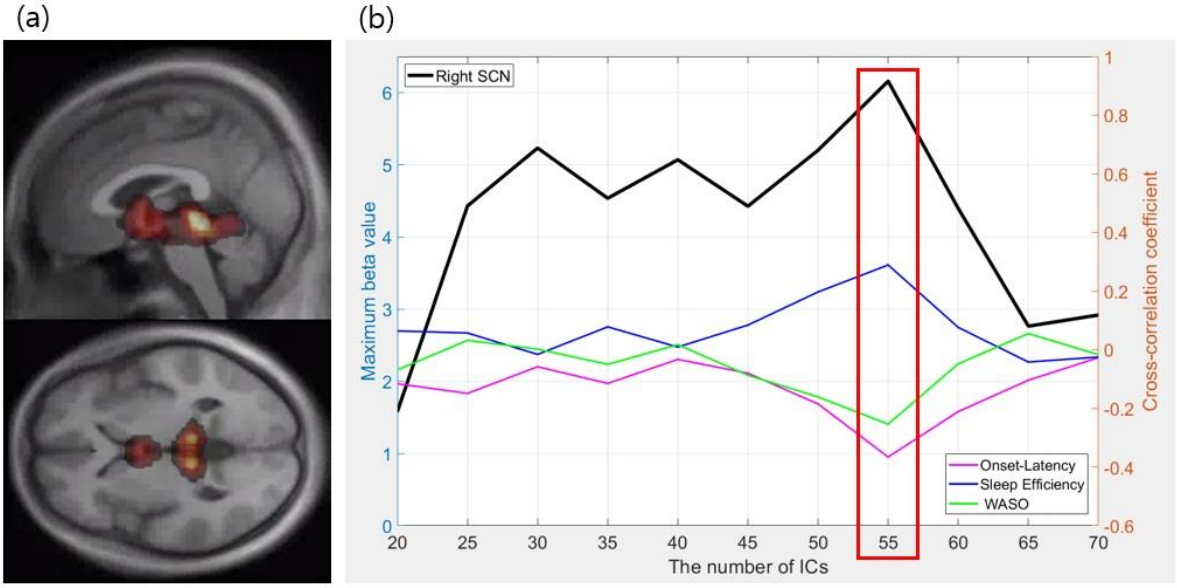
Support: NRF-2018R1D1A1A02086302
NRF-2014M3C7A1046042

Title: Functional network of suprachiasmatic nucleus in the human brain using independent component optimization

Authors: B. KIM[1], Y. JUNG[2], J. BAE[2], H. KIM[2,1], M. BYUN[3], Y. LEE[3], *Y. SON[2,1], D. LEE[3]; [1]Gachon Advanced Inst. for Hlth. Sci. & Technol., Incheon, Korea, Republic of; [2]Gachon Univ., Incheon, Korea, Republic of; [3]Seoul Natl. Univ. Hosp., Seoul, Korea, Republic of

Abstract: Circadian rhythm is important in determining sleep-wake cycle and suprachiasmatic nucleus (SCN) plays a major role as a pacemaker in the brain. Recently, in the resting state functional magnetic resonance imaging (rsfMRI), several functional network have been found, but the sleep-wake cycle network has not been found yet. In this study, we postulate that the

SCN is the major component of the circadian rhythm and its network can be resolved from the rsfMRI signal by increasing the number of the components in the independent component analysis (ICA). The present study included normal adults(n=152, 77 males, 25-86 years) who participated in the Korean Brain Aging Study for the Early Diagnosis and Prediction of Alzheimer's disease (KBASE), which is an on-going prospective cohort study since 2014. All participants underwent 3D T1-weighted MRI scans with a 3T Biograph mMR (PET- MRI) scanner (Siemens; US). Each images were normalized with template image provide by SPM8. Based on the fact that the SCN is located in ventral side of hypothalamus and top of optic chiasm, the regions of interest (ROIs) were set as left (x=3 ,y=4, z=-12) and right SCN (x=-3 ,y=4, z=-12) on the averaged T1 image. ICA was used to decompose rsfMRI signal using functional connectivity toolbox (CONN). As the number of independent component (IC) was increased in the range of 20 to 70, the network having the maximum beta values within the SCN ROI was selected among all beta maps (Fig. 1a). In order to confirm its relevance to the circadian rhythm, correlation was performed between beta values of the SCN and sleep-wake parameters such as onset latency, efficiency, wake after sleep onset (WASO). As the result, the beta value of SCN reached the maximum when the number of ICs was 55(fig. 1b, red box). Onset latency (r: -0.366, p: 0.00001), WASO (r: -0.254, p: 0.001) and efficiency(r: 0.289, p: 0.0003) showed significance with right SCN (Fig. 1b). It is worthy of note that the correlation also reached maximum when the number of ICs was 55. In conclusion, the newly defined network from the rsfMRI may be associated with SCN, circadian rhythm, and sleep.



Disclosures: **B. Kim:** None. **Y. Jung:** None. **J. Bae:** None. **H. Kim:** None. **M. Byun:** None. **Y. Lee:** None. **Y. Son:** None. **D. Lee:** None.

Poster

679. Circadian Clocks

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 679.09/S9

Topic: F.08. Biological Rhythms and Sleep

Title: Gene expression rhythms in the suprachiasmatic nucleus are changed during timed daily restricted feeding

Authors: *T. D. NIEPOKNY[1], A. RASTOGI[2], E. M. MINTZ[3];
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Abstract: The suprachiasmatic nucleus (SCN) of the hypothalamus regulates circadian rhythms of physiology and behavior in mammals. The circadian clock mechanism in the SCN is normally entrained by the daily light/dark (LD) cycle. This regular activity rhythm can be modulated by regular, nonphotic events. In particular, animals respond to periods of restricted food access during the daytime by showing a period of food anticipatory activity, which is thought to represent signaling from a food entrainable oscillator. The response of the circadian clock in the SCN to restricted feeding appears to be both species and strain-specific. In mice, some inbred strains can entrain locomotor activity to normocaloric restricted feeding cycles in constant darkness, while others, such as the C57BL/6J strain, rarely do so. Previous research suggests that C57BL/6J mice do not experience a shift in clock gene expression in the SCN during normocaloric timed restricted feeding, while other brain regions do show changes in clock gene expression. However, such studies were limited and primarily looked at period gene expression. In this series of studies, we sought to measure expression levels of both clock and neuropeptide genes in the SCN of C57BL/6J female mice on a 4-hour daytime restricted feeding schedule. Mice were individually housed with a running wheel on a 12:12 LD cycle with food available ad libitum for two weeks. After entrainment, food restriction occurred from ZT6-ZT10 (daytime restricted feeding), ZT18-ZT22 (nighttime restricted feeding) or ad libitum for 14 days, upon which mice (n = 5 per timepoint per group) were sacrificed every four hours across the circadian cycle. RNA samples from SCN tissue punches were then reverse transcribed into cDNA for quantitative real-time PCR analysis of the clock and neuropeptide genes *Per1, Per2, Cry1, Cry2, Clock, Bmal1, AVP, VIP, Grp* and *Sst.* Analysis of rhythmic expression using JTK_Cycle revealed significant rhythmicity in *Per1*, *Per2*, and *Avp* under baseline ad/lib feeding conditions and nighttime restricted feeding. However, during daytime restricted feeding rhythmicity was also induced in *Clock*, *Bmal1*, and *Cry1*, with near significant rhythms also detected in *Cry2*, and *Grp*. The phase of *Per1, Per2*, and *Avp* was not substantially altered in daytime restricted feeding, but the phase of *Clock* and *Bmal1* appeared to shift such that they peaked shortly after the period genes. Rhythm amplitude was also increased in *Per2* during daytime restricted

feeding. These data suggest that changes in the phase relationship between clock genes may be associated with changes in locomotor activity patterns during timed restricted feeding.

Disclosures: T.D. Niepokny: None. **A. Rastogi:** None. **E.M. Mintz:** None.

Poster

679. Circadian Clocks

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 679.10/S10

Topic: F.08. Biological Rhythms and Sleep

Support: NSF-1749500

Title: Regional specializations of arginine vasopressin neurons in the suprachiasmatic nucleus

Authors: *Y. CARBAJAL[1], R. HOLT[1], J. LESAUTER[2], R. SILVER[3];
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Abstract: Arginine Vasopressin (AVP-) expressing neurons form the major population of the ~20,000 neurons in the Suprachiasmatic Nucleus (SCN). They participate not only in inter-neuronal coupling which serves to synchronize oscillation, but also in the output signal that supports circadian rhythmicity in the rest of the brain and body. Dynamic analysis of SCN oscillation suggests a caudal to rostral wave of activation, pointing to the possibility of functional specializations in the network of these subregions of the nucleus. To explore this hypothesis, we analyzed AVP neurons and their efferents in the SCN. We found that the anterior and posterior populations differ importantly in morphology and projections. The posterior AVP neurons are larger in size than those lying in the anterior area. The majority of fibers of the posterior populations project dorsally and caudally while rostral neurons project rostrally towards the third ventricle. We conclude that there are distinct clusters of regionally specialized AVP neurons in the SCN. The implication of these findings is that these distinct populations differ in the signal they produce and in the targets that they reach.

Disclosures: Y. Carbajal: None. **R. Holt:** None. **J. LeSauter:** None. **R. Silver:** None.

Poster

679. Circadian Clocks

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 679.11/S11

Topic: F.08. Biological Rhythms and Sleep

Support: NIH R01NS091234

Title: Integration of neuropeptide signaling sets the phase of the master circadian clock

Authors: *K. E. ROHR, J. A. EVANS;
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Abstract: Daily rhythms in behavior and physiology are generated by the suprachiasmatic nucleus (SCN) of the anterior hypothalamus. Although intercellular signaling is known to be necessary for SCN function, the signaling mechanisms that sustain master clock function remain unclear. Like other hypothalamic nuclei, the SCN contains a variety of distinct cell types characterized by differences in neurotransmitter and neuropeptide expression. The SCN is typically subdivided into two spatially segregated compartments known as the shell and core, which contain arginine vasopressin (AVP) and vasoactive intestinal polypeptide (VIP) neurons, respectively. Although AVP has been viewed traditionally as an output signal, the SCN itself expresses AVP receptors (V1A and V1B). Despite being the first neuropeptide detected in the SCN, the role of V1 signaling in determining master clock function remains unclear. To gain a deeper mechanistic understanding of V1 signaling in the SCN, we used an *in vitro* bioluminescence assay to interrogate whether V1 receptor agonists reset the circadian clock a the molecular level. We find that V1 signaling shifts the molecular clock in the SCN in a time-dependent manner to elicit phase delays during subjective night, which is the time of highest V1A receptor expression. Interestingly, the magnitude of the resetting response differed by sex and varied across the anteroposterior axis of the SCN, indicating that there are dimorphic and regional differences in V1 receptor function. Further, V1 agonists failed to reset the SCN molecular clock in the absence of VIP, suggesting that AVP signaling interacts with VIP signaling to reset the master clock at either the cellular or network levels. Overall, this work reveals that AVP signaling acts in combination with other important SCN neuropeptides to modulate the emergent properties of the master clock network, which likely has implications for the daily regulation of behavior and physiology.

Disclosures: K.E. Rohr: None. **J.A. Evans:** None.

Poster

680. Central Regulation of Thirst and Water Balance

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 680.01/S12

Topic: F.09. Thirst and Water Balance

Support: Hong Kong Government Research Grant Council Grants GRF HKU17127718

Title: Electrophysiological effects of secretin among distinct neural populations of subfornical organ

Authors: *F. ZHANG[1], L. ZHANG[2], W. YUNG[3], B. K. C. CHOW[1];
[1]Sch. of Biol. Sci., The Univ. of Hong Kong, Hong Kong, China; [2]GHM Inst. of CNS Regeneration, Jinan Univ., Guangzhou, China; [3]The Chinese Univ. of Hong Kong, Hong Kong, Hong Kong

Abstract: In animal's brain, subfornical organ (SFO) is a circumventricular organ that lacks the normal blood-brain barrier, is an important sensor for circulating signal, and has been suggested to have an essential role in maintaining water homeostasis. Recent studies have shown that there are distinct neural populations in the SFO, and excitatory neurons may directly drive drinking behaviour. As the first hormone to be found, Secretin (SCT) is a classical gastrointestinal peptide hormone. In recent years, our laboratory discovered the osmoregulatory actions of SCT in which both acute and chronic intraventricular administration of SCT can significantly increase water intake in mice. Furthermore, SCT and SCT receptor (SCTR) were found to be highly expressed in SFO after water deprivation treatment through immunohistochemistry and *in situ* hybridization staining. However, it is still unclear how SCT acts on SFO neurons, the most upstream water homeostatic centre. In this study, we have recorded the effects of SCT in excitatory neurons (marked by neuronal nitric oxide synthase, nNOS) and inhibitory neurons (marked by glutamate decarboxylase 1, GAD67) of SFO by whole-cell patch-clamp. The population of neurons in SFO was identified by single-cell RT-PCR and electrophysiological properties. Immunofluorescence results showed that c-Fos expression in SFO^{SCTR} neurons was significantly up-regulated after 48 hours water deprivation. In addition, SFO^{nNOS} and SFO^{GAD67} neurons overlap with 61% and 21% of SFO^{SCTR} neurons, respectively. Current-clamp recordings demonstrated that bath-applied 300 nM SCT influences the excitability of the SFO^{nNOS} neurons by eliciting depolarizing (mean 5.38 ± 0.42 mV, 9 of 21 cells), effects which were concentration dependent and reversible. Meanwhile, only a few of SFO^{GAD67} neurons were depolarized by SCT (mean 6.34 ± 1.60 mV, 4 of 24 cells). Moreover, no significant SCT effects were observed in the SFO of the SCTR knockout mice. In line with the electrophysiological results, c-Fos expression in the SFO was found to be up-regulated after intraperitoneal injection of SCT (100 g/kg body weight) and most of it were expressed in SFO^{nNOS} neurons. Present results demonstrated that (1) SCTR was primarily localized on SFO^{nNOS} neurons; (2) circulating SCT can directly influence the excitability of distinct neural populations of the SFO. Based on these data, we hypothesize that up-elevated circulating SCT level during hyperosmolarity may induced water drinking behaviour by activating SFO^{nNOS} neurons. Overall, these data will help to establish a complete mechanistic role of SCT in water homeostasis.

Disclosures: **F. Zhang:** None. **W. Yung:** None. **B.K.C. Chow:** None. **L. Zhang:** None.

Poster

680. Central Regulation of Thirst and Water Balance

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 680.02/S13

Topic: F.09. Thirst and Water Balance

Support: FAPESP (2015/20500-3)
CNPq

Title: Sodium palatability in spontaneously hypertensive rats with angiotensin type 1 receptor blockade in the brain

Authors: E. D. PEREIRA JR, G. M. F. ANDRADE-FRANZÉ, ***J. V. MENANI**, L. A. DE LUCA JR, C. A. F. ANDRADE;
Dept. of Physiol. and Pathology, Dent. School, UNESP, Araraquara, SP, Brazil

Abstract: Excessive salt intake has been associated with the development or worsening of chronic diseases such as hypertension. Spontaneously hypertensive rats (SHR) have an increased preference and palatability for sodium when compared to normotensive strains. In the present study, we tested the changes in sodium appetite and palatability in 24 h water deprived SHR and normotensive rats with or without the blockade of angiotensin II (ANG II) type 1 receptors (AT-1r) centrally. Male SHR (n = 12) and normotensive Holtzman rats (HTZ, n = 10) with stainless steel guide cannulas implanted in the lateral ventricle (LV) and a polyethylene cannula implanted intra-orally (IO) were used. Rats with 24 h of water deprivation (WD) had access to only water during 2 h for partial rehydration (PR) (WD-PR protocol) before receiving LV injections of saline (1 µl) or losartan (100 ng/1 µl). Fifteen min after LV injections, hedonic and aversive orofacial motor responses to intra-oral infusions of 0.3 M NaCl (IO-NaCl, 1 ml/min) were recorded. Immediately after, rats were allowed to freely ingest 0.3 M NaCl and water for one hour (appetite test) and at the end of the test another IO-NaCl infusion was performed. Before sodium appetite test, SHR treated with saline into the LV showed increased number of hedonic (213 ± 30, vs. HTZ: 9 ± 3 reactions/min) and reduced aversive reactions (11 ± 6, vs. HTZ: 38 ± 5 reactions/min) in response to IO-NaCl. Losartan reduced the number of hedonic (34 ± 9), with no effect on aversive (17 ± 5) reactions in SHR. In the sodium appetite test, SHR treated with saline into the LV ingested more 0.3 M NaCl than HTZ (2.8 ± 0.4, vs. 0.8 ± 0.2 ml/100 g/h), an effect abolished by losartan (0.4 ± 0.2 ml/100 g/h). However, losartan did not change the number of hedonic (119 ± 21, vs. saline: 154 ± 28) or aversive (13 ± 5 vs. saline: 3 ± 1) reactions in SHR at the end of the sodium appetite test. The results show increased palatability and sodium intake in SHR submitted to WD-PR. They also suggest that central AT-1r is part of the mechanisms activated to increase sodium intake and palatability in SHR.

Disclosures: **J.V. Menani:** None. **G.M.F. Andrade-Franzé:** None. **E.D. Pereira Jr:** None. **L.A. De Luca Jr:** None. **C.A.F. Andrade:** None.

Poster

680. Central Regulation of Thirst and Water Balance

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 680.03/S14

Topic: F.09. Thirst and Water Balance

Support: BNORC P&F: 2P30DK046200-26
NIH T32 5T32DK007516
NIH DP2 DK105570
NIH DK109930
NIH DK075632
NIH DK096010
NIH DK089044

Title: Estimation of current and future physiological states by insular cortex

Authors: *Y. LIVNEH[1], A. U. SUGDEN[1], J. C. MADARA[1], V. I. FLORES[1], L. A. SUGDEN[2], J. M. RESCH[1], B. B. LOWELL[1], M. L. ANDERMANN[1];
[1]BIDMC, Harvard Med. Sch., Boston, MA; [2]Ctr. for Computat. Mol. Biol., Brown Univ., Providence, RI

Abstract: Interoception, the process of sensing and integrating diverse bodily signals, is essential for regulating physiological homeostasis, cognition, and emotions. Studies in humans highlight the importance of insular cortex (InsCtx) for interoception, yet the underlying cellular activity patterns and circuit mechanisms remain unclear. Here, we performed microprism-based two-photon imaging of InsCtx across natural and artificial states of hunger and thirst. InsCtx neurons were driven by cues predicting food/water, but also showed gradual changes in ongoing activity reflecting physiological state transitions. In sated mice, artificial activation of hypothalamic neurons that drive hunger/thirst restored selective behavioral and InsCtx responses to food/water cues, but it did not restore InsCtx representations of physiological state. Food/water cues transiently shifted the pattern of InsCtx population activity towards representations of a future satiety state. Together with circuit-mapping experiments, these data suggest that InsCtx integrates visceral-sensory inputs regarding current physiological state, with hypothalamus-gated limbic inputs signaling upcoming ingestion of food/water, to compute a prediction future physiological state.

Disclosures: **Y. Livneh:** None. **A.U. Sugden:** None. **J.C. Madara:** None. **V.I. Flores:** None. **L.A. Sugden:** None. **J.M. Resch:** None. **B.B. Lowell:** None. **M.L. Andermann:** None.

Poster

680. Central Regulation of Thirst and Water Balance

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 680.04/S15

Topic: F.09. Thirst and Water Balance

Support: CNPq
CAPES
FAPEMIG

Title: AT_2 angiotensin receptor involved on sucrose intake induced by water deprivation

Authors: M. H. PAES, L. M. CARDOSO, ***L. B. DE OLIVEIRA**;
Biol. Sci., Fed. Univ. Ouro Preto - UFOP, Ouro Preto, Brazil

Abstract: Water deprivation generates endogenous production of angiotensin II, which is associated with water and sodium intake. However, recent studies have also shown an increase in sucrose intake after water deprivation followed by partial rehydration. Thus, this study aimed to verify the central involvement of angiotensin receptors on water deprivation-induced sucrose intake. Therefore, male Wistar rats weighing 300-330g were anesthetized with ketamine (80 mg/kg) and xylazine (7 mg/kg) and a stainless-steel cannula was implanted directed to the right lateral ventricle (LV) in animal's brain. During recovery period (five days), water, 2% sucrose solution and food were offered *ad libitum*. To the intake test, water and sucrose solution were removed for 24 hours. After this period, food was removed and the rats had free access to water (partial rehydration) for 2 hours (water intake was measured at 15, 30, 60, 90 and 120 minutes). At 105 minutes (after the beginning of water offer) the animals received central injection (1µL on LV) of vehicle, AT1 or AT2 angiotensin receptor antagonists (losartan 50nmol/µL or PD 123319 30nmol/µL, respectively). 15 minutes later, 2% sucrose solution was also offered to the animals. Water and sucrose intakes were measured at 135, 150, 180, 210 and 240 minutes. At the end of 4 hours, the animals received food, water and 2% sucrose solution *ad libitum*. Results are expressed as means±SEM. Two-way RMANOVA and pos test Tukey's were used for statistical analyses. Differences were considered significant at $p<0.05$. In the first two hours of experiment (before the central injections), a similar water intake among groups was observed, which corresponds to partial rehydration that occurred in response to water deprivation. After central injections, as expected, there was no significant water intake (vehicle 0.3 ± 0.3, losartan 0.1 ± 0.1 and PD123319 0.2 ± 0.2, $p>0.05$). Animals that received injection of vehicle or losartan ingested a higher amount of sucrose than animals receiving PD123319 injection (vehicle 6.1 ± 1.9, losartan 7.2 ± 1.4, PD123319 0.74 ± 0.79, $p=0.0001$). These results suggest that sucrose intake induced by water deprivation depends on AT2, but not AT1, receptor activation.

Disclosures: M.H. Paes: None. **L.M. Cardoso:** None. **L.B. de Oliveira:** None.

Poster

680. Central Regulation of Thirst and Water Balance

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Topic: F.09. Thirst and Water Balance

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Title: Distinct neural circuits for food- and water-related presystemic regulation of vasopressin release

Authors: *A. KIM[1,2], J. C. MADARA[1], M. L. ANDERMANN[1,2], B. B. LOWELL[1,2];
[1]Div. of Endocrinology, Diabetes, and Metabolism, BIDMC, Boston, MA; [2]Program in Neurosci., Harvard Med. Sch., Boston, MA

Abstract: Vasopressin (VP), an antidiuretic hormone, is key for maintaining water balance. VP release is regulated by two temporally distinct signals: 1) slow systemic signals that convey systemic osmolality information, and 2) rapid 'presystemic' signals that anticipate future osmotic challenges. We recently demonstrated that VP neurons show bidirectional anticipatory presystemic responses to feeding and drinking. To find the source of presystemic regulation, we used rabies and ChR2-assisted circuit mapping to map afferents to neuroendocrine VP neurons. Major inputs to VP neurons come from the lamina terminalis (the SFO and MnPO/OVLT), A1/C1 neurons of ventrolateral medulla, and GABAergic neurons in the perinuclear zone (PNZ), an area surrounding supraoptic nucleus. Using fiber photometry, we found that SFO and MnPO/OVLT neurons, like VP neurons, are rapidly regulated by water-predicting cues and water intake. Inhibition of neurons in the MnPO/OVLT significantly attenuated the presystemic response of VP neurons to water cues and drinking while leaving the food response intact, suggesting that MnPO/OVLT acts as a gateway for water-related presystemic regulation but has no role in presystemic regulation by food. Food-related presystemic regulation is not mediated by A1/C1 neurons, PNZ^{GABA} neurons, nor release of gut hormones as blocking these pathways had no effect on VP response to feeding. Instead, we found that A1/C1 neurons mediate hypotension- and hypoglycemia-induced activation of VP neurons. We are in the process of identifying the source of food-related presystemic regulation. These results suggest VP neurons

are regulated by multiple distinct and dedicated circuits that carry presystemic and systemic information about physiological states of the body.

Disclosures: A. Kim: None. **J.C. Madara:** None. **M.L. Andermann:** None. **B.B. Lowell:** None.

Poster

680. Central Regulation of Thirst and Water Balance

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 680.06/S17

Topic: F.09. Thirst and Water Balance

Support: NIH Grant DK107500

Title: Brattleboro rats are more sensitive to the glucagon-like peptide-1 receptor agonist, exendin-4

Authors: *D. J. BRAKEY, K. C. SCHATZ, M. J. PAUL, D. DANIELS;
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Abstract: Long Evans rats that are homozygous for the Brattleboro mutation lack arginine vasopressin (AVP) and are a model of diabetes insipidus. To defend fluid homeostasis in the face of the lack of AVP, Brattleboro rats consume significantly more water than do wildtype (WT) controls. Despite this excessive water intake, food intake remains relatively normal. Given that activation of the glucagon-like peptide-1 (GLP-1) system decreases both food and water intakes, it suggests that the impact of endogenous GLP-1 on fluid intake is somehow overridden in the Brattleboro rat, while its role in food intake satiety is maintained. Accordingly, we aimed to use Brattleboro rats to better understand the neural mechanisms controlling water intake, separate from those that underlie food intake. As a first step toward this larger goal, we evaluated the response to a central injection of a GLP-1 receptor (GLP-1R) agonist in male and female WT and Brattleboro rats. Food and water intakes were measured 4, 12, and 24 hours post-injection. Evaluation of the timing of water intake between measures was inferred by lickometry. Results show that despite the strong need to consume water, Brattleboro rats were equally, if not more, sensitive to the GLP-1R agonist exendin-4. Most suppression occurred in the first 12 hours, but Brattleboro rats showed suppression that persisted into the last 12 hours of the test. Analysis of drinking microstructure indicated that the decrease in fluid intake caused by exendin-4 was primarily due to a reduction in burst size, which is thought to reflect orosensory components of the fluid. Additionally, sex differences in baseline food and water intakes were present in WT rats, but were detected in Brattleboro rats when controlling for body weight. Additional studies are underway to evaluate proglucagon and GLP-1R expression in brain regions associated with fluid regulation. Although these studies are incomplete, the results to date suggest that

Brattleboro rats provide a unique opportunity to examine the endogenous GLP-1 system and its control of fluid intake.

Disclosures: **D.J. Brakey:** None. **K.C. Schatz:** None. **M.J. Paul:** None. **D. Daniels:** None.

Poster

680. Central Regulation of Thirst and Water Balance

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 680.07/S18

Topic: F.09. Thirst and Water Balance

Support: NIH Grant DK107500

Title: Adult drinking behavior is altered by early life exclusive access to sucrose solution

Authors: *K. L. VOLCKO, D. J. BRAKEY, J. T. PRYZBYZ, D. DANIELS;
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Abstract: Proper fluid balance is critical for life. Severe dehydration is deadly, and modest dehydration can have deleterious consequences on physiology and cognitive function. Learning plays an important role in shaping the appetitive behaviors required for drinking. Children often forego drinking plain water and instead consume beverages such as milk or juice. What effect this may have on adult behavior remains an open question. To model aspects of the human condition, we bred Sprague-Dawley rats in a cage that prevented the pups from obtaining fluid other than from nursing. In one cohort, pups were weaned onto either tap water or a 5% sucrose solution, and given access to only that fluid for the next 8 weeks. In another cohort, pups were weaned onto either tap water or a 0.08 M saline solution, and given access to only that fluid for the next 8 weeks. We then measured intake of water or sucrose/saline after (a) a mild hypertonic saline (HS) injection, and (b) overnight fluid deprivation. We also performed subsequent sucrose/saline preference (two-bottle) tests after HS injection, then maintained all rats on water for one week and repeated the test. Experiments with the saline-maintained cohort are ongoing, but with the sucrose-maintained rats we found that rats maintained on sucrose drank less water than did rats maintained on water after a mild HS injection. After overnight fluid deprivation, rats maintained on sucrose drank less water and more sucrose in the first 10 min of the test, but intake by the end of the test was not different between the groups of rats. Although we observed a comparable number of licks across the whole test, microstructural differences in licking patterns were detected. Rats maintained on sucrose showed a stronger preference for sucrose, but group differences in preference were ameliorated after a week of drinking only water; however, differences in lick patterns for sucrose remained. These data provide evidence that adult drinking behavior is influenced by exclusively drinking sucrose early in life.

Disclosures: **K.L. Volcko:** None. **D.J. Brakey:** None. **J.T. Pryzbyz:** None. **D. Daniels:** None.

Poster

680. Central Regulation of Thirst and Water Balance

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 680.08/T1

Topic: F.09. Thirst and Water Balance

Support: NIH K08 NS099425

Title: Pre-locus coeruleus in rat and mouse

Authors: ***S. GASPARINI**, A. M. GORE, L. PELTEKIAN, J. C. GEERLING;
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Abstract: We identified a unique population of neurons in the hindbrain tegmentum called the pre-locus coeruleus (pre-LC). Pre-LC neurons receive input from the nucleus of the solitary tract, express the neuronal activity marker c-Fos during sodium-deprivation, and express the transcription factor FoxP2. In rats, the pre-LC sits immediately rostral to the locus coeruleus (LC), but in mice the anatomic distinction between pre-LC and LC is more complex. Here we use molecular markers and anterograde axonal tracing to clarify and compare the location, identity, and distribution of pre-LC neurons in mice, relative to rats. First, we label the activity marker c-Fos and the transcription factor FoxP2 in the hindbrain of sodium-deprived rats to show their co-localized distribution, which defines the pre-LC. Next, in both sagittal and axial planes we compare the distribution of this FoxP2+ population with markers for surrounding catecholaminergic and cholinergic neurons. Then, in mice, we use chemogenetic activation of aldosterone-sensitive HSD2 neurons to drive Fos activation and identify the homologous distribution of pre-LC neurons. Combining this information with synaptophysin-mCherry axonal labeling, we find that pre-LC neurons receive dense afferent projections from the infralimbic cortex, arcuate AgRP neurons and paraventricular nucleus of the hypothalamus, and HSD2 neurons in the nucleus of the solitary tract. This information clarifies the location and distribution of pre-LC neurons in mice, providing a foundation for cell-type-specific studies of their properties and functions in the future. Pre-LC neurons receive appetitive and other homeostatic information from a wide range of brain regions (descending from cortex and hypothalamus and ascending from lower brainstem) and may influence behaviors including sodium appetite.

Disclosures: **S. Gasparini:** None. **A.M. Gore:** None. **L. Peltekian:** None. **J.C. Geerling:** None.

Poster

680. Central Regulation of Thirst and Water Balance

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 680.09/T2

Topic: F.09. Thirst and Water Balance

Support: FAPESP #2016/19051-2
FAPESP #2013/09799-1
CNPq #303171/2016-2

Title: Giot1 participates in the modulation of ingestive behavior

Authors: *A. R. TERRA DOS SANTOS[1], W. L. REIS[1], J. B. LIMA[1], J. T. DOMINGUES[1], L. D. DE ARAUJO[1], M. GREENWOOD[2], M. GREENWOOD[2], L. L. K. ELIAS[1], D. MURPHY[2], J. ANTUNES-RODRIGUES[1];
[1]Univ. of Sao Paulo, Ribeirao Preto, Brazil; [2]Univ. Bristol, Bristol, United Kingdom

Abstract: Gonadotropin inducible ovarian transcription factor 1 (*Giot1*) is a kruppel-type zinc finger protein induced by gonadotropin in teca cells of the ovary and also identified in the central nervous system areas related with hydromineral and energy homeostasis. Osmotic challenges induce simultaneously an increase in the *Giot1* and AVP mRNA expressions in the paraventricular nucleus (PVN). Our hypothesis is that Giot1 has a central role on the ingestive behavior, and it may underlie the E2 effects on energy homeostasis. To confirm this hypothesis, female Sprague-Dawley(200g) rats with free access to diet and fluids were maintained on metabolic cages. Water was offered during 8 days followed by water and 0.3M NaCl solution during 12 days. After these 20 days, animals were randomly assigned into the *Giot1* gene knockdown group and submitted to a bilateral microinjection of small hairpin RNA expressing lentiviral vector (shGiot1) into the PVN. shGFP lentivirus was used as control group (Scramble group). After recovery, the ingestive behavior was recorded during 20 days. The estrous cycle was verified daily along the experiment. This study was conducted following the "Guide for the Care and Use of Laboratory Animals" (NIH Publication nº85-23, 1996). The *Giot1* knockdown decreased the salt preference compared with the scramble group (63.4% ± 1.6, n=6 vs. 68.8% ± 2.0, n=6; *p*=0.04). On the other hand, the *Giot1* knockdown group had a higher food intake compared with the scramble group (12.4g ± 0.2, n= 6 vs. 10.2g ± 0.2, n= 6; *p*=0.0001), with no difference in the body weight (shGiot1: 252g ± 2.0, n= 6 vs. Scramble: 246g ± 2.3, n= 6; p=0,06). Radioimmunoassay analysis also revealed a differential hormonal response in AVP (Scramble: 1.0 pg/ml ± 0.01, n=6 vs. shGiot1: 0.6 pg/ml ± 0.1, n=6; p=0.05) and ANGII (Scramble: 31.8 pg/ml ± 9; n=6 vs. shGiot1: 14.8 ± 1.5, n=6; p=0.02) secretion. In a second set of experiments, after 21 days of bilateral microinjection of shGiot1 or shGFP into the PVN, female rats were water deprived (WD) for 48h. After that, water and 0.3M NaCl intake were

evaluated. shGiot1 animals had a decrease in 0.3M NaCl intake (2.7 ml/BW ± 0.2 vs. 3.5ml/BW ± 0.2; n=10; p=0.02), compared with scramble animals. These Giot1 effects were associated with a decrease in the plasma AVP of shGiot1 group compared to Scramble group (1.1 pg/ml ± 0.1 vs. 2.4 pg/ml ± 0.3; n=10; p=0.002) and ANGII (31.5 pg/ml ± 2.3 vs. 66 pg/ml ± 4,7; n=10; p=0.005) concentrations after WD. In conclusion, *Giot1* in the PVN is likely to participate in the regulation of ingestive behavior, modulating food intake as well as salt appetite. The mechanisms underlying these effects of Giot1 need to be further investigated. Support: FAPESP.

Disclosures: **A.R. Terra Dos Santos:** None. **W.L. Reis:** None. **J.B. Lima:** None. **J.T. Domingues:** None. **L.D. De Araujo:** None. **M. Greenwood:** None. **M. Greenwood:** None. **L.L.K. Elias:** None. **D. Murphy:** None. **J. Antunes-Rodrigues:** None.

Poster

680. Central Regulation of Thirst and Water Balance

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 680.10/T3

Topic: F.09. Thirst and Water Balance

Support: NIH Grant DK107500

Title: Angiotensin II-responsive brain areas relay with structures involved in associative learning

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Abstract: Recent studies provide evidence for a role of associative learning in the enhanced response observed after daily injections of angiotensin II (AngII). Specifically, the findings suggest that an observed increased drinking response after daily AngII involves a strengthening of the association between the stimulus (AngII) and the response (drinking). This effect appears to be mediated in part, by NMDA receptor activation, a critical component in associative learning, and there is a rich literature demonstrating the importance of the hippocampus in associative learning. Although the neural pathways that connect drinking-related structures to areas involved in associative learning are poorly understood, we hypothesized the existence of a relay between the median preoptic nucleus (MnPO), a critical area for the drinking response to AngII, and the hippocampus. To test this hypothesis, we made injections of a retrograde tracer (CTb) into the hippocampus and made MnPO injections of an adeno-associated virus (AAV2/10) that is transported anterogradely and expresses mCherry under the CMV promoter. Retrogradely labeled cell bodies and anterogradely labeled fibers were found in several brain areas, but the most striking overlap of the two was in the paraventricular nucleus of the thalamus (PVT). This finding is consistent with the well-studied role of the PVT in learning and memory processes,

and offers a novel circuit by which Ang-II-related signals in the MnPO can access the hippocampus.

Disclosures: Q.E. Carroll: None. **D. Daniels:** None.

Poster

680. Central Regulation of Thirst and Water Balance

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 680.11/T4

Topic: F.09. Thirst and Water Balance

Support: CIHR

Title: The effects of MDMA on central circuits mediating fluid balance in rodents

Authors: *J. C. WYROSDIC, C. W. BOURQUE;
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Abstract: Clinical data discloses a large increase in locomotor activity, and body temperature after MDMA ingestion, due to the context in which the drug is consumed and MDMA's amphetamine qualities. To examine the behavioral aspect and validate the rodent model of MDMA, C57 mice received a subcutaneous telemetry implantation which recorded activity, and body temperature every 120s for 9 consecutive days. The IP administration of MDMA at 15mg/kg, which is equivalent to a human "party" dose caused an increase in body temperature, as well as heightened locomotor activity during the light phase in comparison to the saline injected controls. These two behaviors also stayed elevated in the MDMA treated animals hours after the injection. Clinical data also proposes that MDMA increases water intake by inducing the sensation of thirst, and to promote fluid retention by the kidney. These effects account for the high incidence of cases of hyponatremia (low blood sodium and excel water in serum) in patients visiting hospital emergency departments as a result of experiencing headaches and dizziness (and other signs of hyponatremia) following ingestion of MDMA. Clinical as well as rodent studies also reveal an increase in serum vasopressin levels when MDMA is ingested or administered, which is likely a key factor in fluid retention. To investigate the neurophysiological mechanisms underlying these effects brain slices obtained from transgenic rodent brains (rats and mice) were prepared at a specific angle to preserve circuitry important for the regulation of thirst and vasopressin release. Whole cell current clamp recordings from identified vasopressin neurons revealed that a bath application of 10μm of MDMA causes an excitatory response; mediated by membrane depolarization. Moreover, a proportion of tonically active vasopressin neurons were observed to transition to a phasic firing pattern known to facilitate peptide release. These results suggest that MDMA can act directly on neurons controlling fluid balance thereby promoting hyponatremia.

Disclosures: **J.C. Wyrosdic:** None. **C.W. Bourque:** None.

Poster

680. Central Regulation of Thirst and Water Balance

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 680.12/T5

Topic: F.09. Thirst and Water Balance

Support: NSERC 245395

Title: Anatomical organization of the subfornical organ

Authors: ***A.-I. HICKS**[1], S. KOBRINSKY[2], M. PRAGER-KHOUTORSKY[3];
[1]Physiol., [3]Ctr. for Res. in Neurosci., [2]McGill Univ., Montreal, QC, Canada

Abstract: The subfornical organ (SFO) is one of the brain's sensory circumventricular organs (CVOs), which are highly vascularized midline structures lacking a complete blood-brain barrier (BBB). CVOs are characterized by the presence of tanycytes, specialized glia-like cells lining the ventricular floor of the CVOs and interacting with fenestrated vasculature. Due to the lack of a complete BBB, SFO and other CVOs are unique sites where peripheral circulating factors can penetrate into the central nervous system, influencing neuronal activity and allowing brain cells to monitor blood-borne signals. This provides the brain with information from the periphery and contributes to the generation of centrally-mediated physiological responses to humoral feedback and physiological stressors. Accordingly, SFO plays a key role in the regulation of cardiovascular status, hydromineral balance, energy metabolism. SFO neurons express a variety of receptors for peripheral signals. Moreover, SFO neurons can be activated by numerous circulating molecules associated with fluid balance (e.g. angiotensin II, sodium, endothelin, vasopressin) and energy metabolism (e.g. leptin, ghrelin, glucose). While extensive studies have focused on the characterization of the SFO neurons and their roles in the regulation of cardiovascular and metabolic status, the contribution of non-neuronal cells to this regulation is unclear. In this study, we use histological techniques to characterize the anatomical organization of the SFO and to examine the location of non-neuronal cells, including tanycytes, astrocytes, ependymocytes, fenestrated and non-fenestrated vasculature, as well as neurons, within its confines.

Disclosures: **A. Hicks:** None. **S. Kobrinsky:** None. **M. Prager-Khoutorsky:** None.

Poster

681. Development: Diet and Metabolism

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 681.01/T6

Topic: F.10. Food Intake and Energy Balance

Support: NIDDK Intramural Research Program

Title: Gender-specific regulation of brain inflammation and metabolism by erythropoietin in mice

Authors: S. DEY[1], M. GASSMANN[2], *C. T. NOGUCHI[1];
[1]Mol. Med. Br., Natl. Inst. of Diabetes and Digestive and Kidney Dis., Bethesda, MD; [2]Inst. of Vet. Physiol., Univ. of Zurich, Zurich, Switzerland

Abstract: Diet-induced obesity (DIO) is closely linked with increase in hypothalamic inflammation, disruption of glucose homeostasis, and activation of the hypothalamic-pituitary-adrenal (HPA) axis. Erythropoietin (Epo) is known to regulate metabolism and has been shown to prevent inflammation in white adipose tissue (WAT) and improve insulin sensitivity and glucose tolerance. We hypothesized that Epo signaling in brain could regulate hypothalamic inflammation, maintain metabolic homeostasis, and prevent HPA axis activation in a high fat-diet (HFD)-fed mouse model of DIO. We examined a mouse model of chronic over-expression of transgenic human *EPO* in brain (*Tg21*). HFD-induced weight gain compared to WT mice was significantly lower in male *Tg21* mice only, and not in females. Immunofluorescent staining of the arcuate nucleus (ARC) region of hypothalamus showed increased inflammatory TNFα and activated microglia marker Iba1 expression with HFD-feeding in male and female WT and *Tg21* mice compared to regular-chow-diet (RCD)-fed mice, and a greater inflammatory response in male mice. Furthermore, only males showed lower TNFα and Iba1 in *Tg21* mice than wild type (WT) counterparts. Compared to RCD-fed mice, males also showed the number of cells staining for non-activated microglial marker P2Y12 decreased in HFD WT mice and increased in HFD *Tg21* mice. Similarly, CD169 positive macrophage (Mϕ) recruitment from periphery after HFD was increased in male WT mice and lower in male *Tg21* mice. These changes were not observed in female WT and *Tg21* mice, and female mice did not show any CD169 positive cells, suggesting no Mϕ recruitment. Only males showed HFD-feeding in WT mice increased phospho-Erk in the hypothalamus, Corticotropin-releasing hormone (CRH) expression, serum ACTH and corticosterone levels compared to HFD-fed *Tg21* mice. Interestingly, both male and female *Tg21* mice showed significantly improved glucose tolerance and insulin sensitivity, under both RCD and HFD. Serum Fgf21 was increased in *Tg21* mice on RCD and unchanged on HFD. HFD increased Fgf21 in WT mice only. Adiponectin, a cytokine produced in WAT by Fgf21 response, was lower in HFD-fed WT mice, suggesting Fgf21-resistance developing in WT mice

during DIO. In summary, our studies show that Epo over-expression in male and female mouse brain improved glucose homeostasis possibly through maintaining FGF21 sensitivity of WAT adiponectin production in DIO. We also provide evidence for gender-specific Epo regulation in brain to protect male mice against DIO associated brain inflammation and microglial cell activation in the hypothalamus, and activation of HPA axis.

Disclosures: S. Dey: None. **M. Gassmann:** None. **C.T. Noguchi:** None.

Poster

681. Development: Diet and Metabolism

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 681.02/T7

Topic: F.10. Food Intake and Energy Balance

Support: KAKENHI from JSPS (17K07809)

Title: Dietary oleic acid modulates feeding behavior by controlling OEA response

Authors: *M. IGARASHI[1], K. IWASA[2], K. YOSHIKAWA[2], T. TSUDUKI[3], I. KIMURA[1]; [1]Tokyo Univ. of Agr. and Technol., Fuchu, Japan; [2]Saitama Med. Univ., Iruma, Japan; [3]Tohoku Univ., Sendai, Japan

Abstract: Gastrointestinal tract plays an important role in initiating hormonal and neuronal control for energy metabolism in responding to the nutrients. Previous studies in humans and rodents have suggested that obesity condition reduces levels of gut-derived peptide hormones such as cholecystokinin, and therefore leads to decreased satiety and overeating behavior. In addition to the peptide hormones, oleoylethanolamide (OEA), a derivative of dietary oleic acid, has been reported as a lipid-derived satiety factor in the gut. In this study, we investigated how dietary fat, especially dietary oleic acid, affects biosynthesis of OEA and feeding behavior in mice. Our study indicated that low levels of dietary oleic acid reduced jejunal OEA levels and increased food intake under low-fat diet condition. However, the low oleic acid diet did not affect body weight gain. These effects were not observed when mice were treated with capsaicin. Furthermore, infusion of lipids or oleic acid into upper gut stimulated jejunal OEA production in mice, associating with the reduction of substantial food intake. On the other hand, intestinal OEA production was reduced in the mice fed with a high fat diet that contains high levels of oleic acid, compared to low-fat diet (lab chow). Collectively, these findings suggest that imbalance between oleic acid and fat amount alters the intestinal OEA biosynthesis and satiety, suggesting that balanced dietary fat intake is important in controlling feeding behavior.

Disclosures: M. Igarashi: None. **K. Iwasa:** None. **K. Yoshikawa:** None. **T. Tsuduki:** None. **I. Kimura:** None.

Poster

681. Development: Diet and Metabolism

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 681.03/T8

Topic: F.10. Food Intake and Energy Balance

Support: Proap/CAPES
UFCSPA

Title: Dietary interventions during reproductive period affects metabolic profile in dam's mice and the behavioral parameters of the offspring in a long-term

Authors: J. FISCH, V. FEISTAUER, A. A. ANDRADE, V. B. BOLLIS, C. K. S. OLIVEIRA, A. DE MOURA, R. P. GUEDES, ***A. G. BARSCHAK**, M. GIOVENARDI;
Univ. Federal de Ciências da Saúde de Porto Alegre, Porto Alegre, Brazil

Abstract: Genetic and environmental factors related to maternal diet may predispose offspring to serious diseases. Mounting evidence has shown that maternal nutritional status may affect the progeny not only in a short-term but also in a long-term way, since some dysfunctions may appear only in the adulthood. However, consequences of a maternal diet intervention during gestation and lactation, and its association with caloric restriction after weaning on the progeny are not completely known. Besides, there is a lack of information regarding the impact of nutrition on maternal health. The present study analyzed the metabolic profile and maternal behavior of 30 female BALB/c mice. The animals were divided into three groups (10 per group) and received standard (CONT), hypercaloric (HD) or restrictive diet (RD) during mating, pregnancy and lactation. On the first postpartum day (PPD), the litters were standardized to 6 pups, which were weighted on PPD 3, 8, 12 and 21. Maternal care behavior was assessed by the pup retrieval test on the 7^{th} postnatal day (PND). We also investigate how the different maternal diets may affect the behavior of the female offspring that was also submitted to RD. The female offspring were divided into 6 groups (10 female per group) abbreviated accordingly maternal/offspring diets: CONT/CONT, CONT/RD, RD/CONT, RD/RD, HD/CONT, HD/RD. Around 70 days of age, the animals were submitted to the behavioral tests in the diestrus period. First, the animals were submitted to the open field test, one week later they were analyzed in the elevated plus maze and after another week of interval they were submitted to the novel object recognition test. We found a significant increase in triglycerides ($p=0.0004$) and leptin ($p=0.0007$) concentration of the HD dams group compared to CONT and RD. RD-fed mice exhibited an increase in the number of days necessary to become pregnant in comparison to the CONT group ($p=0.027$), but no differences among groups were found in the maternal care. Offspring from RD-fed dams exhibited a decrease in lateral area locomotion in the open field test ($p=0.001$). Evaluation of anxiety-like behavior and recognition memory showed no significant

difference among groups. In conclusion, HD promoted metabolic dysfunction in the dams and RD did not cause any harmful effect during reproductive period and lactation. The maternal diet, during gestation and lactation, influences behavior responses of the offspring in a long-term.

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Poster

681. Development: Diet and Metabolism

Location: Hall A

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Topic: F.10. Food Intake and Energy Balance

Support: SEP-PRODEP (DPOR) convenio 511-6/17-8021

Title: Maternal consumption of sugar-sweetened beverages in pregnancy and lactation alters food preferences in the Wistar rat offspring

Authors: *D. OLIVO RAMIREZ, C. QUINTERO NARANJO, L. ROJAS ROSAS, G. LÓPEZ RODRÍGUEZ, M. GALVÁN;
Área Académica de Nutrición, Univ. Autónoma del Estado de Hidalgo, Pachuca, Hidalgo, Mexico

Abstract: Consumption of beverages sweetened with caloric-sweeteners is associated with obesity. Maternal diet can influence food preferences in the offspring. The aim of this study was to evaluate body weight, adipose tissue (AT) and food preferences in Wistar rat offspring exposed during pregnancy and lactation to sugar sweetened beverages. Dams of Wistar rats had access to a drink with caloric sweeteners (10% v/w); groups: sucrose (SU), high fructose corn syrup (HFCS) and dextrose (DEX) or water (control group) during pregnancy and lactation. Seven days after weaning, body weight was measured in the pups (n=8 per group). Six males and six females born of each group (CO, SU, HFCS and DEX) were evaluated with a two-choice diet test (standard diet: SD vs high fat diet: HFD) for 6 weeks (postnatal week 5 to 10); body weight and food consumption (Kcal) were measured every 48 hours. At the end of the test, gonadal, mesenteric and retroperitoneal adipose tissue were dissected and weighed. The data was processed with the statistical package SPSS v.16.0 Data are reported as mean ± SEM. Body weight were analyzed with a repeated measures ANOVA; HFD and SD intakes (Kcal/day) and % AT/body weight were analyzed using a one-way ANOVA; Tukey pos hoc test was used in both cases. Seven days after weaning, pups' body weight in CO group was significantly lower (48.80±1.46 g) than the pups of rest of the groups (SU: 69.79±1.47, HFCS: 65.34±1.28, DEX: 57.65±2.01 g: $p<0.05$ in all cases). During the two-choice diet test, males and females offspring

of the HFCS and DEX groups consumed significantly more Kcal per day from the HFD than the CO group (males: AF: 65.69±5.97, DEX: 63.17±3.93 vs CO: 43.95±4.35 Kcal/day; females: AF: 51.28±3.52, DEX: 61.40±3.60 vs CO: 38.88±3.07 Kcal/day). At the end of the food test, females with maternal exposition to caloric beverages were heavier than the CO group (SU: 198.66±6.07, HFCS:184.00±8.06, DEX:193.83±5.51 vs CO:163.33±3.81 g; ANOVA, $p<0.05$) and accumulated more percentage of AT/body weight (SU: 3.33±0.40, HFCS: 4.10±0.30, DEX: 3.81±0.40 vs CO: 2.13±0.16 %; ANOVA, $p<0.05$). The males of the experimental groups did not show differences in body weight, however, those exposed to caloric beverages during pregnancy and lactation accumulated more retroperitoneal AT compared to CO (SU:1.63±0.11, HFCS:1.32±0.12, DEX:1.40±0.10 y CO:0.87±0.10 %; ANOVA, $p<0.05$). These results suggest that the consumption of caloric sweeteners during pregnancy and lactation influences food preferences, body weight and accumulation of AT in the Wistar rat offspring, being these consequences more marked in females than in males.

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Poster

681. Development: Diet and Metabolism

Location: Hall A

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Program #/Poster #: 681.05/T10

Topic: F.10. Food Intake and Energy Balance

Support: NIH R01 DK61935 (MJT)
NIH 5U2C-DK093000 (JK)
NIH 5U24 DK076169-13 (RM): 30835-64 (Subaward KDA)

Title: Estradiol-mediated protection from diet-induced obesity in female mice is associated with changes in gut microbiota

Authors: *K. D. ACHARYA[1], M. GRAHAM[1], H. NOH[2], S. SUK[2], R. FRIEDLINE[2], J. CHEN[3], J. KIM[2], M. TETEL[1];
[1]Wellesley Col., Wellesley, MA; [2]Univ. of Massachusetts Med. Sch., Worcester, MA; [3]Mayo Clin., Rochester, MN

Abstract: A decrease in estrogens in postmenopausal women increases their risk of adiposity and predisposes them to cardiovascular disease, type 2 diabetes, chronic inflammation, and cancer. Similarly, in female rodents, loss of estrogens by ovariectomy and high fat diet (HFD) feeding increases food intake, attenuates physical activity and causes obesity. In addition to estrogens, gut microbiota are also implicated in energy homeostasis. In the current study, we investigated if estrogens alter gut microbiota and if these changes are linked to estrogen-

mediated protection from obesity. Ovariectomized adult C57BL6/J mice received implants containing estradiol (E2; 50 µg) or vehicle (Veh) (n=6/group). Mice were fed a standard diet (SD) for the first two weeks and then fed a HFD for four weeks. Fresh fecal samples were collected during SD and HFD for 16S rRNA gene sequencing. Effects of E2 and HFD on longitudinal metabolic changes, including food intake, energy expenditure, and physical activity, were measured using metabolic cages. Plasma glucose, cytokines and hormones, including insulin, leptin, and resistin, were measured during SD and HFD. Insulin sensitivity and glucose metabolism were measured using hyperinsulinemic clamp in awake mice. Tissue-specific muscle glucose uptake and triglycerides were also measured. E2 treatment protected ovariectomized mice from HFD-induced obesity, primarily by increasing energy expenditure, physical activity, insulin sensitivity, and glucose utilization. Parallel changes in microbial communities were observed as an effect of both E2 and HFD. E2 increased the phylum Verrucomicrobia and its genus *Akkermansia,* implicated in mucin degradation and maintenance of healthy gut epithelial barrier. Veh mice showed greater abundances in the families Clostridiaceae (during both diets), and Erysipleotrichaceae and Streptococcaceae (during HFD only). HFD profoundly affected microbiota by reducing microbial richness and increasing evenness. HFD also increased multiple taxa, including *Bacteriodes* (phylum Bacteriodetes), *Clostridia* (phylum Firmicutes), and *Coriobacteria* (phylum Actinobacteria), which are linked to HFD-induced weight gain in humans. In summary, the current findings suggest that E2-mediated protection against diet-induced obesity and metabolic dysregulation are dependent on changes in gut microbiota. Currently, we are analyzing correlations between specific metabolic and microbial changes to understand how these factors could affect each other. These results may provide important insights in the development of potential microbial targets for the treatment of metabolic dysregulation in women.

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Poster

681. Development: Diet and Metabolism

Location: Hall A

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Program #/Poster #: 681.06/T11

Topic: F.10. Food Intake and Energy Balance

Support: Joel G. Hardman Chair in Pharmacology

Title: The role of CAPS1 RNA editing in energy homeostasis

Authors: *K. M. SHUMATE, R. B. EMESON;
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Abstract: Calcium-dependent activator protein for secretion 1, CAPS1, is a SNARE accessory protein that functions to promote vesicle priming at the plasma membrane during regulated exocytosis. CAPS1 is primarily expressed in the central nervous system and in endocrine tissues, and pre-mRNA transcripts encoding CAPS1 are subject to an adenosine-to-inosine (A-to-I) RNA editing event near the carboxyl-terminal domain, resulting in a glutamate-to-glycine (E-to-G) alteration in the encoded protein. Previous studies from our lab demonstrated that edited CAPS1 enhances the rate of vesicle exocytosis, suggesting that CAPS1 RNA editing may play a role in regulating physiologic events that involve neurotransmitter or peptide hormone release. Using genetically-modified mice solely expressing CAPS1 protein isoforms encoded by edited or non-edited RNAs, we have examined the effects of CAPS1 RNA editing on energy homeostasis. Mice solely expressing the edited isoform of CAPS1 were lean compared to wild-type littermates due to a loss of both lean and fat body mass. No differences were found in circulating levels of plasma growth hormone, insulin-like growth factor-1, thyroid stimulating hormone or total thyroid hormone (T4) levels, suggesting that the observed decrease in body mass for edited CAPS1 animals was not due a dysregulated hormone release from the anterior pituitary, thyroid gland, or liver. Edited CAPS1 animals were hyperactive in both novel and home cage environments, when compared to wild-type littermates, and displayed an increased energy expenditure during the dark phase, but not during light phase. While edited CAPS1 animals showed no difference in total food intake compared to wild-type littermates, increased meal frequency and reduced meal size was observed. These results indicate that mice solely expressing edited CAPS1 may have a dysregulated energy homeostasis that is primarily driven by a hyperactivity-dependent increase in energy expenditure. The absence of a compensatory increase in food intake, along with alterations in meal patterning, may contribute to a chronic energy deficit leading to the observed decrease in body mass. By contrast, mice solely expressing the CAPS1 isoform encoded by the non-edited RNA also were assessed for locomotor, metabolic, and feeding phenotypes, yet no significant differences were found when compared to wild-type animals, suggesting a normal energy homeostasis. Together, these studies provide initial evidence of a modulatory role for CAPS1 RNA editing in the regulation of energy balance.

Disclosures: K.M. Shumate: None. **R.B. Emeson:** None.

Poster

681. Development: Diet and Metabolism

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 681.07/T12

Topic: F.10. Food Intake and Energy Balance

Support: CONACyT A1-S-28619
PAPIIT IN224119

PAPIIT RA204618
UNAM DGAPA PAPIIT IN217117

Title: High fat diet modifies the feeding behavior and induces brain, colon and liver alterations which is not exacerbates by E17

Authors: *D. DIAZ-URBINA[1], E. I. MEDINA REYES[2], N. L. DELGADO BUEN-ROSTRO[2], V. E. LÓPEZ ALONSO[1], R. E. ESCARTIN PÉREZ[1], J. M. MANCILLA DÍAZ[1], J. L. REYES[1], M. I. GONZALES[2], Y. I. CHIRINO LÓPEZ[2];
[1]Lab. de Neurobiologia de la Alimentación, [2]Unidad de Biomedicina, Facultad de Estudios Superiores Iztacala-Unam, Mexico, Mexico

Abstract: High-fat diets not only modify the metabolism but also cause anxious symptomatology, producing increments of frequency and meal's size. Additionally, high-fat diets might be accompanied by the consumption of potentially risky food additives. Among these additives, food grade titanium dioxide (E171) has been related to tumor formation in the colon, which highlights its potential toxicity. After oral consumption, E171 is translocated to bloodstream reaching several tissues and crossing the blood-brain barrier may induce brain inflammation. The possibility that E171 may induce alterations in the brain raises the concern of exacerbation of the disturbances induced by high-fat diets, for instance, changes in satiety processing. Aim: To evaluate if oral consumption of E171 (5 mg/kg BW) modifies the satiety process and induce or exacerbate the alterations in brain, colon, spleen, and liver using a mice model feed with a high-fat diet during 16 weeks. POMC and AgRP gene expression was measured in the hypothalamus and was used as a marker of satiety. Methods: C57BL6 mice were divided into 4 groups as follows: a) Regular diet, b) regular diet + E171, c) high-fat diet and d) high-fat diet + E171, and they were maintained in the corresponding condition for 16 weeks. Body weight gain, and food and water intake were monitored weekly. In the last week of the study, the microstructure of feeding was analyzed during a 60-min period of continuous recording at the onset of the dark phase. The behavioral categories analyzed were meal size (g/min) and frequency, meal duration (s), latency for the first meal (s), local feeding rate, and inter-meal intervals. Next, mice were euthanized and brain, colon, spleen, and liver were extracted and mounted for histological analyses. Result: Both groups treated with E171 gradually decreased their weekly food intake compared to regular diet and regular diet + E171 groups. High-fat diet and high-fat diet + E171 groups gained up to 49% more body weight than mice with the regular diet and regular diet + E171. High-fat diet + E171 group consumed less food, had a reduction of the meal frequency and local feeding rate but increased the latency for the first meal and inter-meal intervals duration compared with the high-fat diet group. High-fat diet induced liver steatosis and colon adenomas, however high-fat diet + E171 did no exacerbate this effect. Conclusion: Oral intake of E171 did not exacerbate the high-fat diet effects on the colon (adenomas), liver (steatosis), and high-fat diet per se modified the feeding behavior in C57BL/6 male mice after 16 weeks

Disclosures: D. Diaz-Urbina: None. **E.I. Medina Reyes:** None. **N.L. Delgado Buen-Rostro:** None. **V.E. López Alonso:** None. **R.E. Escartin Pérez:** None. **J.M. Mancilla Díaz:** None. **J.L. Reyes:** None. **M.I. Gonzales:** None. **Y.I. Chirino López:** None.

Poster

681. Development: Diet and Metabolism

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 681.08/T13

Topic: F.10. Food Intake and Energy Balance

Support: NIH Grant R01AG042890

Title: Human umbilical derived mesenchymal stem cell transplant in adipose tissue improve fear conditioning memory in a diet-induced obese mouse model

Authors: *S. SAIEVA[1,3], B. KRISHNAN[1], N. ABATE[2], G. TAGLIALATELA[1];
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[3]Biomedicine, Neurosci. and Advanced Diagnostics, Univ. of Palermo, Palermo, Italy

Abstract: Insulin resistance characterizes Type 2 Diabetes mellitus (T2DM) as well as of Alzheimer's Disease (AD), particularly in CNS areas associated with cognitive performance, such as the hippocampus. A major risk factor for insulin resistance and T2D is adipose tissue (AT) dysfunction, which is mainly caused by obesity. High-caloric diets may lead to adipose tissue (AT)-insulin resistance, resulting in fatty acid spillover and ectopic fat deposition. Notably, high levels of FFA have been reported in AD patients; likewise, rodents fed with high-fat diets display peripheral insulin resistance, as well as hippocampal synaptic deficiencies with reduced insulin signaling and memory deficits. These observations suggest that improving peripheral insulin resistance may result in beneficial effects in CNS. Interestingly, the AT of T2DM/prediabetic patients show depletion of their mesenchymal stem cell (MSC) reservoirs, thus impairing adipocyte turnover and fat storage ability, thus suggesting that an exogenous delivery of mesenchymal stem cells directly in the adipose tissue could help in halting/reversing the insulin resistance and its systemic complications, including CNS deficits. To test this hypothesis, we transplanted human umbilical cord-derived mesenchymal stem cell in the epididymal adipose tissue of high-fat diet-induced obese (DIO) mice and tested their effect in both periphery and CNS. Along with a significant improvement of glycemia, we observed an improvement of freezing behavior in the contextual fear conditioning test in transplanted mice (accompanied by a tendential but not significant improvement in the cued environment). This memory benefit of the peripheral transplant, however, was not associated with any change in insulin receptor response in synaptosomes isolated from different areas of the brain, suggesting that further studies exploring diet-induced neuroinflammation and oxidative stress will be needed to fully explore the involved mechanisms. Nonetheless, these collective results suggest that retrieving the insulin signaling in periphery is also beneficial for CNS, thus potentially providing a novel viable therapeutic approach to treat obesity/T2DM-induced CNS deficits and possibly alleviate the impact of T2DM-related insulin resistance on clinical onset/progression of AD.

Disclosures: **S. Saieva:** None. **B. Krishnan:** None. **N. Abate:** None. **G. Taglialatela:** None.

Poster

681. Development: Diet and Metabolism

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 681.09/T14

Topic: F.10. Food Intake and Energy Balance

Title: Sensitivity to ghrelin is increased in female offspring of rat model of vertical sleeve gastrectomy

Authors: *R. A. SPANN, B. A. WELCH, B. E. GRAYSON;
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Abstract: Bariatric surgery is the most effective and durable means of treating obesity and its comorbidities. Women make up 80% of those receiving weight loss surgery and they experience improvements in fertility. Unfortunately, bariatric surgery in the context of pregnancy is associated with complications including intrauterine growth restriction (IUGR) and small for gestational age offspring (SGA). SGA offspring, then, have a greater risk for obesity in adulthood. The mechanism for this SGA-induced obesity is unknown. We have previously shown in a rat model of vertical sleeve gastrectomy (VSG), changes to ghrelin signaling, a stomach-derived hormone that increases appetite and induces growth hormone secretion. Pregnant VSG dams have a reduction in total and active circulating ghrelin compared to sham operated dams, and in placenta tissue, there is an increase in ghrelin O-aclytransferase (GOAT) mRNA expression in VSG dams, suggesting a drive to increase available ghrelin in the developing fetus. Here we hypothesize that postnatal VSG offspring will have an increased sensitivity to ghrelin compared to offspring of sham dams, in response to reduced *in utero* ghrelin. Exogenous ghrelin (100 ug/kg, IP) administered at postnatal day (PND) 14 to VSG and sham pups does not alter milk intake at all, consistent with the literature that postnatal week 2 pups do not respond to ghrelin. At PND21, male and female VSG offspring have an increase in mRNA expression for the ghrelin receptor (growth hormone secretagogue receptor) in the hypothalamus compared to sham offspring, and expression of GOAT is lower in females compared to males. Expression of other genes in the growth hormone system (growth hormone releasing hormone and growth hormone) are not altered. Plasma levels of total ghrelin at PND21 are also not different between VSG and sham pups. At PND112, one hour chow intake of female but not male VSG offspring given 100 ug/kg of exogenous ghrelin by IP injection is greater than sham offspring given exogenous ghrelin. These results indicate that maternal VSG surgery has an impact on ghrelin signaling in offspring and that as adults, female VSG offspring may be functionally more responsive to ghrelin. Future work will determine the contribution of ghrelin signaling to IUGR and SGA-induced obesity.

Disclosures: **R.A. Spann:** None. **B.A. Welch:** None. **B.E. Grayson:** None.

Poster

681. Development: Diet and Metabolism

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Program #/Poster #: 681.10/T15

Topic: F.10. Food Intake and Energy Balance

Support: NIH R01NS50465
NIH Grant R01 DK104363

Title: The conundrum of gaining weight: Blame it on genetics?

Authors: *Z. YING[1], G. ZHANG[1], X. YANG[1], F. GOMEZ-PINILLA[1,2];
[1]Integrative Biol. and Physiol., UCLA, Los Angeles, CA; [2]Dept. of Neurosurg., UCLA Brain Injury Res. Ctr., Los Angeles, CA

Abstract: One of the most fascinating questions in biomedical research is why individuals react differently to the same challenge or treatment. Metabolic challenges are among the most powerful driving forces of biological adaptations, with long-lasting consequences on homeostatic control and disease stages. High fructose consumption is increasingly recognized as a risk factor for the escalating prevalence of metabolic syndrome, posing significant risk for type 2 diabetes, cardiovascular diseases, obesity, and non-alcoholic fatty liver disease. We systematically examined the metabolic parameters and tissue-specific gene regulation in response to fructose treatment in multiple inbred mouse strains C57BL/6J (B6), DBA/2J (DBA), and FVB/NJ (FVB) due to their divergence in genetic composition. DBA mice showed the highest susceptibility to gain adiposity and glucose intolerance. Elevated insulin was found in DBA and FVB mice, and cholesterol levels were uniquely elevated in B6 mice. The transcriptional profiles of liver, hypothalamus, and adipose tissues showed strain- and tissue-specific pathways altered by fructose, including fatty acid and cholesterol pathways for B6 and PPAR signaling for DBA in liver, and oxidative phosphorylation and eating behavior for B6 and protein processing for DBA in hypothalamus. Using network modeling, we predicted potential strain-specific key regulators of fructose response such as *Fgf21* (DBA), *Lss* (B6) in liver, and validated the regulatory action of *Fgf21* and *Lss* in primary hepatocytes. Our findings show that fructose elicits specific arrangements in the organization of genes and pathways in separate tissues across genetically diverse mice, which seem responsible for distinct metabolic functions across genetically diverse mice. Our results suggest that the interaction between dietary challenges and genetics influences systemic metabolism by engaging gene regulatory pathways that are tissue specific.

Disclosures: **Z. Ying:** None. **G. Zhang:** None. **X. Yang:** None. **F. Gomez-Pinilla:** None.

Poster

681. Development: Diet and Metabolism

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 681.11/T16

Topic: F.10. Food Intake and Energy Balance

Support: UIUC start-up fund from the Department of Psychology to NCL

Title: Sex differences in the metabolic and cognitive outcomes of high fat diet preference and exercise in rats

Authors: *T. Y. YANG[1], Z. GAO[1], F. NAJERA[1], G. PETRUS[1], N.-C. LIANG[2];
[2]Psychology, [1]Univ. of Illinois-Urbana Champaign, Champaign, IL

Abstract: The modern obesogenic environment promotes overeating palatable, high fat (HF) foods and favors a sedentary lifestyle. Both factors work in combination to disrupt energy homeostasis and exacerbate the development of obesity. As a treatment intervention, exercise facilitates weight and fat loss to a greater extent in males than females. Using a two-diet choice (chow vs. HF) and wheel running (WR) paradigm, we have previously reported that running-induced HF diet avoidance is more common and persists longer in male than female rats. Given this, we hypothesized that sex differences in HF diet preference may predict sex-specific metabolic and cognitive outcomes of long-term HF feeding and that exercise would attenuate these HF-induced deficits. To test this hypothesis, rats underwent an oral glucose tolerance test before and after 6 weeks of WR and diet choice to assess the effects of HF feeding on glucose homeostasis. During the last week, rats were trained on the Barnes Maze and underwent tests of reversal learning to assess HF-mediated deficits in learning and cognitive flexibility. All sedentary (Sed) rats preferred the HF diet throughout the study. Female WR rats reversed running-induced HF diet avoidance ~3 weeks earlier than males. Following that reversal, WR females expressed higher whereas WR males maintained lower HF diet preference than their respective Sed controls. These sex differences in HF diet preference and adiposity were reflected in metabolic outcomes. Exercise suppressed weight gain and adiposity in males but not females. Only male WR rats showed improved glucose tolerance from that of their pre-HF feeding. These findings suggest that the ability for exercise improve energy metabolism and balance differs between the sexes. The interpretation of HF-induced deficits in cognitive flexibility was confounded by the finding that our Sprague-Dawley rats used a serial search strategy rather than spatial cues to locate the escape box on the Barnes Maze. Nevertheless, all rats learned to escape on the maze and on average, females had shorter latencies than males. Regardless of sex, WR rats had shorter latencies than Sed rats, which suggests that exercise may improve learning similarly for both sexes. Taken together, our results suggest that exercise may attenuate the

deleterious outcomes of HF feeding in a sex-dependent manner and highlights the importance of developing sex-specific treatment interventions for obesity.

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Poster

681. Development: Diet and Metabolism

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 681.12/T17

Topic: F.10. Food Intake and Energy Balance

Support: HHMI Precollege and Undergraduate Science Education Program
Washington & Lee University Lenfest & Levy Funds
Virginia Commonwealth Health Review Board, grant #349-02-15

Title: Access to snacks in female rats from weaning onward causes weight gain and signs of metabolic syndrome but does not alter hypothalamic POMC and NPY

Authors: H. R. ARCHER, R. A. CURTO, C. L. RODRIGUEZ, L. F. SMITH, M. A. SAMUEL, C. A. EASTERLIN, A. N. MINUTILLO, R. C. CLAWSON, K. A. BEZOLD, ***H. I'ANSON**; Biol., Washington & Lee Univ., Lexington, VA

Abstract: We have shown that snacking on healthy (HS) or unhealthy (US) snacks, in addition to chow, from weaning to adulthood causes weight gain, deposition of abdominal adipose tissue and symptoms of metabolic syndrome in a female rat model (*Phys. & Behav. 201:165-174, 2019).* Unlike high fat diet-induced obesity studies in adult human and animal models, HS and US rats experienced weight gain without an increase in daily caloric intake compared to control, chow-fed (CC) rats, suggesting that constant access to energy facilitated weight gain due to a change in feeding patterns rather than hyperphagia. Obesity and metabolic syndrome have been associated with hypothalamic neuronal injury and a decrease in proopiomelanocortin (POMC) cell number *(J. Clin. Invest. 122:153-162, 2012).* We therefore determined if snacking caused a similar decline in POMC cell neuron number in the hypothalamus of HS and US rats compared to CC rats. POMC neurons were visualized in the anterior hypothalamus (AH) and arcuate nucleus (ARC) of CC, HS and US female rats using immunocytochemistry. While there were similar significant POMC cell number differences across regions in all groups (AH and rostral, medial and caudal ARC; $P<0.0001$), there was no difference in total POMC cell number between snacking and control rats ($P=0.4$). These data suggest that development of metabolic syndrome due to snacking does not result in a decline in hypothalamic POMC neurons in our model. We next determined gene expression of POMC and Neuropeptide Y (NPY) within the hypothalamus using RT-qPCR since these neuron populations are considered critical components in regulating

energy balance. Relative gene expression analysis revealed similar expression patterns in both POMC and NPY between snacking and control rats (p=0.3 and 0.6, respectively). These data suggest that snacking from weaning does not cause inappropriate hypothalamic POMC and NPY neuron functioning, as has been demonstrated in adult animal studies. Further, because our rats show altered feeding behavior with both healthy and unhealthy snacking, but no increase in caloric intake, our findings indicate that the temporal effects of snacking and not the nutrient composition may alter metabolism if snacks are added to the diet from weaning onwards.

Disclosures: H. I'Anson: None. **H.R. Archer:** None. **R.A. Curto:** None. **C.L. Rodriguez:** None. **L.F. Smith:** None. **M.A. Samuel:** None. **C.A. Easterlin:** None. **A.N. Minutillo:** None. **K.A. Bezold:** None. **R.C. Clawson:** None.

Poster

681. Development: Diet and Metabolism

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 681.13/T18

Topic: F.10. Food Intake and Energy Balance

Title: Early hipercaloric diet exposure reduces brain BDNF content and impacts on episodic memory in Wistar rats

Authors: *K. BERTOLDI[1], R. P. PALAZZO[1], A. GREFENHAGEN[1], B. B. DA SILVA[1], L. C. F. DE MEIRELES[2], I. L. S. TORRES[1], I. R. SIQUEIRA[1];
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Abstract: Exposure to hypercaloric caloric diets has been related to cognitive function impairment in the offspring at adulthood. However, the diet effects on early developmental phases and the neurochemical mechanisms involved needs more studies. It has been demonstrated that gestational exposure to hypercaloric diets may alter central BDNF levels as well as HDAC5 expression, moreover a relationship between HDAC5 levels and BDNF expression has been proposed. Our aim was to evaluate the effect of early exposure - gestational and lactational phases - to cafeteria diet on memory performance and eating behavior as well as HDAC5 and BDNF content in hippocampus and olfactory bulbs of male and female *Wistar* rats. The Institutional Committee for Animal Care and Use of the Hospital de Clínicas de Porto Alegre (GPPG/HCPA #160561) approved all procedures. Pregnant females were randomized in standard or cafeteria diet groups. The cafeteria diet group was exposed to diet in gestational and lactational phases. The offspring weight was evaluated in PND 2 and PND 21. The nest odor preference and eating behavior tests were performed in PND 7 and PND 20, respectively. Rats were decapitated 24 h after the eating behavior test (PND 22). Hippocampus and olfactory bulbs were dissected out and used to quantify HADC5 and BDNF contents by western blot. Animals

exposed to the cafeteria diet showed lower weight compared to standard diet animals only in PND 2 (p=0.013). Pups whose dams were exposed to cafeteria diet up to PND 7 showed the classic paradigm of conditioning, since they demonstrated reduced preference for the nest bedding compared to standard diet animals. The early exposure to hypercaloric diet increased the number of meals associated with a lower first inter-meal interval in both gender; moreover the total food consumption increased (p=0.009) which can suggest the diet impact on episodic memory of a meal in PND 20, without any impact on weight. Exposure to cafeteria diet reduces the BDNF content in olfactory bulb (p=0.002) and hippocampus (p=0.006). Additionally, we observed an increase in HDAC5 content in hippocampus (p=0.02), however, this increase was observed only in olfactory bulbs of female rats (p=0.005). It is possible to infer that lower BDNF levels in the olfactory bulb and hippocampus can reflect a worse episodic memory. Moreover, the reduced BDNF levels induced by our diet protocol might be related to an increase in HDAC5 content since this epigenetic marker has been associated with BDNF expression regulation.

Disclosures: **K. Bertoldi:** None. **R.P. Palazzo:** None. **A. Grefenhagen:** None. **B.B. da Silva:** None. **L.C.F. de Meireles:** None. **I.L.S. Torres:** None. **I.R. Siqueira:** None.

Poster

681. Development: Diet and Metabolism

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Topic: F.10. Food Intake and Energy Balance

Support: CNPq Brazil
Doc-Fix FAPERGS/CAPES 09-2012
CAPES/PNPD 07/2016
GPPG/HCPA Brazil Grant 11-0455

Title: Hypercaloric-induced obesity is influenced by chronic stress and can be modulated by transcranial direct-current stimulation (tDCS) in male wistar rats

Authors: *D. J. STEIN[1,3], J. S. DE FREITAS[2], C. DE OLIVEIRA[2,4], I. C. MACEDO[5], I. L. S. TORRES[2,3];
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Abstract: Chronic stress and metabolic diseases are intricately associated and influence the escalating prevalence of obesity observed in humans in the past few decades. This medical condition has reached epidemic proportions, leading to a global public health issue. Associated with several comorbidities, obesity raises mortality rates in modern societies mainly because of

the lack of prevention and poor treatment options. In this study, we investigated the effects of bicephalic tDCS on hypercaloric-induced obesity in adult male Wistar rats (n = 80) that were or not exposed to restraint stress. Animals were randomly allocated to one of the following groups: standard diet + sham tDCS (SDS), standard diet + tDCS (SDT), standard diet + sham tDCS + stress (SDSS), standard diet + tDCS + stress (SDTS), hypercaloric diet + sham tDCS (HCDS), hypercaloric diet + tDCS (HCDT), hypercaloric diet + sham tDCS + stress (HCDSS), hypercaloric diet + tDCS + stress (HCDTS). Obese and control rats were evaluated for behaviors in the open-field and in the elevated plus-maze tests. Caloric intake, body weight gain, liver, adrenal and adipose tissue weight were measured. Additionally, central BDNF, NPY, IL-10, IL-1β, and TNF-α were evaluated at the end of the experimental protocol. Palatable food consumption test was performed in obese and control animals under fasting and feeding conditions. Hypercaloric diet rapidly increased weight gain and visceral fat mass. After 40 days of diet and stress, eight daily 20 min. sessions of 0.5 mA tDCS reduced weight gain only in obese rats while restraint stress has exacerbated this reduction. tDCS reduced BDNF and inflammatory markers in the cerebral cortex and decreased the amount of palatable food consumed under both fasting and feeding conditions. Restraint stress produced an anxiogenic effect only in control animals. These results suggest that bicephalic tDCS may change palatable food consumption and alter inflammatory parameters in the cortex, both influenced by stress and obesity.

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Poster

681. Development: Diet and Metabolism

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Topic: F.10. Food Intake and Energy Balance

Support: FAPESP Grant 2016/13136-6
CAPES

Title: Maternal food restriction reduces cocaine and amphetamine regulated transcript (CART) neurons in the lateral hypothalamic area of aged rats

Authors: *C. M. MACHADO[1,3], M. G. MARTINS[2], I. Z. GUIATI[4], J. C. BITTENCOURT[5], J. C. HORTA, Jr.[1];
[1]Anat., [2]Physiol., Inst. of Biosci. of Botucatu, Botucatu, Brazil; [3]Faculdades Integradas de Bauru, Bauru, Brazil; [4]Basic Sci., Sch. of Dent., Araçatuba, Brazil; [5]Anat., Inst. of Biomed. Sci., Sao Paulo, Brazil

Abstract: Maternal nutrition during critical periods of individual development is essential, since nutrient deficiency during pregnancy and lactation causes significant changes in body weight, energy balance, food intake and neuropeptides expression. The cocaine and amphetamine regulated transcript (CART) is a neuropeptide widely expressed in the lateral hypothalamic area (LHA) that is involved in the regulation of energy balance and feeding behavior, in which CART plays an anorexigenic role. However, there is no information about the long-lasting effects of maternal food restriction on CART neurons in the LHA. Our aim was to analyze the number and distribution of CART neurons and their ultrastructure in the LHA of rats whose mothers were subjected to food restriction during pregnancy and lactation. After pregnancy confirmation, female Wistar rats were divided in two groups: control group (CG), ad libitum standard chow, and caloric restriction group (RG), 50% chow restriction compared to the control group during pregnancy and lactation. The male pups from both groups were divided into five age subgroups (n = 8): PND 21, 28, 50, 90 and 540. Biometric parameters, food intake and glycemia were also evaluated. Brains were processed for analysis of number, distribution and ultrastructure of CART neurons in the LHA, according to immunohistochemistry protocols for light (n=5) and transmission electron microscopy (n=3). The mapping and estimate of CART neurons in the LHA were performed using 3-D reconstruction and stereological study. Quantitative data were statistically analyzed ($p<0.05$). Our data indicated that maternal caloric restriction decreased body weight, body length, brain weight and visceral and retroperitoneal adipose tissues throughout life. No differences between groups were observed in the glucose metabolism and food efficiency, although the relative food intake was increased in RG. Stereological data have shown a decreased number of CART neurons in the LHA of RG540. LHA area and volume were smaller in RG in PND 21, 50 and 90. Changes were also observed in the distribution of CART neurons in RG540, with lower number of neurons in the perifornicial region and caudal sections of LHA. No ultrastructural alterations in CART neurons were caused by maternal caloric restriction during pregnancy and lactation. In conclusion, maternal food restriction during pregnancy and lactation changed biometric parameters in the offspring and their food intake. Furthermore, maternal undernutrition decreases CART neurons and their distribution in LHA of the aged rats, with no effects on this neuropeptide ultrastructure.

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Poster

681. Development: Diet and Metabolism

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Support: BBRF 2015 Young Investigator NARSAD

Texas Woman's University Research Enhancement Program
Texas Woman's University Startup funds
Texas Woman's University Chancellor Research Fellowship

Title: Gestational exposure to high fat diet in mice alters hypothalamic MeCP2 expression in a sexually dimorphic way

Authors: S. BISHOP, J. FRAYRE, P. FRAYRE, C. MANI, M. J. MORRIS, ***E. NA**;
Texas Woman's Univ., Denton, TX

Abstract: Obesity is a worldwide epidemic that affects 650 million people globally. Obesity is a major risk factor for a number of different diseases such as cardiovascular disease, hypertension, diabetes, as well as some forms of cancer. Given the negative health consequences associated with obesity, it is considered to be one of the most serious public health challenges facing westernized societies. Particularly noteworthy is the scarcity of data regarding the sexually dimorphic effects of obesity on brain function, specifically areas of the brain relevant to food intake such as the hypothalamus. Methyl-Cp-G binding protein 2 (MeCP2) is a neuroepigenetic factor that has been associated with the neurodevelopmental disorder, Prader-Willi syndrome which is characterized by morbid obesity in children and in which there are mutations in *Mecp2* function. Past data have shown that disruption in MeCP2 function results in obesity in mice, thereby recapitulating the effects of MeCP2 dysfunction in Prader-Willi syndrome children. We are using a diet-induced obesity mouse model in order to assess the sexually dimorphic effect that gestational or postnatal exposure to high fat diet has on MeCP2 expression in the hypothalamus. Our current data suggest that gestational exposure to high fat diet significantly decreases MeCP2 protein expression in the hypothalamus of female mice, effects that are not seen when high fat diet is given to mice during adulthood. Moreover, these effects are seen specifically in a subregion of the hypothalamus known as the arcuate nucleus as demonstrated by immunohistochemical data. Interestingly, body weight appears to be more adversely affected by high fat diet during adulthood, suggesting that perhaps high fat diet exposure during adulthood may be affecting mechanisms independent of MeCP2 function. Collectively, our data demonstrate that there are developmentally sensitive periods in which MeCP2 expression can be influenced by high fat diet exposure in a sexually dimorphic manner.

Disclosures: S. Bishop: None. **J. Frayre:** None. **P. Frayre:** None. **C. Mani:** None. **M.J. Morris:** None. **E. Na:** None.

Poster

681. Development: Diet and Metabolism

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 681.17/U2

Topic: F.10. Food Intake and Energy Balance

Title: Dietary augmentation with monosodium glutamate: Behavioral and neurophysiological correlates in a rat model

Authors: *F. LI[1], E. P. WIERTELAK[2];
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Abstract: Monosodium glutamate (MSG) is a popular food additive in Chinese and Japanese culture as well as in the US. In the 1970s, the substance was accused of causing the "Chinese Restaurant Syndrome" (Kwok, NEJM, 1968) which was ultimately said to include such symptoms as headache, facial pressure, sweating, chest pain heartburn, and abdominal pain. Previous research examining animals exposed to MSG provided mixed conclusions on the potential effect of MSG-treated diets. However, to the best of our knowledge, the great majority each had used animals that have not reached maturation, or used a remarkably large amount of MSG, or injected the substance into the animal's system, all of which pose problems for reasonable interpretation. An observation of the Chinese and the Japanese diet have demonstrated no harmful effects in humans who include MSG as a part of their daily diet. The current study was designed to examine dietary supplementation analogous to human levels of consumption of MSG on a daily basis. Adult (140 days at onset of experimentation) male and female Sprague Dawley rats were given free access to foods containing 1% of MSG by weight. A sodium control group received foods containing the same level of sodium as the MSG-added diet. Food intake was monitored throughout the duration of the study. The animals were weight at the beginning and the end. An open can test was implemented to test anxiety levels. The animals were also tested on their spatial memory and learning ability in the Morris Water Maze. Two tail-flick tests were administered at different time points during the study to assess potential thermal nociceptive threshold differences. Reliably, no significant differences were found when comparing food intake, weight changes, anxiety level, spatial memory, and thermal nociceptive threshold. The results of this study do not support the contention that an MSG-treated diet can cause any cognitive deficits, altered pain response or abnormal weight changes. These data have implications for the inclusion of MSG in adult diets, providing support in favor of MSG supplementation in the elderly, recently reported to counter wasting syndromes. Glutamatergic mechanisms are discussed.

Disclosures: F. Li: None. **E.P. Wiertelak:** None.

Poster

681. Development: Diet and Metabolism

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 681.18/U3

Topic: F.10. Food Intake and Energy Balance

Support: CAPES; Finance Code 001

CNPq; grant number 153494/2018-2

Title: Hypercaloric diet in juvenile rats induced adult overweight, decreased striatal and increased hypothalamic monoamines activities in adulthood

Authors: *N. MOREIRA[1], J. M. DACLÉ[1], P. R. SILVA[1], T. B. KIRSTEN[1], J. C. FLÓRIO[2], T. M. REIS-SILVA[1], A. C. S. SAMPAIO[1], M. C. GALVÃO[1], K. E. KIATAQUI[1], E. F. BONDAN[1], L. V. BONAMIN[1], M. M. BERNARDI[1];
[1]Paulista Univ., São Paulo, Brazil; [2]Univ. of São Paulo, São Paulo, Brazil

Abstract: Overweight and obese condition in juvenile age constitutes a major health problem that increases the risks for several diseases, including type 2 diabetes, cardiovascular disease, psychiatric disorders, endocrine and immune dysfunction. In this context, the present study investigated the long-term effects of feeding high-calorie diet (HD) on body weight during the juvenile period and monoamine levels in the adulthood of male rats. After weaning (postnatal day 23), the rats were randomly divided into two groups: high hypercaloric diet (HD group) or normocaloric diet (ND group) from postnatal day 23 to 65. After postnatal day 65 the diet was returned to balanced laboratory chow. The body weight gains in the juvenile period and in adulthood were assessed. The striatal and hypothalamic serotonin (5-HT), dopamine (DA) and noradrenaline (NOR) levels as well as its metabolites were assessed in postnatal day 90-95. For the statistical analysis was used the student t test, and the results were considered significant at $p < 0.05$. The results showed a significant increase in weight gain in the juvenile period ($p < 0.0001$) and adulthood ($p = 0.02$), decreased 5-HT ($p < 0.0001$) in the striatum, and increased DA ($p = 0.006$) and 5-HT ($p = 0.02$) in hypothalamus. NOR was not significantly different in the structures evaluated ($p > 0.05$). The present results show that hypercaloric diet intake during the juvenile period could be a strongest and earliest predictor of adulthood obesity, and revealed specific and permanent central neurochemical disturbances. Thus, as these neurochemical disorders are related to psychopathological disease, such as anxiety, depression and binge eating disorder, it is a topic that needs further investigation. Funding Source: This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoa de Nível Superior (CAPES; Finance Code 001), and from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq; grant number 153494/2018-2).

Disclosures: **N. Moreira:** None. **J.M. Daclé:** None. **P.R. Silva:** None. **T.B. Kirsten:** None. **J.C. Flório:** None. **T.M. Reis-Silva:** None. **A.C.S. Sampaio:** None. **M.C. Galvão:** None. **K.E. Kiataqui:** None. **E.F. Bondan:** None. **L.V. Bonamin:** None. **M.M. Bernardi:** None.

Poster

681. Development: Diet and Metabolism

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 681.19/U4

Topic: F.10. Food Intake and Energy Balance

Support: FAPESP 2015/26156-2

Title: Effects of chronic central insulin infusion on food intake of offspring from mild hyperglycemic rats

Authors: *A. C. KISS[1,2], M. G. MARTINS[1,2], G. P. OLIVEIRA[1], A. G. CRUZ[1,2], B. C. WOODSIDE[3];
[1]Physiol., Sao Paulo State University, Campus Botucatu, Botucatu, Brazil; [2]Physiol., Univ. of São Paulo, São Paulo, Brazil; [3]Concordia Univ., Montreal, QC, Canada

Abstract: Changes on maternal metabolism, such as maternal diabetes, during pregnancy and lactation can influence the development of offspring central pathways regulating food intake. There is evidence that insulin acts on the brain reducing food intake of normo and hyperglycemic animals. However, it remains a question whether offspring of diabetic rats respond differently to central insulin administration. Therefore, the aim of the present study was to evaluate the effects of chronic central insulin infusion on food intake of offspring from mild hyperglycemic rats. At birth, female Sprague Dawley rats were assigned either to Control (subcutaneous (sc) citrate buffer; n=10) or STZ group (streptozotocin (STZ) -100 mg/kg- sc.; n=10). Rats were mated at 90 days old and delivered naturally around pregnancy day 22. The litters were culled to 6 pups, 3 females and 3 males. On postnatal day (PND) 75, four experimental groups were formed according to maternal metabolic state (Control or STZ) and treatment (saline or insulin): Control saline (n=10), Control insulin (n=10), STZ saline (n=10) and STZ insulin (n=10). Only one male offspring from each litter was used on each experimental group, thus the litter was the experimental unit. Food intake and body weight were followed up 7 days before and 7 days after surgery for implantation of a cannula in the lateral ventricle. The cannula was connected by a polyethylene tube to an osmotic pump (Alzet® model 2001), which released saline or 10 mU of insulin per day for 7 consecutive days. Food intake rate and body weight changes were calculated. The chronic central infusion of insulin reduced food intake and its anorectic effect was more pronounced in the offspring of rats with mild hyperglycemia. The present study shows that the presence of maternal hyperglycemia during pregnancy alters the development of brain circuits regulating food intake of the offspring.

Disclosures: A.C. Kiss: None. **M.G. Martins:** None. **G.P. Oliveira:** None. **A.G. Cruz:** None. **B.C. Woodside:** None.

Poster

681. Development: Diet and Metabolism

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 681.20/U5

Topic: F.10. Food Intake and Energy Balance

Title: Knockout of SNAT10 (SLC38A10) in mice causes a lowered body weight in adolescent and adult mice, along with altered levels of amino acids in plasma, but do not give rise to a behavioural phenotype

Authors: *F. A. LINDBERG, K. NORDENANKAR, R. FREDRIKSSON;
Pharmaceut. Biosci., Uppsala Univ., Uppsala, Sweden

Abstract: Sodium-coupled neutral amino acids transporter 10 (SNAT10) is a member of the solute carrier (SLC) 38 family. The SLC38 family has eleven members, SLC38A1-11, and are amino acidtransporters. Our group has earlier established that SNAT10 is a bidirectional transporter of L-glutamine, L-glutamate, L-alanine and D-aspartate through *in vitro* studies.
In this exploratory study, a knockout mouse model of SNAT10 (KO) was investigated in order to understand the *in vivo* importance of this transporter. Mice were weighed three times per week between the age of three to seven weeks, and once per week when they reached adult age. KO mice were found to weigh less than control ($SNAT10^{+/+}$) mice, but $SNAT10^{+/-}$ mice were unaffected. Food intake was therefore measured in adult mice, but no differences were observed. Neither was there any difference in body size on embryonic day 15.5.
Plasma samples were collected from adult mice, and levels of amino acids were measured. Levels of glutamine and glutamic acid was found to be lower in the KO mice when compared with control mice. Plasma from $SNAT10^{+/-}$ mice were not tested.
The behavioural profile was studied in the Y-maze, open field, marble burying and the rotarod tests. Grip strength was also investigated. However, no behavioural phenotype was found in KO mice as compared with control mice.
In conclusion, the SNAT10 KO mouse was smaller than control, caused minor changes in plasma levels of glutamine and glutamic acid, but do not seem to give rise to a behavioural phenotype. The cause of the lowered body weight is from this study still unknown but could possibly be due to an affected mTOR pathway. However, this needs to be studied further.

Disclosures: F.A. Lindberg: None. **K. Nordenankar:** None. **R. Fredriksson:** None.

Poster

681. Development: Diet and Metabolism

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 681.21/U6

Topic: F.10. Food Intake and Energy Balance

Title: Hypertensive and arrhythmogenic effects of an energizing naturist supplement in young university students in the state of Hidalgo, Mexico

Authors: *J. ARIAS-RICO[1], O. A. JARAMILLO-MORALES[2], E. V. RAMIREZ-JIMENEZ[2], M. BAUTISTA-AVILA[3], E. RAMIREZ-MORENO[2], R. C. JIMENEZ-SANCHEZ[2], R. BARRERA-GALVEZ[2];
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Abstract: Introduction: Currently, nutritional supplements are a group of commercially available products that are consumed as an addition to the usual diet. Its consumption without measure is justified by its natural origin, seeking mainly physical, aesthetic or miraculous ends, without in any case taking into account the possible harmful effects that its use can entail. On the other hand, beverages known as energizers are stimulant preparations, whose main composition is caffeine and carbohydrates (glucose, glucoronolactone, fructose or sucrose), accompanied by dietary supplements (taurine, vitamins, minerals) or plant extracts and additives acidulants (citric acid and sodium citrate It is very important to mention that these products are consumed in a large proportion in the adolescent population, mainly students, which belong to the youngest and most vulnerable segment of the population, in this sense, **the objective** of the present study was to evaluate the cardiovascular effects of nutritional supplements in healthy young university students of the Institute of Health Sciences of the state of Hidalgo. **Materials and methods**: We used a cross-sectional correlational experimental study that was carried out in a methodological plan divided into four phases, in which the subjects with a minimum risk were chosen to present a stress test following the Bruce protocol. . The population was constituted by young people between an age range of 18 - 24 years and a random sampling was carried out. For data analysis, the IBM SPSS Statistics 23 program was used, using descriptive statistics and to test the hypothesis the chi square was calculated. **Results**: Healthy young patients who consumed the nutritional supplement showed significant alterations in the type of recovery (Cardiac Frequency, Arterial Blood Pressure), QT and QTC figures of the electrocardiogram and in the duration of the bruce protocol phases compared to patients who received the placebo. **Conclusion:** Our data show for the first time that the consumption of dietary supplements generates cardiovascular alterations of great importance in healthy young people. However, more studies are needed in order to clarify a possible mechanism of action of these alterations.

Disclosures: **J. Arias-Rico:** None. **O.A. Jaramillo-Morales:** None. **E.V. Ramirez-Jimenez:** None. **M. Bautista-Avila:** None. **E. Ramirez-Moreno:** None. **R.C. Jimenez-Sanchez:** None. **R. Barrera-Galvez:** None.

Poster

681. Development: Diet and Metabolism

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 681.22/U7

Topic: G.03. Emotion

Support: KAKENHI JP 18K10852

Title: Identification of exercise-specific functional brain network and its exercise-intensity dependency

Authors: ***N. KUBOTA**, H. KASAHARA, S. AMEMIYA, T. NISHIJIMA, I. KITA; Tokyo Metropolitan Univ., Tokyo, Japan

Abstract: Accumulating evidence suggests that physical exercise has beneficial effects on psychological health via mediating activation of diverse brain regions involved in emotion. However, the exercise-specific functional brain network underlying the beneficial effects of exercise, and its exercise-intensity dependency remains unclear. Here, we tried to identify the exercise-specific functional brain networks using 30-min acute treadmill running at different intensities (HSR: high speed, 25 m/min; LSR: low speed, 15 m/min; SED: control, only sitting on the treadmill) in rats. According to previous study (Wheeler et al., 2013), we quantified neural activity across 28 brain regions involved in emotion and motor functions using c-Fos expression, and then visualized the functional connectivity of the brain regions based on correlation analysis and graph theory. The acute treadmill running enhanced c-Fos expression in several regions in a manner that depended on intensity, whereas c-Fos expression in the interfascicular part of dorsal raphe was significantly enhanced only by LSR. The matrices of inter-regional correlations for Fos expression showed less co-activation in acute exercise (both LSR and HSR) compared to that in SED. The functional networks obtained based on a scale-free degree distribution showed that the nod size and weight of the connection in functional network in LSR were different from those in HSR. In addition, we identified the structure of clusters and the region as hub in the network, using graph theory analysis with the modularity and the centrality of degree and betweenness respectively, and found that those parameters were different between LSR and HSR. These results suggest exercise-intensity dependency on functional networks recruited by acute exercise. Understanding the exercise-specific functional brain network recruited by acute exercise at various conditions, including intensity, duration, and type of exercise, may provide new insights into establishment of optical exercise regimens for psychological health.

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Poster

682. Food Reward

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 682.01/U8

Topic: F.10. Food Intake and Energy Balance

Support: Productos Medix 3247
Atencion Problemas Nacionales 464
Fundación Miguel Alemán

Title: Activation of the lateral hypothalamus GABAergic neurons enhance hedonic value to nearest stimuli and promotes consummatory behavior

Authors: *D. A. GARCIA[1], J. LUIS ISLAS[2], A. I. HERNANDEZ-COSS[2], L. PURON SIERRA[2], R. GUTIERREZ[2];
[1]Inst. de Fisiologia Celular, UNAM, Ciudad de Mexico, Mexico; [2]Farmacologia, CINVESTAV, Ciudad de Mexico, Mexico

Abstract: Hedonic value or palatability is encoded by an unidentified population of LH neurons. It is known that photostimulation of LH GABAergic neurons promotes appetitive and consummatory behavior to different stimuli, regardless of their nutritional value. Also, the activation of these neurons induced approach behavior to the closest stimulus. We reasoned that activation of LH GABAergic neurons might increase the palatability of stimuli, thereby promoting the described behaviors. To test this idea, we placed sated mice that expressed ChR2 in GABAergic neurons (Vgat-ChR2) in an operant box with three ports, where they -concurrently- had access to 3% sucrose (left port), 18% sucrose (right port) or water (central port). We found that transgenic mice increased consumption of 18% sucrose in 5-min laser on blocks compared to 5-min off blocks. These results can be explained because mice spent more time near the 18% sucrose port, and thus during photostimulation (2s On 4s Off), they consume more 18% sucrose. To determine if this manipulation promoted the ingestion of the stimulus with the highest palatability or the nearest-although less palatable- one, the same animals were trained in a similar task, but this time the laser was activated when the mice made a head entry in the central port. All transgenic mice self-stimulated, but one group increased the water consumption over sucrose, and the other instead moved to consume 18% sucrose. Therefore, these inter-subjects variability shows activation of LH GABAergic neurons may modulate two components: proximity and palatability. Subsequently, in the same task, we replaced the water in the central port for either no solution (dry licks), quinine or airpuffs. The three conditions increased the number of head entries (self-stimulation), but the aversive stimuli (quinine and

airpuffs) decreased the number of licks in the central port. However, if photostimulation was delivered from head-entry to lick once the central sipper (i.e., the airpuff now were inescapable), the transgenic mice stopped self-stimulation. Thus, LH GABAergic neurons activation does not override aversive stimuli. Also, we put 18% sucrose in the central sipper, and transgenic mice drastically overconsum ed it. Finally, by using a brief access test, we confirmed that activation of LH GABAergic neurons increased the hedonic value of the less palatable stimulus: decreased the latency to start consumption and increased the lick rate of low palatable over the most palatable stimulus. We concluded that activation of LH GABAergic neurons could enhance the hedonic value of stimuli, thereby promoting approach consummatory behavior to the nearest stimuli.

Disclosures: D.A. Garcia: None. **J. Luis Islas:** None. **A.I. Hernandez-Coss:** None. **L. Puron Sierra:** None. **R. Gutierrez:** None.

Poster

682. Food Reward

Location: Hall A

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Program #/Poster #: 682.02/U9

Topic: F.10. Food Intake and Energy Balance

Support: Productos Medix 3247
Problemas Nacionales 464
Fundación Miguel Alemán

Title: Opposite codification of sucrose palatability by GABAergic and glutamatergic lateral hypothalamus neurons

Authors: *A. HERNANDEZ-COSS[1], M. HERNANDEZ LUNA[2], R. GUTIERREZ[3];
[1]CINVESTAV, Mexico, Mexico; [2]Pharmacol., CINVESTAV, Gustavo A. Madero, Mexico;
[3]CINVESTAV - IPN, Mexico City, Mexico

Abstract: The increasing prevalence of overweight and obesity calls for a deeper understanding of the causes of such disorders. Arguably the most relevant cause for the energetic disbalance that leads to overweight and obesity is the overconsumption of sugar, due to its ubiquity in the food industry and the ease to consume it far beyond our physiological needs. In previous works using extracellular recordings, we investigated the Lateral Hypothalamic Area (LHA) in mice, an important node on the feeding circuit and found two distinct subpopulations of neurons that had different electrophysiological responses to the consumption of increasing concentrations of sucrose, one of these populations increased activity directly proportional to the sucrose intensity (i.e., concentration) and was found to be comprised of GABAergic neurons, the other was inversely proportional to sucrose intensity and was hypothesized as non-GABAergic. In this work we sought to identify if a functional difference between glutamatergic and GABAergic

neurons explained the heterogeneous response of LHA neurons to sucrose palatability. We achieved this using fiber photometry to measure the calcium activity of glutamatergic and GABAergic neurons separately in the LHA during a Brief Access Taste Test (BATT), in which 7 different stimuli were presented to the mice semi-randomly in 4 s windows. The stimuli were water, artificial saliva and different concentrations of sucrose (1.5, 3, 10, 18 and 32 wt/vol %). Calcium activity information was acquired from GCaMP6m fluorescent indicators expressed in either GABA or glutamatergic neurons in the LHA of freely moving animals and the lick rate and bout sizes were used as measures for palatability. We observed a common rise of calcium activity in both groups following the stimulus presentation compared to their baseline, and we found that GABAergic neuron activity was directly proportional to the palatability of the stimulus, while glutamatergic neuron activity was inversely proportional to it, decreasing its normalized fluorescence intensity as the sucrose concentration increased. Our findings shed light on the functional difference of these two subpopulations of neurons and how they might complement each other in the encoding of sucrose palatability.

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Poster

682. Food Reward

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 682.03/U10

Topic: F.10. Food Intake and Energy Balance

Support: Productos Medix 3247, Atención Problemas Nacionales 464, Fundación Miguel Alemán.

Title: Nucleus accumbens and lateral hypothalamus neural responses during appetitive and consummatory behaviors in an instrumental task with solid and liquid rewards

Authors: *B. I. DURAN-SOSA, R. GUTIERREZ;
Farmacología, CINVESTAV, Mexico City, Mexico

Abstract: It is well known that Lateral Hypothalamus (LH) and Nucleus Accumbens (NAc) are two important nodes for feeding behavior and reward. The communication between these brain regions has been widely studied but, it hasn't been explored, neither directly compared, how they respond to the anticipation and consumption of solid vs. liquid food rewards with different hedonic values. To answer these questions, we designed a fixed ratio (FR4) task with alternated trials rewarded with food pellets or liquid sucrose that effectively separates appetitive and consummatory part of feeding behavior. C57BL/6J mice were required to press four times a lever to receive either a 20 mg chocolate pellet or a 2 s opportunity window to lick for sucrose (3µL/drop/lick), by pressing a different lever. At pellet rewarded trials, only the pellet associated lever was available, after the fourth press it was retracted and a pellet was delivered, then a sucrose trial would begin, by exposing the sucrose associated operandum. Since sight of food modulates other hypothalamic neurons (e.g., AgRP neurons) related with hunger and thirst, we also decided to test if seeing the pellet evoked the same responses in LH and NAc neurons. To this end, we included a condition during the pellet trials, giving a 50% chance of delivering the pellet right after the fourth lever press, thus the reward was visible as the subject was approaching the pellet port, while the other 50% trials the pellet was dropped at the port until the head entry. After training, subjects were implanted with a 16 microelectrode array in NAc or LH. We found that mice would press the pellet lever faster than the one rewarded with sucrose, suggesting the solid chocolate pellet has a greater hedonic value over liquid sucrose. Interestingly, mice would take longer to move towards the pellet port than to the sucrose port, which suggests that our condition at the pellet trials creates a feeling of uncertainty that delays the approach to the reward. Our recordings show very heterogenous modulations from both brain regions with task related neurons found in every epoch. We found a group of neurons that responded equally to both rewards, while others preferred to fire more for pellet or for sucrose rewards. Interestingly, NAc and LH have a group of neurons that modulate their firing rate in response to anticipation of the solid reward, increasing firing rate during the approach while the pellet was visible was the most common response. This suggests both regions encode information about hedonic value of pellets and sucrose rewards, right from the appetitive phase of feeding (lever presses), including the approach and during consummatory behavior.

Disclosures: B.I. Duran-Sosa: None. **R. Gutierrez:** None.

Poster

682. Food Reward

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 682.04/U11

Topic: F.10. Food Intake and Energy Balance

Support: F31 DK118944

Title: Central oxytocin signaling inhibits motivated responding for palatable food

Authors: *C. M. LIU, A. N. SUAREZ, R. A. FATEMI, E. E. NOBLE, S. E. KANOSKI; USC, Los Angeles, CA

Abstract: Central oxytocin signaling reduces food intake in humans and in experimental rodent models. However, the behavioral mechanisms through which these effects occur are poorly understood. Here we examined the effects of central oxytocin signaling in rodents on conditioned aspects of feeding behavior using behavioral procedures that require motivated responding to obtain palatable sweet-tasting foods. First, male Sprague-Dawley rats (n=12) were administered lateral intracerebroventricular (ICV) oxytocin (1μg/μl) or vehicle (within-subjects design) and tested in the differential reinforcement of low rates of responding (DRL) task, a procedure measuring food impulsivity that requires animals to refrain for 20 seconds from making an operant response for sucrose. Results revealed that ICV oxytocin significantly increased efficiency in the DRL task relative to vehicle treatment, suggesting that central oxytocin reduces impulsive responding for palatable food. We next examined the effects of central oxytocin on effort-based food-related decision making in a concurrent progressive ratio procedure that involves a choice between free consumption of bland food (standard rodent chow) vs. effort-based (lever pressing on a progressive ratio reinforcement schedule) consumption of palatable sucrose. We found that food-restricted rats (n=11; within-subjects design) that received ICV oxytocin decreased the ratio of sucrose calories consumed over total calories, thus reducing motivation to work for sucrose in the presence free chow. Lastly, we utilized the conditioned place preference procedure in order to study the effects of central oxytocin signaling on appetitive responding for palatable food (high fat, sucrose-enriched diet) in the absence of consumption and postingestive feedback. Results revealed that in comparison to vehicle-injected rats, rats that received ICV oxytocin (n=9/group; between-subjects design) immediately prior to a place preference test in which no food was available showed significantly reduced food seeking behavior as measured by the ratio of time spent in a context previously paired with palatable food vs. a context in which the rats had equivalent previous exposure, but without food access. These results indicate that central oxytocin alters conditioned food seeking behavior in the absence of immediate postingestive feedback. Collectively, these findings reveal that central oxytocin inhibits conditioned motivated behaviors directed towards acquiring palatable food, including food impulsivity, effort-based food-related decision making, and food seeking behavior in the absence of consumption.

Disclosures: C.M. Liu: None. **A.N. Suarez:** None. **R.A. Fatemi:** None. **E.E. Noble:** None. **S.E. Kanoski:** None.

Poster

682. Food Reward

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 682.05/U12

Topic: F.10. Food Intake and Energy Balance

Title: MCH neuron activity is sufficient for reward and reinforces feeding

Authors: I. AKLAN, ***N. S. ATASOY**, Y. YAVUZ, D. ATASOY;
Univ. of Iowa, Iowa City, IA

Abstract: Melanin Concentrating Hormone (MCH)-expressing neurons of lateral hypothalamus (LH) have long been implicated in regulation of energy homeostasis and reward. The role of MCH neuron electrical activity in short term modulation of appetite and reward has not been fully understood. Here we investigated short-term behavioral and physiological effects of MCH neuron activity manipulations. We used a combination of optogenetic and chemogenetic approaches in *Pmch-cre* transgenic mice to acutely stimulate or inhibit MCH neuronal activity, while probing food intake, locomotor activity, anxiety-like behaviors, glucose homeostasis and reward. MCH neuron activity is neither required nor sufficient for short-term control of appetite for chow food unless stimulation is temporally paired with consummatory period. While MCH neuronal activity does not affect short-term locomotor activity, its inhibition improves glucose tolerance and has mildly anxiolytic effect. Finally, using two different operant tasks we show that activation of MCH neurons alone is sufficient to induce reward. Collectively, these experiments confirm diverse behavioral and physiological functions of MCH neurons and suggest a direct role in reward function. Our results support a role for MCH neurons in reinforcement of ongoing consumption, rather than directly increasing the motivation to eat.

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Poster

682. Food Reward

Location: Hall A

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Program #/Poster #: 682.06/U13

Topic: F.10. Food Intake and Energy Balance

Support: CIHR-102722
NSERC-105936

NSERC Discovery Grant RGPIN-2017-06272

Title: Getting to the nitty-gritty: Probing the mechanism of interaction between ghrelin and endocannabinoid systems at ventral tegmental area dopamine neurons

Authors: *A. W. EDWARDS, L. HYLAND, M. J. CHEE, A. ABIZAID;
Neurosci., Carleton Univ., Ottawa, ON, Canada

Abstract: Ghrelin and endocannabinoids (eCBs) promote food intake by activating the growth hormone secretagogue receptor (GHSR) and cannabinoid receptor 1 (CB-1R), respectively. In the hypothalamus (HYP), ghrelin requires eCB signalling to promote food intake, as deletion or antagonism of CB-1Rs prevents ghrelin-induced feeding. Both GHSRs and CB-1Rs are also expressed in the ventral tegmental area (VTA) and GHSR activation stimulates dopaminergic (DA) neurons in this region to promote food motivation and consumption. Similar to what is seen in the HYP, global and intra-VTA CB-1R antagonism blunts the feeding motivation and food intake induced by intra-VTA ghrelin, thus it appears that ghrelin requires functional CB-1Rs to fully promote motivated feeding in the VTA. The mechanism by which CB-1R antagonism prevents the orexigenic effects of ghrelin in the VTA is not yet known, therefore we examined the mechanisms underlying the effect of ghrelin and its interaction with CB-1R activation on putative DA neurons. We performed whole cell patch-clamp recordings from GFP-labelled neurons that express tyrosine hydroxylase (TH) in the VTA of *TH-cre:L10-GFP* mouse brain slices and first confirmed the stimulatory effects of ghrelin on these putative VTA DA neurons. We found that bath application of ghrelin (500 nM) produced a 3-fold increase in action potential firing frequency by directly depolarizing these neurons; these effects reversed upon ghrelin washout. To test if ghrelin can also stimulate excitatory glutamatergic tone onto VTA DA cells, we recorded spontaneous excitatory postsynaptic current (sEPSC) events and showed that ghrelin also reversibly increased the frequency of sEPSCs in VTA DA neurons to approximately 3 times that of baseline. Thus, ghrelin can stimulate VTA DA neurons by promoting neuronal excitability and excitatory glutamatergic tone to this region. To determine if CB-1R antagonism can prevent ghrelin-mediated activation of VTA DA neurons, we pretreated slices with the CB-1R antagonist rimonabant (5 μM) to test if bath application of ghrelin would still increase the neuronal excitability of these cells. We found that the rimonabant pretreatment did not block ghrelin-mediated excitation of VTA DA neurons, suggesting CB-1R signalling is not essential for ghrelin to excite these cells. In summary, while ghrelin has a robust excitatory effect on VTA neurons, it does not appear to rely on CB-1R activation directly at VTA DA neurons. Studies are currently underway to test if presynaptic activation of CB-1Rs acts to modulate ghrelin-mediated excitation of VTA DA neurons.

Disclosures: **A.W. Edwards:** None. **L. Hyland:** None. **M.J. Chee:** None. **A. Abizaid:** None.

Poster

682. Food Reward

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 682.07/U14

Topic: F.10. Food Intake and Energy Balance

Support: NSERC Discovery Grant 06272
NSERC USRA

Title: The role of glutamatergic transmission in melanin-concentrating hormone neurons in the lateral hypothalamus

Authors: *A. S. SANKHE[1], D. BORDELEAU[1], D. M. ALFONSO[1], G. WITTMANN[2], M. J. CHEE[1];
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Abstract: Melanin-concentrating hormone (MCH) neurons are exclusively expressed within the lateral hypothalamic area. We and others have found that MCH neurons coexpress the vesicular glutamate transporter 2 (vGLUT2), thus in addition to MCH, these neurons can release glutamate. MCH has well-known roles in feeding and energy expenditure, but the relative contribution of glutamate to these roles remains unclear. MCH administration into the brain stimulates food intake and mice with MCH deletion become lean, hyperactive, and do not overeat a palatable high fat diet, which is normally seen in wildtype littermates. These findings indicate that MCH is an orexigenic neuropeptide that can regulate homeostatic and hedonic feeding. It has recently been shown that glutamate from MCH neurons may increase feeding and body weight, but the role of glutamate in hedonic feeding is not known. To study the role of glutamate release from MCH neurons, we crossed a *Mch-cre* mouse with a *Vglut2-flox* mouse to selectively delete vGLUT2 from MCH neurons in *Mch-Vglut2-KO* mice. We determined the colocalization of MCH immunoreactivity with *Vglut2* mRNA by *in situ* hybridization and found that *Vglut2* colocalizes with more than 90% of MCH neurons. Only 15% of MCH neurons expressed *Vglut2* in *Mch-Vglut2-KO* animals. *Mch-Vglut2-KO* mice had similar body weights to *Vglut2-flox* controls. There was also no difference in baseline ambulatory activity, but *Mch-Vglut2-KO* animals have reduced ambulatory activity in a novel environment, such as following a cage change. To determine the role of glutamate in feeding, we compared the food intake of *Mch-Vglut2-KO* and *Vglut2-flox* animals on a chow and then a 45% high fat diet (HFD). Both groups consumed the same amount of calories on a chow diet. Within 24 hours of switching to HFD, all animals become hyperphagic relative to their chow intake. Interestingly, *Mch-Vglut2-KO* animals consumed 25% more calories during this period than control animals. In summary, our findings suggest that glutamate, in contrast to MCH, may not alter baseline body weight,

ambulatory activity, or chow feeding; but context-dependent stimuli, like HFD, revealed differing roles between glutamate and MCH.

Disclosures: **A.S. Sankhe:** None. **D. Bordeleau:** None. **D.M. Alfonso:** None. **G. Wittmann:** None. **M.J. Chee:** None.

Poster

682. Food Reward

Location: Hall A

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Program #/Poster #: 682.08/U15

Topic: F.10. Food Intake and Energy Balance

Support: BBSRC Grant #BB/M007391/1
European Commission #GA-631404
Leverhulme Trust grant #RPG-2017-417

Title: Impact of protein appetite on the dopamine mesolimbic system

Authors: ***F. NANEIX**[1], G. CHIACCHIERINI[1], K. Z. PETERS[1], E. M. S. SNOEREN[2], J. E. MCCUTCHEON[1];
[1]Dept. of Neuroscience, Psychology and Behaviour, Univ. of Leicester, Leicester, United Kingdom; [2]Dept. of Psychology, UiT The Arctic Univ. of Norway, Tromso, Norway

Abstract: Maintenance of protein homeostasis is an essential process in the control of food intake as many amino acids cannot be synthetized *de novo*. However, the underlying neurobiological circuits remain poorly understood. Recently, our lab developed a model of protein appetite in which rats maintained on a low protein diet (5%; protein-restricted) present a strong conditioned preference for a flavored casein (milk protein) solution versus an isocaloric flavored maltodextrin (carbohydrate) solution. This protein preference is not observed in control, non-protein restricted, rats. Using viral expression of the calcium indicator GCaMP6s in ventral tegmental area (VTA) neurons and *in vivo* fiber photometry recordings, we first observed that protein preference was associated with elevated VTA activation during casein consumption, relative to maltodextrin. Moreover, protein preference and VTA responses were still observed when protein homeostasis was restored, suggesting long-lasting adaptations. By contrast, the switch to protein restricted state of control rats induced a rapid behavioral shift as well as changes in the VTA response to casein intake. Further experiments confirmed this rapid development of the protein preference as rats showed an almost immediate preference for casein, relative to maltodextrin, even without previous exposure to the solutions. Furthermore, using quinine adulteration of casein, we showed that, although protein appetite is associated with an initial increased palatability of casein, this does not seem to be essential for driving behavioral preference. Current experiments are investigating the specific involvement of dopamine

signaling in the nucleus accumbens by using the genetically encoded dopamine sensor, dLight1, in behaving rats and *ex vivo* fast scan voltammetry recordings in brain slices. Taken together our results highlight for the first time the involvement of mesolimbic circuits in behavioral processes underlying protein appetite.

Disclosures: **F. Naneix:** None. **G. Chiacchierini:** None. **K.Z. Peters:** None. **E.M.S. Snoeren:** None. **J.E. McCutcheon:** None.

Poster

682. Food Reward

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 682.09/U16

Topic: F.10. Food Intake and Energy Balance

Title: Opioid receptor-mediated physical dependence following sugar intake expressed in a model of withdrawal-suppressed behavior

Authors: *B. D. FISCHER, C. KROLL;
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Abstract: Studies in animal models have suggested that sugar deprivation following excessive intake elicits opioid-like withdrawal. However, little has been done to investigate sugar induced physical dependence using established preclinical assays of opioid withdrawal. The present study used both a withdrawal jumping procedure and an operant procedure to assess further the development of opioid receptor-mediated physical dependence following excessive sucrose intake. These two endpoints were chosen to assess behaviors that are either elicited (withdrawal jumping) or suppressed (operant behavior) during naloxone-precipitated opioid withdrawal. C57BL/6 mice were given daily 14-hour access to a 10% sucrose solution in addition to water and food. Over a 28-day period, mice consumed an average (± SEM) of 2.3 ± 0.8 g of sucrose per day. Naloxone-precipitated opioid withdrawal experiments were conducted weekly. In the withdrawal jumping procedure, precipitated withdrawal was assessed in individual plexiglas observation cylinders. Jumping was measured for 5 minutes immediately following administration naloxone (1.0 mg/kg i.p.). In this procedure, naloxone failed to precipitate increased withdrawal jumping behavior in the mice self-administering sucrose. In the operant behavior procedure, mice were trained on a fixed-ratio schedule of reinforcement. In this procedure, naloxone (0.1-1.0 mg/kg, i.p.) produced dose- and time-dependent decreases in operant response rates following the 28-day period of sucrose self-administration. Parallel experiments were conducted in mice administered morphine (100 mg/kg, i.p.) twice daily for 6 days, in which naloxone precipitated withdrawal in both the withdrawal jumping and operant behavior procedures. Together, these findings raise the possibility that opioid receptor-mediated physical dependence following excessive sucrose consumption may be expressed in assays of

withdrawal-suppressed behaviors. Further, these data suggest that assays of withdrawal-suppressed behaviors may be useful for further study related to opioid receptor-mediated sugar dependence.

Disclosures: B.D. Fischer: None. **C. Kroll:** None.

Poster

682. Food Reward

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 682.10/U17

Topic: F.10. Food Intake and Energy Balance

Support: UNAM DGAPA PAPIIT IN217117

Title: The dopamine D4 receptor antagonist L-745,870 decreases body weight gain, food intake and food-reinforced behavior in rats exposed to an energy-dense diet

Authors: *R. ESCARTIN-PEREZ[1], R. CRUZ-TRUJILLO[2,3], F. CORTÉS-SALAZAR[1], D. DÍAZ-URBINA[1], J. SUÁREZ-ORTÍZ[1,2], A. HERNÁNDEZ-GUTIÉRREZ[3], V. LÓPEZ-ALONSO[1], J. MANCILLA-DÍAZ[1];
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Abstract: The global obesity epidemic remains one of the major risk factors for the occurrence of a number of chronic diseases, including diabetes, cardiovascular diseases and different types of cancer. Recurrent over-consumption of energy-dense foods is a common feature of obese individuals and this phenomenon has been replicated in animal models of diet-induced obesity. Accordingly, it has been shown that energy-dense diets that are highly palatable induce activation of the brain reward circuit, a mechanism that explains in over-consumption of food in obese individuals and experimental animals. The finding that diet-induced obese mice overexpress the dopamine D4 receptor (D4r) mRNA in specific cerebral regions, including the ventral region of the lateral septum (LS), suggests a potential role of D4r receptors in the genesis and/or development of obesity induced by energy-dense diets. Consequently, alterations in the reward system associated with diet-induced obesity are potentially related to changes in the dopaminergic transmission mediated by presynaptic D4r of LS projections. This idea is supported by findings that showed regulatory inputs to the nucleus accumbens and the ventral tegmental area from the LS. Accordingly, we propose the hypothesis that the pharmacological blockade of D4r will prevent the development of excessive body weight gain in rats chronically exposed to an energy-dense diet and will decrease the motivation for palatable food. Thus, the aim of this study was to evaluate the effects of chronic administration (ip, daily administrations during 14 days) of the D4r selective antagonist, L-745,870 (1mg/kg), on body weight gain (g),

food consumption (g) and motivation for palatable food (breakpoints, 45 mg chocolate-flavored sucrose pellets, operant task) in male Sprague Dawley rats exposed to an energy-dense diet (high-fat diet, HF, 60% of calories from fats). The pharmacological treatment started after 52 days of exposure to the HF diet; adipose tissue, glucose, triglycerides, and cholesterol (total, LDL and HDL), as well as locomotor activity, were also measured. We found that chronic administration of L-745,870 prevented the increase of body weight gain, and decreased food consumption and breakpoints, as well as the abdominal adipose tissue accumulation and the serum glucose levels and triglycerides. We concluded that chronic systemic blockade of D4R may inhibit feeding behavior and motivation for palatable food, despite the subjects had access to the HF diet. Furthermore, accumulation of body weight gain and abdominal adipose tissue decreased, suggesting that D4r antagonist may be useful for the pharmacological treatment of obesity.

Disclosures: R. Escartin-Perez: None. **F. Cortés-Salazar:** None. **V. López-Alonso:** None. **J. Mancilla-Díaz:** None. **D. Díaz-Urbina:** None. **J. Suárez-Ortíz:** None. **R. Cruz-Trujillo:** None. **A. Hernández-Gutiérrez:** None.

Poster

682. Food Reward

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 682.11/U18

Topic: H.01. Animal Cognition and Behavior

Support: NIDA IRP

Title: Evolution of neural ensembles coding reward seeking and taking in the medial prefrontal cortex

Authors: *Y. ZHANG[1], G. BARBERA[1], B. LIANG[1], L. ZHANG[1], Y. LI[2], Y. SHAHAM[1], D.-T. LIN[1];
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Abstract: Seeking natural rewards such as food is of fundamental importance for an individual's survival and well-being. The medial prefrontal cortex (mPFC) is critical for reward-seeking. However, it remains unclear how spatially and temporally organized neural activity in the mPFC codes reward seeking and taking. In this study, we employed a custom miniature fluorescence microscope (miniScope), to simultaneously track calcium activity from hundreds of neurons longitudinally at single cell resolution in the mPFC. We imaged mPFC neural activity in which mice learned to lever press for food reward, to reveal how neural ensembles that encode reward seeking and taking. We found that different subgroups of neurons showed increased activity

around distinct behavioral events (i.e. lever press/cue presentation as reward seeking, and food retrieval as reward taking). We also trained an artificial neural network using a machine-learning algorithm to predict the timing of lever pressing using neural activity and showed that the identified neural ensemble carried most behavioral relevant information. Together, our results reveal the evolution of dynamic neural ensembles in the mPFC that encode reward seeking and taking.

Disclosures: **Y. Zhang:** None. **G. Barbera:** None. **B. Liang:** None. **L. Zhang:** None. **Y. Li:** None. **Y. Shaham:** None. **D. Lin:** None.

Poster

682. Food Reward

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 682.12/U19

Topic: F.10. Food Intake and Energy Balance

Support: NIH Grant MH112105

Title: Endocannabinoid modulation of chemosensation underlying altered food preferences in *C. elegans*

Authors: *A. LEVICHEV[1], S. FAUMONT[1], R. Z. BERNER[2], Z. PURCELL[2], S. R. LOCKERY[1];
[1]Inst. of Neurosci., [2]Univ. of Oregon, Eugene, OR

Abstract: The mammalian endocannabinoid system, comprised of the endocannabinoids AEA (N-arachidonoyl-ethanolamine) and 2-AG (2-Arachidonoylglycerol), their receptors, CB1 and CB2, and their metabolic enzymes, is thought to integrate internal energy state and sensory food cues to modulate feeding. For example, cannabinoids, acting on CB1, can increase preference for more palatable, calorically dense food: a response called *hedonic amplification*, colloquially known as “the munchies.” In mammals, cannabinoids can increase sensitivity to odors and sweet tastes, which may underlie amplification. We are developing *C. elegans*, an omnivorous bacterivore, as a model in which to investigate the neurophysiology of hedonic amplification. We found that exposure to AEA, an endogenous cannabinoid common to mammals and *C. elegans*, further increases the worm's preference for strongly preferred (more palatable) bacteria over weakly preferred (less palatable) bacteria, mimicking hedonic amplification in mammals. Furthermore, AEA acts bidirectionally, increasing consumption of strongly preferred bacteria while decreasing consumption of weakly preferred bacteria. We also found that deletion of the *C. elegans* CB1 ortholog, *npr-19*, eliminates hedonic amplification, which can be rescued by expression of wild type *npr-19* or human CB1, establishing a humanized worm for cannabinoid signaling studies. Deletion of the olfactory neuron AWC, which directs chemotaxis to food,

abolishes hedonic amplification. Consistent with this finding, calcium imaging revealed that AEA bidirectional modulates AWC activity, increasing its responses to strongly preferred food and decreasing its responses to weakly preferred food. In a GFP expression analysis, we found that *npr-19* is expressed ~21 neuron classes but, surprisingly, not in AWC. Although AEA's effect could be mediated by NPR-19-expressing neurons presynaptic to AWC, nearly complete elimination of fast synaptic transmission, via the mutation *unc-13(e51)*, had no effect on modulation. We are now testing the hypothesis that AEA modulates AWC by activating one or more NPR-19-expressing neurons that release a diffusible neuromodulator to which AWC is sensitive.

Disclosures: A. Levichev: None. **S. Faumont:** None. **R.Z. Berner:** None. **Z. Purcell:** None. **S.R. Lockery:** None.

Poster

682. Food Reward

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 682.13/U20

Topic: G.02. Motivation

Title: Leptin receptor-expressing neurons in lateral hypothalamus regulates food-seeking behavior

Authors: *Y. LEE, D.-S. HA, J. PARK, H. SONG, H. CHOI;
Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: The symptom of eating disorders that is difficult to treat is a dissociation between food-seeking behavior and metabolic needs. The lateral hypothalamus (LHA) regulates various motivated behaviors including food intake. Among those subpopulations, LHA GABAergic neurons are known to be involved in modulation of food reward and consumption. Previous studies showed that activation of LHA GABAergic neurons enhance food intake and compulsive behaviors in mice. However, specified behavioral phenotypes and functions of the subset of LHA GABAergic neurons are unclear. Thus, our research aimed to identify the food-related behavioral phenotypes that are regulated by leptin receptor-expressing neurons in LHA. We performed food-seeking test, operant chamber test, overall chow and palatable food intake test and marble burying test. Interestingly, through behavior assays, we found that chemogenetic activation/inhibition of LHA leptin receptor neurons only modulate 'food-seeking' behavior. However, activation of LHA GABAergic neurons increased both food intake and compulsive behaviors without affecting food-seeking. These results suggest that food-seeking is independent from food intake, and LHA leptin receptor expressing neurons are specifically involved in food-seeking behavior that can be targeted to treat eating disorders.

Disclosures: **Y. Lee:** None. **D. Ha:** None. **J. Park:** None. **H. Song:** None. **H. Choi:** None.

Poster

682. Food Reward

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 682.14/U21

Topic: G.02. Motivation

Support: NIH-1F31-DK111194-01
NIH-R01DK106188
NIH-R01DK115526

Title: Enhanced incentive motivation, interactions between susceptibility to obesity and NAc CP-AMPAR mediated transmission

Authors: R. C. DERMAN, F. SANCHEZ CONDE, ***C. R. FERRARIO**;
The Univ. of Michigan, Ann Arbor, MI

Abstract: Stimuli paired with palatable foods (i.e., food cues) powerfully influence food-seeking behaviors. These incentive motivational responses to food cues rely on excitatory transmission in the nucleus accumbens (NAc) and can be influenced by individual susceptibility to obesity. For example, the magnitude of incentive motivational responses to food cues is stronger in obesity susceptible vs. obesity resistant rats prior to the development of obesity. Further, cue-triggered food-seeking in the form of Single Outcome Pavlovian-to-instrumental transfer (SO PIT) is mediated by NAc CP-AMPA receptors (CP-AMPAR) in selectively bred obesity-prone but not obesity-resistant rats. However, it's unclear whether the role of CP-AMPARs in this behavior generalizes to outbred rats identified as susceptible to diet induced obesity. Moreover, SO PIT does not distinguish between sensory specific vs. affective mechanisms of PIT. Thus, it is unclear which of these processes is enhanced in susceptible groups. Finally, how consumption of a sugary, fatty "junk food" diet alters motivational responses to food cues in susceptible vs. resistant populations remains unknown. We address these questions in 3 experiments. First, we show that in outbred rats, the degree to which NAc CP-AMPAR blockade attenuates SO PIT and conditioned approach is strongly correlated with subsequent weight. This suggests that the role for NAc CP-AMPARs in the expression of Pavlovian motivation may be unique to obesity susceptible individuals. Next, we show that the magnitude of General PIT is positively correlated with subsequent weight in outbred rats and that General PIT is stronger in selectively bred obesity-prone vs. obesity-resistant groups. These data suggest that affective mechanisms of PIT are enhanced in obesity susceptible populations. Finally, we show that basal expression of conditioned approach is stronger in obesity-prone vs. obesity-resistant rats, but "junk food" consumption enhances conditioned approach in both groups. These data suggest that that the neural alterations induced by "junk food" enhance incentive motivation, regardless of individual

susceptibility. Data overall reveal phenotypic enhancements in incentive motivation unique to obesity susceptible populations, and that junk-food enhances incentive motivation regardless of individual differences. This supports the idea that enhanced neurobehavioral responsivity to food cues found in humans is likely the result of phenotypic differences between those that are more vs. less vulnerable to diet-induced weight gain, and that "junk food" consumption alters the brain in ways that enhance incentive motivation.

Disclosures: R.C. Derman: None. **F. Sanchez Conde:** None. **C.R. Ferrario:** None.

Poster

682. Food Reward

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Topic: G.02. Motivation

Support: NIH Grant R01DK106188
NIH Grant R01DK115526
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NIH Grant T32DA007268

Title: Input specific alterations in CP-AMPAR mediated transmission in the NAc core following junk-food diet consumption

Authors: *T. L. FETTERLY, C. R. FERRARIO;
Pharmacol., The Univ. of Michigan, Ann Arbor, MI

Abstract: Excitatory transmission within the nucleus accumbens (NAc) mediates cue-triggered motivation in the contexts of both food- and drug-seeking behavior. In humans, greater activation in the NAc in response to food cues has been observed in obesity-susceptible individuals, suggesting that there are differences in NAc function in obesity-susceptible vs. obesity-resistant populations. Work from our lab rats has found that incentive-motivational responses to food-cues are enhanced in obesity-susceptible rats as compared to obesity-resistant rats, and that this behavior is mediated by calcium permeable-AMPARs (CP-AMPARs) in the NAc. Furthermore, when placed on a sugary, fatty "junk-food" diet, a rapid and persistent increase in both NAc CP-AMPAR transmission and expression is observed in obesity-susceptible, but not obesity-resistant rats. While this demonstrates an alteration in glutamatergic transmission in the NAc following junk-food consumption, it does not provide information about which specific circuits are altered. The NAc receives glutamatergic input from several brain regions, including the medial prefrontal cortex (mPFC) and basolateral amygdala (BLA). Our current study utilizes an optogenetic strategy to dissect the contribution of the mPFC and BLA inputs to changes in NAc glutamatergic transmission following junk-food consumption (10 days)

in our selectively bred obesity-prone and obesity-resistant rat populations. Following stereotaxic injection of pAAV-CamKII-Chronos-GFP into either the mPFC or BLA, we prepared *ex vivo* brain slices containing the NAc and then recorded optically-evoked AMPA currents in medium spiny neurons using whole-cell patch-clamp electrophysiology. The contribution of CP-AMPARs to overall AMPA transmission was then determined using naspm (200 uM), a CP-AMPAR selective antagonist. Preliminary data show that junk-food increases CP-AMPAR transmission at mPFC inputs to the NAc in obesity-prone rats compared to chow fed controls. In contrast, CP-AMPAR mediated transmission at mPFC inputs was similar between obesity-resistant chow and junk-food groups. Studies examining effects in BLA inputs are ongoing. Additionally, basal differences in CP-AMPAR transmission at the mPFC and BLA inputs will be compared using control rats maintained on a standard chow diet. Combined, these studies identify specific circuits altered by junk-food consumption and will help design behavioral experiments connecting cue-triggered motivation to circuit-specific changes in glutamatergic transmission within the NAc.

Disclosures: T.L. Fetterly: None. **C.R. Ferrario:** None.

Poster

682. Food Reward

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Program #/Poster #: 682.16/U23

Topic: G.02. Motivation

Support: 1F99NS108549-01
R01DK106188-02-S1
CONACyT grant 424822
R01DK106188
1R01DK115526-01
R21DA045277

Title: Effects of the estrous cycle and junk-food diet on nucleus accumbens core medium spiny neuron excitability

Authors: *Y. ALONSO CARABALLO[1], H. PAPACOSTAS QUINTANILLA[2], C. R. FERRARIO[3];
[1]Neurosci. Grad. Program, Univ. of Michigan, Michigan, MI; [2]Farmacobiologia, CINVESTAV, México DF, Mexico; [3]Pharmacol., The Univ. of Michigan, Ann Arbor, MI

Abstract: The nucleus accumbens (NAc) plays critical roles in motivated behaviors, including food-seeking in response to Pavlovian cues. We have found that selectively-bred male and female obesity-prone rats show stronger motivational responses to food-cues than obesity-

resistant rats. Consistent with this, in males, basal intrinsic excitability of medium spiny neurons (MSN) in the NAc core is enhanced in obesity-prone vs. obesity-resistant rats. However, it is unknown if similar differences exist in females and whether consumption of sugary, fatty "junk-food" alters MSN excitability. Whole-cell patch clamp recordings were conducted to examine MSN intrinsic excitability in female obesity-prone and obesity-resistant rats. Rats were given chow or 10 days of free access to "junk-food" followed by 1-2 days of "junk-food" deprivation prior to recording from MSNs. In chow fed controls, MSN intrinsic excitability was greater in female obesity-prone vs. obesity-resistant rats during metestrus/diestrus (M/D), but comparable during proestrus/estrus (P/E). This was due to cycle effects on excitability in obesity-prone but not obesity-resistant rats. Furthermore, junk-food reduced intrinsic excitability in female obesity-prone, but not obesity-resistant rats. Interestingly, this effect of junk-food was apparent during M/D, but not during P/E, suggesting dissociable mechanisms underlying cycle vs. food effects on excitability. These differences in MSN excitability between female obesity-prone and obesity-resistant rats are similar to the pattern found in male rats, with the addition of effects of the cycle on MSN excitability. These data suggest that enhanced basal excitability may contribute to stronger motivational responses to food-cues in obesity-prone vs. obesity-resistant populations. In addition, they reveal previously unidentified effects of the cycle on MSN excitability in the NAc core.

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Disclosures: Y. Alonso Caraballo: None. **H. Papacostas Quintanilla:** None. **C.R. Ferrario:** None.

Poster

682. Food Reward

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 682.17/U24

Topic: G.02. Motivation

Support: NIH Grant R15DA046375

Title: Mu opioid receptors in the medial orbital cortex regulate licking microstructure and the expression of reward value

Authors: *S. R. WHITE, M. LAUBACH;
Ctr. for Behavioral Neurosci., American Univ., Washington, DC

Abstract: Abnormal sensitivity to reward underlies the development of drug dependence and addiction. Mu opioid receptors mediate the primary effects of opioid drugs and are prominent in

the frontal cortex. Only a few published studies have examined how these receptors contribute to the control of reward-guided behavior (e.g. Mena et al., 2013; Castro and Berridge, 2017). The medial orbital cortex is a key frontal region for processing of reward information. Reversible inactivation of this region eliminates incentive contrast effects and reduce measures of palatability (Parent et al., 2015). Neuronal activity in this area is modulated when rats initiate consummatory licking (Horst and Laubach, 2013) and encodes the value of liquid sucrose rewards (Amarante et al., 2017). It is not known how mu opioid receptor stimulation affects reward signaling in the medial orbital cortex. To investigate this issue, we tested rats in an incentive contrast licking task. Adult male rats were trained to lick on a contact-sensitive spout to receive access to liquid sucrose. Concentrations of sucrose alternated between relatively high (16%) and low (4%) over alternating 30 second periods. With training, rats learned to persistently lick when the higher value fluid was available and to suppress licking when the lower value fluid was available. Rats were implanted with bilateral drug cannulae targeting the medial orbital cortex and tested following infusions of the selective mu-opioid receptor agonist DAMGO (1μg/μL) and following reversible inactivation via the selective GABA-A receptor agonist muscimol. Effects of muscimol were similar to Parent et al. (2015): Rats showed reductions in the ratio of licks for high vs low concentrations of sucrose, reductions in the durations of their licking bouts especially when licking for the higher value fluid, and emitted more licking bouts. In a similar way, DAMGO reduced the durations of licking bouts and had a more dramatic effect on the number of bouts that were emitted: Rats emitted nearly three times as many bouts with DAMGO infused compared to vehicle. Effects of ratios of high and low value licks were dramatic and yet heterogeneous over rats. DAMGO had no effects on neither inter-lick intervals, total lick counts, nor the duration of task engagement. Together, these data suggest that opioid stimulation in the medial orbital cortex controls licking microstructure and the expression of reward value. We are currently examining the neuronal basis for these effects using chronic recording methods combined with intracortical pharmacology.

Disclosures: **S.R. White:** None. **M. Laubach:** None.

Poster

682. Food Reward

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 682.18/U25

Topic: G.02. Motivation

Support: NIH Grant 1R15DA046375-01
NSF GRFP

Title: Time matters: Effects of instantaneous fluid volume on reward signals in the rat medial frontal and orbitofrontal cortex

Authors: *L. M. AMARANTE[1], M. MITCHELL[2], J. WILSON[2], K. ALDENDERFER[3], J. NEWPORT[3], M. LAUBACH[1];
[1]Ctr. for Behavioral Neurosci., [2]Neurosci. Program, [3]Physics Dept., American Univ., Washington, DC

Abstract: The medial frontal cortex (MFC, also known as mPFC) and orbitofrontal cortex (OFC) are known to be involved in processing reward information across species. Previous studies (from our lab and others) have found reward related neural activity in both brain areas in rats that is time-locked to consummatory behavior. Specifically, our lab has found that the strength of phase locking to the rat's lick cycle encodes reward size, both for rewards that vary in nutrient concentration (Amarante et al., 2017) and fluid volume (Amarante, 2018 SfN abstract 688.04). Here, we investigated if these signals track differences in reward size based on the instantaneous volume of fluid that is delivered. Commercial lab equipment is not available to deliver precise fluid volumes on a microliter scale, and can only currently be done through either using different sized syringes from two different pumps, or through leaving a syringe pump running or solenoid valve open for different periods of time. As such, published studies of magnitude coding have confounded fluid volume with reward delivery time (e.g. Fiorillo et al., 2003; Bermudez and Schultz, 2010). To investigate this issue, we developed an open-source syringe pump control circuit using commonly available parts, a Teensy microcontroller, and custom written code. The syringe pump can deliver different volumes from one syringe over a common time epoch. The pump's functionality is achieved by changing the motor's velocity and acceleration. Using our device, we assessed how differences in reward magnitude are encoded by the rat MFC and OFC upon the immediate receipt of different fluid volumes. We found that lick-entrained neural activity in both MFC and OFC encoded the instantaneous volume of fluid delivery. Phase locking was stronger to licks for the large volume (30 uL) as opposed to a small volume (10 uL) over the same timescale (500 ms). A second series of experiments found stronger phase locking for licks that delivered a larger instantaneous volume of fluid (30 ul over 200 ms) compared to a smaller instantaneous volume (30 ul over 600 ms). Notably, the same total volume was delivered per fluid delivery, suggesting that the MFC and OFC are sensitive to instantaneous fluid volume. Our findings confirm extended properties of reward encoding in the rat frontal cortex and additionally suggest that classic studies of reward coding should be re-evaluated for effects of the duration of fluid delivery. That is, are these results reflecting the value or temporal information of the reward?

Disclosures: L.M. Amarante: None. **M. Mitchell:** None. **J. Wilson:** None. **K. Aldenderfer:** None. **J. Newport:** None. **M. Laubach:** None.

Poster

682. Food Reward

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 682.19/U26

Topic: G.02. Motivation

Support: NIH DA016285-04
State of Washington

Title: Sex differences in motivation to consume sucrose following abstinence and environmental enrichment in Long-Evans rats

Authors: *J. W. GRIMM, F. SAUTER, D. MACDOUGALL, E. SPAULDING, S. GIADONE, K. STENSGAARD, M. HARDY;
Psychology, Western Washington Univ., Bellingham, WA

Abstract: Background and Rationale: There are clinically-significant sex differences in addiction behaviors including craving and relapse. We have previously observed robust sex differences in motivation to consume sucrose in adult Long-Evans rats.
Method: In the present study, motivation to consume 10% sucrose was assessed with lever press responding (0.2 mL per reinforcement) on the progressive ratio (PR) schedule in daily 3 h sessions for one week following either overnight (acute) or one month (chronic) environmental enrichment (EE). EE consisted of a large cage with 3 rats and novel toys. Controls were housed in standard single housing. Acute EE was provided immediately after initial training or after 29 days abstinence. Males and females were segregated by sex throughout the study.
Results: Females responded to higher break points during training and post-EE testing. For both sexes, there was an abstinence-dependent increase (incubation) of PR responding for sucrose in subjects tested after one month vs. one day of abstinence. Both acute and chronic EE decreased subsequent PR responding, but the persistence of the effect differed by sex and length of abstinence. For testing following one day of abstinence from sucrose, acute EE with males resulted in decreased responding for sucrose persisting 2 days. The effect persisted in females for 1 day. For testing starting after 29 days of abstinence from sucrose, acute EE with males resulted in decreased responding persisting 3 days. For females, the effect persisted 1 day. Chronic EE with males decreased their responding for 3 days but had no effect on responding by females.
Conclusion: These results replicate our previous findings of greater motivation to consume sucrose by females, demonstrate an incubation of PR responding for both sexes, and an overall more persistent anti-sucrose taking effect of EE with males.

Disclosures: J.W. Grimm: None. **F. Sauter:** None. **D. MacDougall:** None. **E. Spaulding:** None. **S. Giadone:** None. **K. Stensgaard:** None. **M. Hardy:** None.

Poster

682. Food Reward

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 682.20/U27

Topic: D.09. Multisensory Integration

Support: NIH Grant R01DK080153

Title: Fmri and satiety related hormones pre and post sleeve gastrectomy

Authors: S. ENAYET[1], S. BABOUMIAN[2], J. HO[1], ***M. ZHONG**[3], S. PANTAZATOS[4], O. CHINCHWADKAR[3], A. FLEET[3], A. GELIEBTER[2,5];
[1]Inst. of Human Nutrition, Columbia Univ. Med. Ctr., New York, NY; [2]Icahn Sch. of Med. at Mount Sinai, and St. Luke's Mount Sinai Hosp., New York, NY; [3]St. Luke's Mount Sinai Hosp., New York, NY; [4]Mol. Imaging and Neuropathology Div., New York State Psychiatric Inst. and Dept. of Psychiatry at Columbia Univ., New York, NY; [5]Touro Col. and Univ. Syst., New York, NY

Abstract: Bariatric surgery is currently the most effective long-term treatment for obesity. Besides gastric restriction, sleeve gastrectomy (SG) induces neuroendocrine changes, which may contribute to satiety. At 1 mo pre and 5 mo post intervention, we examined the effects of SG (n= 9), a low-calorie diet (n = 14), and no treatment (n = 16) on the satiety-related gut peptides GLP-1 and PYY before and after a standardized meal prior to fMRI. We also examined brain activation in response to high-energy dense (HED) vs low-energy-dense (LED) visual and auditory food stimuli. Postprandial PYY and GLP-1 both increased significantly following SG, but not following the low-calorie diet or no treatment ($p < 0.05$). The fMRI analysis was based on whole brain statistical maps, with a cluster extent threshold at $p < 0.05$ corrected. The SG group experienced greater brain activation in the dorsolateral prefrontal cortex (dlPFC) and lower activation in the parahippocampal (PHG)/fusiform region in response to HED vs LED stimuli as compared to the low-calorie diet or no treatment, suggesting that SG led to greater inhibitory control (dlPFC) over HED foods and reduced attention (PHG/fusiform) to HED foods. The postsurgical changes in postprandial PYY and GLP-1 may be contributing to the changes in brain responsivity to food cues.

Disclosures: S. Enayet: None. **S. Baboumian:** None. **J. Ho:** None. **M. Zhong:** None. **S. Pantazatos:** None. **O. Chinchwadkar:** None. **A. Fleet:** None. **A. Geliebter:** None.

Poster

682. Food Reward

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 682.21/U28

Topic: F.10. Food Intake and Energy Balance

Support: R21MH097583

Title: Brain substrates of hedonic hunger: Cortical-subcortical imbalance and the brain response to food cues

Authors: *J. ELKIND[1], A. R. CHILDRESS[4], P. S. REGIER[2], A. M. TEITELMAN[3], K. JAGANNATHAN[2];
[1]Univ. of Pennsylvania, Philadelphia PA, PA; [2]Dept. of Psychiatry, [3]Univ. of Pennsylvania, Philadelphia, PA; [4]Psychiatry, Univ. PENN Perelman Sch. Med., Philadelphia, PA

Abstract: Objective and Rationale: The brain plays an integral role in modulating hunger and regulating motivated behaviors related to eating. It has been found that people with increased sensitivity to environmental food cues are more likely to overeat and become obese. Therefore, it is important to understand the neural mechanisms underlying behavioral responses to food that may contribute to hedonic hunger and overeating. The purpose of this study was to examine the association of hedonic hunger, measured by power of food scale (PFS) scores, with the brain response to food cues in brain regions associated with motivation and reward. Determining the relationship between hedonic hunger and brain response to food cues may inform targeted behavioral interventions to address obesity treatment and prevention. We hypothesized that greater hedonic hunger would be associated with heightened response to food cues in reward regions of the brain.
Methods: This secondary analysis assessed female participants (n=52; initially recruited for a Behavior in Urban Female Risk Study), scanned with event-related BOLD fMRI. Brain response to presentations of 500 msec appetitive food cues (e.g., cheesecake, French fries) was correlated with PFS scores. Three contrasts were analyzed as a function of PFS scores: novel food cues, repeated food cues, and change in brain activity to repeated (vs. novel) food cues.
Results: The brain activity to novel food cues in cortical areas (medial/middle frontal gyrus, anterior cingulate gyrus) showed an inverse relationship with PFS scores ($p < 0.01$, $k > 200$). In addition, the change in brain activity to repeated (vs. novel) food cues in several reward-related regions (e.g., hippocampus, parahippocampus) was positively correlated with PFS scores ($p < 0.01$, $k > 200$).
Conclusions: Although the analyses did not fully support our hypothesis that heightened cue-reactive (e.g., mesolimbic) regions would correlate with higher PFSs, the results present an interesting dynamicGreater hedonic hunger was associated with . Added together, lower cortical activity to novel food cues to novel food cues and greater increasing change in change brain activity to repeated (vs. novel) food cues. of response from novel to repeated cues in cue-reactive regions in those with greater hedonic hungerThis suggests an a potential imbalance of top-down/bottom up processing of appetitive food cues that may reflect less a lack of control in desire to eat.

Disclosures: J. Elkind: None. **A.R. Childress:** None. **P.S. Regier:** None. **A.M. Teitelman:** None. **K. Jagannathan:** None.

Poster

683. Central Pathways Controlling Food Intake and Energy Balance

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 683.01/U29

Topic: F.10. Food Intake and Energy Balance

Support: Wellcome Trust Sir Henry Dale Fellowship 206207/Z/17/Z

Title: Neuroimaging of the sensory and nutrient components of food rewards in humans

Authors: *P. A. KHORISANTONO[1], P. C. FLETCHER[2], I. S. FAROOQI[3], F. GRABENHORST[1];
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Abstract: Neural reward systems regulate eating behavior by detecting nutrients from sensory food properties and using this information to guide food valuation and choice. For example, fat, sugar and associated sensory characteristics, such as sweetness and texture, are particularly effective rewards that are implicated in obesity. Although oral-sensory food properties experienced during consumption critically shape eating behavior, human neuroimaging studies typically focus on valuations of visual food stimuli. Accordingly, it remains unclear how neural responses to oral food rewards derive from specific nutrients and sensory components. Moreover, although structures such as the orbitofrontal cortex, amygdala and hypothalamus are known to respond to oral food rewards, how these responses contribute to economic food valuations and real-life eating phenotypes is unknown. Here we address these questions by combining psychophysical and neuroimaging experiments with a subsequent real-life eating test. Non-obese healthy participants consumed well-defined liquid foods with various fat, sugar and protein contents during behavioral testing and fMRI scanning. We assessed the subjective economic value of the foods using a Becker-DeGroot-Marschak (BDM) auction in which participants placed bids to consume 250 ml of the offered liquids. Behavioral data indicate that economic valuations of orally delivered foods depended primarily on subjective sweetness (beta=0.358, $p<0.0001$) and thickness (beta=0.254, $p<0.0001$). Accordingly, across participants, the stimulus with the highest fat and sugar content consistently ranked highest in subjective value ($F(6,727)=30.33$, $p<0.0001$). By contrast, the stimulus with lowest fat and sugar content was valued the least, and stimuli with either low fat or low sugar content ranked in between. Substituting high fat content with either protein or a fat-free thickening agent approximated the reward value of high-fat stimuli. Analysis of neuroimaging data will show how these sensory and nutrient components elicit responses in neural reward and feeding systems. In turn, we will examine relationships between the nutrient-sensitivity of these neural systems and participants' real-life eating phenotypes as measured through a free-eating paradigm.

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Poster

683. Central Pathways Controlling Food Intake and Energy Balance

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 683.02/U30

Topic: F.10. Food Intake and Energy Balance

Support: NSF Grant DGE-1321845
NIH Grant DK078749-10

Title: Select innervation of target regions by individual arcuate nucleus proopiomelanocortin neurons

Authors: ***M. J. METZ**, S. T. HENTGES;
Colorado State Univ., Fort Collins, CO

Abstract: Proopiomelanocortin (POMC) neurons in the arcuate nucleus of the hypothalamus produce peptides, including the potent anorexigenic factor α-MSH and the endogenous opioid β-endorphin, and can also release the fast amino acid transmitters GABA and glutamate. This array of transmitters allows for POMC neurons to participate in diverse processes including analgesia, energy balance and reward. However, whether an individual POMC neuron, or a subset of POMC neurons, projects to unique downstream targets to mediate specific actions is not known. To begin to address this, retrograde-labeling agents were injected into distinct target sites of male and female mice to determine if individual POMC neurons innervated more than one target area. The results indicate that POMC neurons projecting to a particular brain region typically do not project to another injected target region simultaneously. POMC neurons have been characterized as a heterogeneous population based on a number of factors including differential responsiveness to regulatory factors such as serotonin, insulin and leptin. Thus, we characterized intrinsic electrical properties of POMC neurons projecting to known target sites and assessed their responsiveness to regulatory agents. Together, these results suggest that distinct subpopulations of POMC neurons may participate in select physiologic functions through unique projection patterns and pre- and post-synaptic regulation. This adds to evidence that POMC neurons should not be treated as a unified population of cells and that manipulating these cells in a subpopulation-specific manner will provide more reliable results in future studies. Studies aimed at determining whether specific subpopulations are activated by distinct physiologic states such as pleasure, pain or satiety are now warranted in order to better understand how POMC neurons contribute to these states.

Disclosures: **M.J. Metz:** None. **S.T. Hentges:** None.

Poster

683. Central Pathways Controlling Food Intake and Energy Balance

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 683.03/U31

Topic: F.10. Food Intake and Energy Balance

Support: This research is funded by ETH Zürich.
MPL is supported by a Doctoral Foreign Study Award from the Canadian Institutes of Health Research.

Title: Hypothalamic microRNA-7 regulates energy homeostasis *in vivo*

Authors: *M. P. LAPIERRE, S. GODBERSEN, M. STOFFEL;
Inst. of Mol. Hlth. Sci., ETH Zürich, Zürich, Switzerland

Abstract: The hypothalamus, in particular the arcuate (ARC) and paraventricular (PVN) nuclei, play critical roles in the regulation of food intake, energy expenditure, and nutrient metabolism. MicroRNAs (miRs) modulate many biological processes by binding to the mRNA of target genes to repress their expression[1], and the inhibition of microRNA biogenesis in the hypothalamus causes obesity in mice[2]. Among the most highly enriched microRNAs in the ARC and PVN are the miR-7 family members, miR-7a1, miR-7a2, and miR-7b[3]. MiR-7 is known to protect against neuronal cell death in models of Parkinson's disease[4,5]; however, whether it affects hypothalamic neuron function remains unknown. We have observed upregulation of miR-7 in the hypothalamus of obese *ob/ob* mice and downregulation during fasting, suggesting that hypothalamic miR-7 may be involved in the regulation of energy homeostasis. To address this hypothesis, we ablated all three members of the miR-7 family via Cre-lox recombination in POMC-, AgRP-, LepR-, and SIM1-expressing neurons. We also used UBC-Cre-ERT2 to generate a global, tamoxifen-inducible miR-7 knockout mouse line. In each of these five models, we performed metabolic phenotyping (body weight; random-fed blood glucose; glucose and insulin tolerance tests) of both males and females fed a normal diet or high-fat diet, and we observed that loss of miR-7 in these different neuronal populations leads to varying degrees of diet-induced obesity. In order to understand the mechanism underlying the observed phenotypes, we will perform RNA sequencing to identify the regulated miR-7 target genes and other relevant genes. In addition, we are exploring the relationship between miR-7 and the circular RNA, Cdr1as, which acts as a "sponge" to sequester miR-7 via its numerous miR-7 binding sites[6,7]. We have found that these sites outnumber miR-7 by 50-fold in the hypothalamus, suggesting enormous capacity for miR-7 inhibition. We anticipate that the results of this study will expand our knowledge of hypothalamic pathways regulating energy homeostasis.
[1]Bartel DP, Cell 2009; [2]Vinnikov IA et al., J Neurosci 2014; [3]Herzer S et al., J Neuroendocrinol

2012; [4]Junn E et al., PNAS 2009; [5]Chaudhuri AD et al., JBC 2016; [6]Memczak S et al., Nature 2013; [7]Hansen TB et al., Nature 2013

Disclosures: **M.P. LaPierre:** None. **S. Godbersen:** None. **M. Stoffel:** None.

Poster

683. Central Pathways Controlling Food Intake and Energy Balance

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 683.04/U32

Topic: F.10. Food Intake and Energy Balance

Support: HL 134850
HL 084207
18EIA33890055

Title: PVN RGS2 is critical for the regulation of energy homeostasis

Authors: *Y. DENG, U. SINGH, K. SAITO, H. CUI;
Pharmacol., Univ. of Iowa, Iowa City, IA

Abstract: Obesity has become a major public health concern due to its high risk of developing life-threatening chronic diseases, such as hypertension and diabetes, and its prevalence has been increasing worldwide. While there is a consensus that the central nervous system (CNS) plays a crucial role in obesity, the underlying neural substrates mediating the dysregulation of energy balance remain incompletely understood. Accumulating evidence suggests that the paraventricular nucleus of hypothalamus (PVN) is a key intersection point that regulates energy homeostasis through multiple mechanisms. However, the detailed regulatory components involved in these alternations have not been thoroughly identified. Regulator of G protein signaling (RGS) proteins function as endogenous negative regulators of GPCR signaling. RGS2 is a member of the B/R4 family of RGS proteins with ubiquitous expression, and it is reported that *RGS2* knockout mice exhibit resistance to age-related weight gain, suggesting its involvement in the energy metabolism. Since the role of central RGS2 is largely unknown, we investigated the function of PVN RGS2 in the regulation of energy metabolism. Our RNAscope analyses revealed that RGS2 is highly expressed in PVN neurons, many of which also co-express melanocortin 4 receptor (MC4R), which is a G protein-coupled receptor (GPCR) known to be substantial for energy homeostasis. Thus, we hypothesized that PVN RGS2 is important for the regulation of whole-body energy balance. The expression of RGS2 within the PVN of $RGS2^{Flox}$ mice was disrupted through stereotaxic microinjection of AAV-Cre-GFP. Surprisingly, compared to their wild-type littermates, $RGS2^{Flox}$ animals exhibit significantly higher body weight while no difference is observed in food intake and resting metabolic rate (RMR). Body composition analysis by nuclear magnetic resonance (NMR) suggests that both fat mass and lean

mass are increased in *RGS2^{Flox}* mice. Additionally, PVN RGS2 deletion leads to elevated digestive efficiency in female *RGS2^{Flox}* mice, suggesting its potential role in the neuroendocrine regulation. Our results clearly state that PVN RGS2 deletion mice have distinct body weight phenotype compare to whole-body RGS2 knockout animals, indicating the divergence of central and peripheral RGS2 function in the regulation of energy homeostasis. Future studies will focus on the detailed mechanistic study aimed at understanding the potential modulatory role of RGS2 on different GPCRs in PVN neurons.

Disclosures: **Y. Deng:** None. **U. Singh:** None. **K. Saito:** None. **H. Cui:** None.

Poster

683. Central Pathways Controlling Food Intake and Energy Balance

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 683.05/U33

Topic: F.10. Food Intake and Energy Balance

Support: NIH R01AG055059
NIH 1R21 NS 098362

Title: Role of p75 in leptin signaling

Authors: J. C. RYU[1], Y. LIU[1], B. PODYMA[2], B. XU[4], A. D. GULER[2], C. DEPPMANN[3], *S. YOON[1];
[1]Ohio State Univ., Columbus, OH; [3]Biol., [2]Univ. of Virginia, Charlottesville, VA; [4]Dept. of Neurosci., Scripps Res. Inst. Florida, Jupiter, FL

Abstract: P75 was reported to influence metabolism, wherein its null mice remained lean without hypophasia, and do not develop insulin resistance even with high-fat diet (HFD). This effect was attributed in part to its role in white adipocytes. We found that p75 levels increased significantly with HFD in the hypothalamus, in particular in the arcuate nucleus, dorsomedial nucleus, and tanycytes of the medial eminence. Neurons in these nuclei are involved in feeding and energy expenditure in response to leptin. We thus asked whether p75 null mice are similarly recalcitrant to developing leptin resistance. P75 colocalizes with the leptin receptor in these neurons, and 70 and 40% of NPY/AgRP and POMC neurons, respectively, express p75 in the arcuate nucleus. We found that p75 null mice exhibited greater sensitivity to leptin than the wild type both with normal chow and 4 months of HFD feeding. Corollary to the phenotype, a greater number of neurons in p75 null mice express p-STAT3 in the arcuate and dorsomedial nuclei in response to leptin compared to the wild type. In line with these data, we found that p75 attenuates STAT3 activation, while enhancing ERK activation by leptin in 293T cells. The mechanism by which p75 influences leptin signaling appears to involve p75 interacting with the leptin receptor by sharing SHP2 as an adaptor in response to leptin. To investigate whether there

is a genetic interaction between p75 and leptin signaling, p75 null mice were then crossed with leptin-defective (ob/ob) and leptin receptor-defective (db/db) mice. To our surprise, ob/ob:$p75^{KO}$and db/db:$p75^{KO}$mice failed to eat, began losing weight beginning 7 weeks of age, and died of starvation by 15 weeks. These results suggest that p75 is necessary to control feeding in the absence of normal leptin signaling.

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Poster

683. Central Pathways Controlling Food Intake and Energy Balance

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 683.06/U34

Topic: F.10. Food Intake and Energy Balance

Support: NSF Grant IOS-1656626 (CAG)
VA Grant 121 BX002085 (LPR)
VA Grant IO1 BX001804 (LPR)

Title: Identification of leptin-sensitive raphe neuron projections to the hypothalamic nuclei

Authors: *N. D. MAXWELL[1], L. P. REAGAN[1,2], J. R. FADEL[1], F. Z. LOYO-ROSADO[1], C. A. GRILLO[1];
[1]Pharmacology, Physiol. & Neurosci., Univ. of South Carolina Sch. of Med., Columbia, SC;
[2]WJB Dorn VA Med. Ctr., Columbia, SC

Abstract: Leptin is an adipocyte hormone that controls a myriad of homeostatic functions. Most notably, leptin acts on neurons in the hypothalamus through the leptin receptor-mediated JAK/STAT pathway to control energy homeostasis and appetite. Leptin has not only been shown to act on hypothalamic neurons, but also on other select areas of the brain such as the raphe nuclei, the primary source of serotonin (5-HT) in the brain. We are interested in studying the connections between raphe and hypothalamic nuclei and their ability to control food intake. Although these connections have been described anatomically, their functional roles remain to be elucidated. Our objectives are: (1) to define raphe neurons sensitive to leptin that send projections to the hypothalamic nuclei; and (2) to determine whether a population these neurons are serotonergic. In order to accomplish this goal, we injected fluorescently tagged cholera toxin-subunit-B (fCTB, a retrograde tracer) into the arcuate nucleus or the lateral hypothalamus (LH). One month following the tracer administration, the rats were injected with leptin into the lateral ventricle and perfused with paraformaldehyde 1 hour later. We hypothesize that there are leptin-sensitive serotonergic neurons in the raphe nucleus that send projections to different nuclei within the hypothalamus including the arcuate, as well as other phenotypes of neurons.

Immunohistochemistry and immunofluorescence were performed on these brain sections, primarily focusing on the raphe nucleus. In order to observe colocalization between our targets, we triple-labeled with antibodies against phosphorylated STAT3 (pSTAT3), a marker for leptin activated neurons, and tryptophan hydroxylase (TPH), a marker of serotonergic neurons along with the fCTB from the injection into the arcuate or LH. First, we show through the colocalization of fCTB and TPH in the raphe nucleus that serotonergic neurons do in fact project to the arcuate, and to a lesser extent the LH. More importantly, we observed that serotonergic and non-serotonergic raphe neurons that project to the arcuate nucleus are activated by leptin. These data support our hypothesis that there is an existing leptin-mediated raphe pathway projecting to the hypothalamus. We aim to characterize this pathway and tease apart the role that it may play in feeding behavior regulated by leptin.

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Poster

683. Central Pathways Controlling Food Intake and Energy Balance

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 683.07/U35

Topic: F.10. Food Intake and Energy Balance

Support: NIH R01DK10367

Title: Ventromedial hypothalamus neuronal nitric oxide synthase expressing neurons project to the lateral hypothalamus

Authors: *P. SARKAR, H. WAJID, B. TRIAS, K. B. KNAPP, A. SINGH, V. H. ROUTH; Pharmacol, Physiol & Neurosci, RBHS: New Jersey Med. Sch., Newark, NJ

Abstract: A functional relationship with regard to energy balance exists between the lateral (LH) and ventromedial (VMH) hypothalamus. However, the anatomical correlate(s) underlying this functional relationship are not known. The VMH possesses glucose-inhibited (GI) neurons which increase their activity as glucose levels decline. We have shown that VMH GI neurons are critical for restoring euglycemia after insulin-induced hypoglycemia. This suggests that VMH GI neurons regulate glucose homeostasis. AMP-activated protein kinase (AMPK)-induced activation of neuronal nitric oxide synthase (nNOS) increases the activity of VMH GI neurons in low glucose. VMH AMPK activation also inhibits brown fat thermogenesis and white fat browning leading to decreased energy expenditure and weight gain. Estrogen promotes weight loss by inhibiting VMH AMPK. Bone morphogenetic protein 8B (BMP8B) mediates estrogen's thermogenic effect. The effect of BMP8B is dependent on activation of LH orexin neurons. We found that estrogen blunts activation of VMH nNOS-GI neurons in low glucose by inhibiting

AMPK. These data suggest that estrogen's thermogenic effect is due, in part, to inhibition of VMH nNOS-GI neurons. *Therefore, we hypothesize that VMH nNOS neurons which express BMP8B project to the LH.* This hypothesis was tested by injecting fluorescently labelled Retrobeads™ (retrograde tracer) into the LH of c57bl6 mice (8-12 weeks) to determine whether Retrobeads™ co-localized with VMH nNOS expressing neurons. Retrobeads™ were observed throughout the ventrolateral (vl), dorsomedial (dm), and central VMH. Retrobead™ labelling was found in subpopulations of both nNOS expressing and non-nNOS expressing cell bodies of the vl and dm VMH. In separate set of experiments, we used immunohistochemistry to determine whether nNOS and the BMP8B receptor, BMPR1a, co-localize in the VMH of mice. A larger percentage of vlVMH cells were BMPR+ (50.6±4.3% of total in males, n=4; 67.0±5.7% in females, n=4) than were nNOS+ (39.6±3% in males and 47.9±3.3% in females). BMPR1a was co-localized in 31.6±4.5% of nNOS+ vlVMH cells in male mice (n=4) vs. 55.6 ± 9.3% in females (n=4). Thus, some VMH nNOS expressing neurons project to the LH and some express BMPR1a. Moreover, this pathway appears to be sexually dimorphic. These data suggest that LH projecting nNOS neurons express BMPR1a. This observation supports our hypothesis and suggests that VMH nNOS-GI neurons may mediate some of estrogen's effects on energy homeostasis.

Disclosures: P. Sarkar: None. **H. Wajid:** None. **B. Trias:** None. **K.B. Knapp:** None. **A. Singh:** None. **V.H. Routh:** None.

Poster

683. Central Pathways Controlling Food Intake and Energy Balance

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 683.08/U36

Topic: F.10. Food Intake and Energy Balance

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AGW, GSW: NIH R01 NS029728
AJJ: JDRF 3-PDF-2014-115-A-N
JDH: The Kavli Foundation

Title: Systematic analysis of high-spatial resolution mapping of hypothalamic markers involved in energy homeostasis regulation using Axiome neuroinformatics tools

Authors: *C. GARCIA-LUNA, G. SANCHEZ-WATTS, A. J. JOKIAHO, J. D. HAHN, A. G. WATTS;
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Abstract: The hypothalamus plays a fundamental integrative role in energy balance to enact appropriate behavioral, autonomic and endocrine responses that change food intake and energy expenditure. Given the peptidergic heterogeneity of hypothalamic neurons and the variety of research models and analytical methods, it is a challenge to construct high-spatial resolution network models that identify key hypothalamic subregions and the spatial interaction between neuropeptides involved in the regulation of energy homeostasis in both health and disease. Neuroinformatics tools may be employed to assist understanding of the organization of neural circuits implicated in energy balance regulation. Here we have used Axiome (created by JDH): a suite of modular computational tools based on systematized and interactive Excel templates that facilitate rigorous entry and comparative analysis of brain data (currently tailored for use with the Swanson rat brain atlas). To identify hypothalamic regions that integrate peripheral and central signals in naïve or metabolic-challenged rats, we mapped (using Axiome C module) the regional locations of various neuronal markers onto sequential hypothalamic atlas levels. They include: the neuronal projection markers pseudorabies virus (PRV) and vascularly injected fast blue; chemical phenotypic markers (orexin; glucagon-like peptide 1 receptor [GLP1R] mRNA expression) from animals receiving PRV injections in the adrenal glands; and a neuronal activation marker (Fos) from animals subjected to slow- or rapid-onset hypoglycemia. Accurate mapping was achieved by referencing gray matter regions with dark field photomicrographs, together with the distribution of the norepinephrine synthetic enzyme, dopamine-beta hydroxylase. Some data used for mapping are previously published, but are now analyzed here using Axiome. By cross-referencing data from the different markers and metabolic conditions recorded in Axiome C, we identified the lateral hypothalamic area (LHA) juxtadorsomedial (LHAjd) and dorsal (LHAd) regions as important integrative and output nodes following rapid-onset hypoglycemia, and the dorsomedial hypothalamic nucleus (DMH) to slow-onset hypoglycemia. This identifies the LHAjd, LHAd and DMH as potential contributors to a hypothalamic output network that controls sympatho-adrenal output during hypoglycemia.

Disclosures: C. Garcia-Luna: None. **G. Sanchez-Watts:** None. **A.J. Jokiaho:** None. **J.D. Hahn:** None. **A.G. Watts:** None.

Poster

683. Central Pathways Controlling Food Intake and Energy Balance

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 683.09/U37

Topic: F.10. Food Intake and Energy Balance

Support: Miami University Biology Dept.

Title: Expression of ERα in hippocampus, amygdala, and hypothalamus during altered energy states are dependent on sex

Authors: *K. KROLICK[1], H. SHI[2], X. LIU[1];
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Abstract: Obesity and metabolic disturbances continue to be a top health concern. Estrogens are recognized for their neuroprotective and anorexigenic effects in males and females. Metabolic effects of estrogens primarily work through estrogen receptor alpha (ERα), which is differently expressed between the sexes not only in hypothalamic regions associated with controlling food intake but also in limbic regions that are not typically associated with feeding such as the hippocampus and amygdala. This could account for why estrogens differentially affect metabolic disturbances in two sexes depending on the brain region of injection. While researchers continue to elucidate the pathways responsible for estrogen's actions, it is surprising that no study has mapped the expression of ERα in extra-hypothalamic areas during different energy states between the sexes. We propose that ERα is expressed differently depending on (1) energy status of the animal, (2) sex of the animal, and (3) nuclei of brain regions. Two key extra-hypothalamic nuclei new to our understanding of regulation of feeding are the amygdala and hippocampus. Long-Evans rats were individually housed and separated into different treatment groups, reflective of different energy statuses seen in Western high-fat diet (HFD) and with HFD-induced obesity. Both short-term (4 days) and long-term (4 weeks) conditions of each treatment were used. Treatment groups are: normal rodent diet (chow; 3.003 kcal/g; 14% calories from fat); HFD (4.728 kcal/g; 45% calories from fat); HFD pair-fed (HFD-PF) which allows us to ascertain the effects of dietary fat as opposed to obesity; 24-hour fasting; and 30% chow-restricted . Chow and HFD had closely matched amounts of protein and carbohydrates, but quite different amounts of fat. Immunohistochemical staining of ERα was performed using monoclonal antibody (Santa Cruz, sc-514857) and ImmunoCruzTM mouse ABC Staining Systems (sc-2017). Photoshop was used to stitch together images taken using light microscopy and ImageJ was used to quantify the number of positive cells. Two-way ANOVA (dietary condition x sex) for each brain region of interest will be used with $P < 0.05$ considered statistically significant. The expression in different nuclei in each brain structure is quantified, as differences in ER expression may be overlooked in studies that do not take this into account. ERα is differently expressed in the amygdala and the hippocampus dependent on energy status and sex of the animal. Findings from this project will contribute to the cellular mechanisms responsible for sex differences in the role of estrogen in the extra-hypothalamic circuitry as it relates to energy metabolism.

Disclosures: K. Krolick: None. **H. Shi:** None. **X. Liu:** None.

Poster

683. Central Pathways Controlling Food Intake and Energy Balance

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Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 683.10/U38

Topic: F.10. Food Intake and Energy Balance

Support: Academia Sinica Grant

Title: Functional mapping of the K_{ATP} channel-dependent central glucose regulatory circuit

Authors: Y. CHEN[1], ***H. TSAI**[2], S. YANG[1];
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Abstract: Glucose homeostasis involves processes that manage food intake, stable energy storage, and spending during times on different caloric states. Glucose, which conveys short-term fuel availability to the CNS, acts on the hypothalamic neurons to modulate the physiological responses that control energy homeostasis. However, the anatomic distribution of glucose-excited neurons and their function in energy homeostasis remained poorly understood. We use activity-dependent genetic labeling to characterize neurons activated by transient hyperglycemia. Our preliminary results showed that this transient hyperglycemia labeled the neurons in the paraventricular nucleus (PVN), dorsomedial nucleus (DMH), lateral nucleus (LH), arcuate nucleus (ARC) and ventromedial nucleus (VMH). Since earlier studies have shown that the ATP-sensitive potassium channel (K_{ATP}) is crucial for glucose sensing in the hypothalamus, we examined whether the mice lacking functional K_{ATP} channels may alter the anatomical distribution of the activity-labeled neurons in the basomedial hypothalamus. We found that mice lacking K_{ATP} channels had a similar amount of glucose-labeled neurons as the wild-type control mice (PBS injected) in the DMH, LH, VMH, and ARC, indicating that neurons lacking functional K_{ATP} channels can not sense glucose. Our RNA *in situ* hybridization results showed that the mRNA of KCNJ11, the Kir6.2 coding gene, was wildly expressed in hypothalamus with the highest levels in VMH and LH. Furthermore, we also noticed that a large portion of the activity-labeled neurons co-expressed KCNJ11 in the LH and VMH. Delivering Kir6.2-rAAV into the basomedial hypothalamus rescued the glucose intolerance in mice lacking functional K_{ATP} channels. In conclusion, our results highlighted the potential importance of the neuronal circuits that utilize K_{ATP} channel to regulate glucose homeostasis.

Disclosures: Y. Chen: None. **H. Tsai:** None. **S. Yang:** None.

Poster

683. Central Pathways Controlling Food Intake and Energy Balance

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 683.11/U39

Topic: F.10. Food Intake and Energy Balance

Support: 5R01DK106476

Title: Sexually dimorphic expression of melanocortin 3 receptors in neural circuits that link control of metabolism with reproductive state

Authors: *M. N. BEDENBAUGH[1], P. R. SWEENEY[2], K.-Y. YAM[1], R. D. CONE[2,3], R. B. SIMERLY[1];
[1]Vanderbilt Univ., Nashville, TN; [2]Life Sci. Inst., [3]Univ. of Michigan, Ann Arbor, MI

Abstract: The physiological systems regulating reproduction and metabolism must communicate with each other in order to maintain homeostasis. While it is clearly evident that reproduction and energy balance are closely intertwined, the neural circuits integrating these two processes are poorly understood. Recent functional data suggests the melanocortin 3 receptor (MC3R) mediates the exchange of information between reproductive and metabolic state. Additionally, females exhibit uniquely aberrant metabolic and reproductive phenotypes after deletion of MC3R. However, the cellular identity of MC3R-expressing neurons has not been determined in males and females, nor have their central circuits been defined. Here, we have begun to neurochemically define and map MC3R expression using RNAScope, immunohistochemistry, axonal labeling, tissue clearing and lightsheet microscopy. Using MC3R-GFP mice, we have found that MC3R is expressed in brain regions known to play a role in the control of reproductive and metabolic state, including the anteroventral periventricular nucleus (AVPV), arcuate nucleus (ARH), paraventricular nucleus of the thalamus (PVT), ventral tegmental area (VTA), and discrete regions of the caudal brainstem. The AVPV contains three times as many MC3R neurons in females compared with males, and MC3R is expressed in a majority of both AgRP and POMC neurons in the ARH, but to a significantly greater extent in males. MC3R is also coexpressed with kisspeptin neurons and ESR1 in both the AVPV and ARH. The projections of MC3R neurons, visualized through genetically targeted axonal labels, extend to a surprising variety of functional neuronal systems that include circuits known to control body weight, gonadotropin secretion, motivated behavior and reward. Taken together, these results suggest that MC3R signaling functions differently in males and females to regulate circuits involved in the coordination of reproductive and metabolic state, and may explain the unique roles for MC3R females.

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Poster

683. Central Pathways Controlling Food Intake and Energy Balance

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Topic: F.10. Food Intake and Energy Balance

Support: Princeton Neuroscience Institute's Innovation Award

CV Starr Fellowship
Brain and Behavior Research Foundation's NARSAD Young Investigator Award
Foundation for Prader-Willi Research
American Diabetes Association Pathway to Stop Diabetes Program
American Diabetes Association Core Program

Title: Dorsal raphe nucleus GABA neurons regulating energy balance

Authors: *V. M. BHAVE[1], M. SCHNEEBERGER[2], T. D. BANERJEE[1], L. PAROLARI[2], P. WANG[2], J. FRIEDMAN[2], A. NECTOW[1];
[1]Dept. of Neurosci., Princeton Univ., Princeton, NJ; [2]The Rockefeller Univ., New York, NY

Abstract: The central regulation of energy balance is critical for survival. The processes responsible for energy homeostasis are regulated at both the autonomic and behavioral levels. These processes are thought to be regulated by neurons within the hypothalamus and brainstem. However, the cell types and circuits within the brainstem regulating these processes are less well understood. We have recently identified a population of inhibitory, GABAergic neurons—within the dorsal raphe nucleus (DRN) of the mouse brainstem—that are critical for regulating energy intake and expenditure. In particular, we have found that these so-called "DRN Vgat" neurons are activated by food deprivation and ambient warmth, two signals critical for conveying an animal's internal and external environments. Here, we demonstrate that these neurons exhibit vast projections that ascend divergently into the forebrain (to structures such as the bed nucleus of the stria terminalis, the dorsomedial hypothalamus, and the medial preoptic area). DRN Vgat also exhibit projections that descend to the raphe pallidus (within the medulla) and ultimately to interscapular brown adipose tissue (iBAT). Optogenetic and chemogenetic modulation of these projections demonstrates a divergent pattern of regulation, with respect to both feeding and different types of thermogenesis. Together, this work establishes DRN Vgat neurons as a critical node embedded within the extended circuitry mediating energy homeostasis.

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Poster

683. Central Pathways Controlling Food Intake and Energy Balance

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Topic: F.10. Food Intake and Energy Balance

Support: PNI Innovation Award
Princeton University CV Starr Fellowship
NARSAD Young Investigator Award

Foundation for Prader- Willi Research
American Diabetes Association Pathway to Stop Diabetes Program
American Diabetes Association Core Program
JPB Foundation

Title: Regulation of food intake and thermogenesis by the dorsal raphe nucleus

Authors: *T. DAS BANERJEE[1], V. M. BHAVE[1], M. SCHNEEBERGER PANE[2], A. R. NECTOW[1];
[1]Princeton Univ., Princeton, NJ; [2]Mol. Genet., The Rockefeller Univ., New York, NY

Abstract: In mammals, energy balance is tightly regulated and changes in metabolic state result in compensatory effects on both food intake and energy expenditure. We have recently identified and characterized the dorsal raphe nucleus (DRN) as a novel node in the extended neural circuitry regulating energy homeostasis. Previous pharmacological and electrophysiological studies have suggested a role for the DRN in controlling food intake and other aspects of energy balance, but the specific cell types mediating these effects were not well understood. We have recently reported that DRN neurons expressing the vesicular transporters Vgat and VGLUT3 play a role in controlling food intake and body weight. These so-called DRN^{Vgat} and DRN^{VGLUT3} neurons are anatomically distinct, and reciprocally regulate food intake such that activation of DRN^{Vgat} neurons increases feeding while activation of DRN^{Vglut3} suppresses feeding. Optogenetic modulation of $DRNV^{GLUT3}$ neurons bidirectionally affected food intake in a reciprocal fashion to that of DRN^{Vgat} neurons. Here we show that DRN^{Vgat} neurons, but not DRN^{VGLUT3} neurons, are activated by an increase in ambient temperature suggesting a possible role of DRN^{Vgat} neurons in regulating body temperature, independently of DRN glutamatergic activity. We further demonstrate that chemogenetic modulation of the DRN^{Vgat} neurons potently regulates energy expenditure through changes in both thermogenesis and locomotion. Interestingly, while optical activation of DRN^{VGLUT3} neurons significantly increases acute locomotor activity, inhibition of these neurons has no effect on movement. Collectively, these studies establish the DRN as an important node in regulation of energy expenditure.

Disclosures: T. Das Banerjee: None. **V.M. Bhave:** None. **M. Schneeberger Pane:** None. **A.R. Nectow:** None.

Poster

683. Central Pathways Controlling Food Intake and Energy Balance

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Topic: F.10. Food Intake and Energy Balance

Support: NIH Grant R01DK106229

NIH Grant T32DA07287

Title: Glutamate release from the PVN-NAc pathway decreases intake of high-fat food

Authors: *A. E. SMITH[1], J. M. KASPER[2], L. F. OCHOA[3], J. PERIS[4], G. VARGAS[3], J. D. HOMMEL[2];
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Abstract: Obesity is an alarming chronic health crisis that currently affects 39.8% of the adult population in the United States. An important driver of obesity is overconsumption of highly-palatable food, including high-fat food, beyond nutritional energy requirements. Homeostatic feeding is regulated by the paraventricular nucleus of the hypothalamus (PVN), which functions to integrate central and peripheral signals about energy balance. A subset of PVN neurons project to the nucleus accumbens (NAc). The NAc is closely associated with hedonic feeding, and administration of glutamate (Glu) antagonists in the NAc increases intake of high-fat food. To date, the role of the PVN→NAc pathway in mediating intake of high-fat food remains unknown. **Therefore, we hypothesized that the PVN→NAc pathway modulates Glu to control intake of high-fat food.** The goal of these studies was to determine the structural, functional and behavioral significance of the PVN→NAc pathway on intake of high-fat food. We used viral tracing techniques coupled with immunohistochemistry to characterize neurons in the PVN→NAc pathway. Our results indicate that PVN→NAc neurons are localized to parvocellular regions of the PVN, and co-localize with vesicular glutamate transporter 1 presynaptically in the NAc. Next, we quantified neurotransmitter release from PVN→NAc neurons in real time using microdialysis with on-line capillary electrophoresis and laser-induced fluorescence. Pharmacogenetic stimulation of PVN→NAc neurons using the hM3D DREADD resulted in robust and sustained Glu release in the NAc. We also used hM3D to determine the behavioral significance of the PVN→NAc pathway on intake of high-fat food. We observed a decrease in intake of high-fat food upon pharmacogenetic stimulation of PVN→NAc, which is consistent with increased Glu release. Overall, glutamatergic PVN→NAc transmission plays a regulatory role in intake of high-fat food, and represents a novel target that will critically advance efforts to improve treatment outcomes in obesity and metabolic dysregulation.

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Poster

683. Central Pathways Controlling Food Intake and Energy Balance

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Topic: F.10. Food Intake and Energy Balance

Support: R01EY027077 NIH-NEI
R01EY027711 NIH-NEI
R01NS091066 NIH-NINDS

Title: Hypothalamic OPN5 regulates thermogenesis in mammals

Authors: *K. X. ZHANG[1,2], B. A. UPTON[1,2], S. P. D'SOUZA[1,2], C. J. MADDEN[3], S. KERNODLE[4], A. J. HOLT[5], S. VEMARAJU[2], G. NAYAK[2], S. F. MORRISON[3], R. J. SEELEY[4], A. SWEENEY[5], R. A. LANG[1,2];
[1]Developmental Biol., [2]Pediatric Ophthalmology, Cincinnati Children's Hosp. Med. Ctr., Cincinnati, OH; [3]Neurolog. Surgery, Oregon Hlth. & Sci. Univ., Portland, OR; [4]Nutr. Obesity Res. Ctr., Univ. of Michigan, Ann Arbor, MI; [5]Physics & Astronomy, Univ. of Pennsylvania, Philadelphia, PA

Abstract: The thermogenic potential of brown adipose tissue (BAT) is a promising therapeutic target in the treatment of obesity and metabolic disorders. The preoptic area (POA) is a region in the anterior hypothalamus responsible for autonomic thermoregulation by means of modulating BAT activity through sympathetic nerve activity (SNA). Neurons in the POA express opsin-5 (OPN5), an atypical opsin found in various extraretinal tissues and known to respond to near-UV wavelengths with a lambda-max of 380 nm. OPN5 has previously been shown to regulate seasonal breeding behavior in birds. Loss of OPN5 in mice have been demonstrated to impair circadian photoentrainment. We have also shown OPN5 to be required in retinal ganglion cells for *in vivo* entrainment of a retina circadian clock independent of the suprachiasmatic nucleus. To date, no other physiological role for mammalian OPN5 has been proposed. The same POA neurons that express OPN5 also engage the central thermoregulatory circuit that modulates BAT activity. Using a genetically targeted glycoprotein-deleted rabies virus injected into the POA, we identified labeled neurons in the rostral raphe pallidus (rRPa), the lateral parabrachial nucleus (LPB), and the dorsomedial hypothalamus (DMH), all nuclei known to participate in central BAT thermoregulation. *Opn5*$^{-/-}$ mice better defend their core body temperature during acute 4°C challenge. Our results indicate this effect to be due to increased BAT thermogenesis and not heat retention or pyrexia. Furthermore, BAT thermogenesis target gene transcripts (*Ucp-1*, *Prdm16*, *Pgc-1a*) were elevated in these cold stressed *Opn5*$^{-/-}$ animals. To demonstrate the importance of OPN5's near-UV light sensing function in cold defense, C57BL/6J mice reared from E16.5 without 380 nm light phenocopy *Opn5*$^{-/-}$ animals when acutely cold challenged. Direct 380 nm photostimulation of the POA also blunted BAT thermogenesis, showing that hypothalamic OPN5 can respond acutely to near-UV light. We also found that *Opn5*$^{-/-}$ mice consume more food and have a higher total daily energy expenditure than controls. Our results suggest a mechanism where near-UV sensitive hypothalamic OPN5 neurons regulate BAT thermogenesis directly, proposing that the mammalian autonomic thermoregulatory apparatus is light responsive.

Disclosures: **K.X. Zhang:** None. **B.A. Upton:** None. **S.P. D'Souza:** None. **C.J. Madden:** None. **S. Kernodle:** None. **A.J. Holt:** None. **S. Vemaraju:** None. **G. Nayak:** None. **S.F. Morrison:** None. **R.J. Seeley:** None. **A. Sweeney:** None. **R.A. Lang:** None.

Poster

683. Central Pathways Controlling Food Intake and Energy Balance

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Topic: F.10. Food Intake and Energy Balance

Support: NIH Grant DK105510
NSF Grant 1652060

Title: Tachykinin-1-expressing neurons in the parasubthalamic nucleus (PSTN) signal food availability and suppress food consumption

Authors: O. BARNHILL, J. SPERBER, F. GULAMALI, J. KIM, T. LEGAN, *M. CARTER; Williams Col., Williamstown, MA

Abstract: The motivation to eat depends on the relative balance of activity in orexigenic and anorexigenic neuronal populations. Previous studies implicate neurons in the parasubthalamic nucleus (PSTN), a small population of neurons in the posteriorlateral hypothalamus, as potentially regulating appetite, but the role of these neurons in food intake behavior has not been characterized. Here, we report that PSTN neurons can be subdivided into populations of neurons that express tachykinin 1 (Tac1) or corticotropin releasing hormone (CRH). Tac1 PSTN neurons, but not CRH PSTN neurons, increase expression of Fos, an indirect marker of neuronal activation, during a meal or after administration of anorexigenic hormones. *In vivo* fiber photometry recordings show that Tac1 PSTN neurons become active during the consumption of food in hungry mice, but only when food is accessible. Optogenetic or chemogenetic stimulation of Tac1 PSTN neurons decreases food intake while chemogenetic inhibition of Tac1 PSTN neurons increases food intake. Tac1 PSTN neurons project to the external lateral parabrachial nucleus and nucleus of the solitary tract, two brain areas that contain anorexigenic neuronal populations, suggesting a potential mechanism for their suppression of food intake. Taken together, these results demonstrate that Tac1 PSTN neurons signal food availability and negatively regulate food intake behavior.

Disclosures: O. Barnhill: None. **J. Sperber:** None. **F. Gulamali:** None. **J. Kim:** None. **T. Legan:** None. **M. Carter:** None.

Poster

683. Central Pathways Controlling Food Intake and Energy Balance

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Topic: F.10. Food Intake and Energy Balance

Support: NIH DK 106476

Title: Leptin suppresses GLP-1 innervation to the paraventricular nucleus of the hypothalamus and impairs postsynaptic signaling

Authors: *J. E. BIDDINGER[1], R. M. LAZARENKO[1], M. M. SCOTT[2], R. B. SIMERLY[1]; [1]Vanderbilt Univ., Nashville, TN; [2]Dept. of Pharmacol., Univ. of Virginia, Charlottesville, VA

Abstract: The nucleus of the solitary tract (NTS) is critical for the central integration of signals from visceral organs and is the first central target of vagal afferents that signal nutritional status from gut to brain. The NTS contains preproglucagon (PPG) neurons that send direct projections containing glucagon-like peptide-1 (GLP-1) to the paraventricular nucleus of the hypothalamus (PVH), which regulates a variety of homeostatic physiological responses. Nearly all GLP-1 neurons express leptin receptors and are directly responsive to leptin in neonatal mice, as well as in adulthood. Leptin functions during development to impact the organization of intra-hypothalamic metabolic circuitry, but whether it specifies brainstem-hypothalamic connections is unknown. To address this question, we used PPG-cre mice to target a fusion protein of synaptophysin and tdTomato to PPG neurons in order to visualize neuronal projections in leptin-deficient *Lep$^{ob/ob}$* mice. In contrast to development of projections from the arcuate nucleus to the PVH, projections from PPG neurons show an increase in the PVH of *Lep$^{ob/ob}$* mice compared with controls, with no change in numbers of PPG neurons. Moreover, a similar increase in PVH innervation is seen in mice with disrupted leptin receptor expression (*LepRbTB* mice). Crossing *LepRbTB* and PPG-cre mice, resulted in mice with LepRb signaling restored in PPG neurons on an otherwise null LepRb background. GLP-1 innervation of the PVH was rescued to wt levels in these mice, suggesting a cell-autonomous action of LepRb on development of GLP-1 projections to the PVH. The increase in PVH innervation observed in *Lep$^{ob/ob}$* mice is also reflected in the ability of visceral sensory information to activate PVH neurons, as evidenced by an increase in cFos labeling in the PVH of mice that received i.p. injections of cholecystokinin, and this action also appears to be controlled by the cell autonomous action of leptin on PPG neurons. Because PPG neurons are glutamatergic, we recorded mEPSCs from PVH neurons that express GLP-1 receptors (GLP-1 R) by using whole-cell patch recordings in PVH slices derived from GLP-1 R-cre:tdTomato mice. An increase in mEPSC frequency was observed in *Lep$^{ob/ob}$* mice, compared with wt mice, with no change in mEPSC amplitude, suggesting increased excitatory neurotransmission in GLP-1 R neurons in the absence of leptin. Together, these findings indicate

that leptin acts during development to suppress the representation of excitatory afferents from PPG neurons, thereby diminishing the impact of visceral sensory information on GLP-1 receptor neurons in the PVH.

Disclosures: J.E. Biddinger: None. **R.M. Lazarenko:** None. **M.M. Scott:** None. **R.B. Simerly:** None.

Poster

683. Central Pathways Controlling Food Intake and Energy Balance

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Topic: F.10. Food Intake and Energy Balance

Support: HHMI PERSIST Grant 52008125 awarded to AMK (PI: S. Aley)
NIH Grant GM09187 awarded to AMK

Title: The hypothalamic chemoarchitecture project, year 5: High-spatial resolution atlas-based mapping of neuronal populations expressing melanin concentrating hormone, hypocretin/orexin, and calbindin in the hypothalamus of the adult male rat

Authors: A. MARTINEZ[1], V. I. NAVARRO[1], K. ARIAS[1], J. BARNETT[1], A. CARREON[1], B. CASTANEDA[1], M. FLORES[1], J. MAGADAN[1], D. HEREDIA[1], J. HOOPER[1], T. LOPEZ[1], A. LOZANO[1], S. MENDEZ[1], N. MERCER[1], A. MUNOZ[1], L. ROSARIO MOJICA[1], R. SANCHEZ[1], K. SIERRA[1], D. SOTELO[1], X. STEVENS[1], A. TOCCOLI[1], Y. VERMA[1], H. VIZCARRA[1], *A. M. KHAN[2,1];
[1]HHMI/UTEP PERSIST Program: Brain Mapping and Connectomics Lab., [2]Dept. of Biol. Sci., Univ. of Texas at El Paso, El Paso, TX

Abstract: Hypothalamic circuits contribute to bodily homeostasis, in part, through signals encoded by neuropeptides. Although previous work reports localization of hypothalamic neuropeptides in the rat, their spatial distributions are not understood in the context of a rigorously defined, hierarchically organized set of gray matter regions in a digital, open access atlas reference space. The research presented here is the latest installment of an ongoing hypothalamic mapping project that has been carried out by four previous cohorts of undergraduate students in “Brain Mapping & Connectomics”, an HHMI-funded laboratory course at the University of Texas at El Paso. Students were taught how to map neuropeptide distributions across levels 24-29 of a rat brain atlas (LW Swanson, 2004, *Brain Maps: Structure of the Rat Brain, 3rd edition*). Melanin-concentrating hormone (MCH) and hypocretin/orexin (H/O) contribute to the regulation of sleep-wake cycles and hunger and emotional states. In contrast, the intracellular macromolecule calbindin (CalB) binds calcium to control neuronal firing, and is often used as a biomarker to mark neurons. To better understand the spatial

distributions of MCH, H/O, and CalB, students used fluorescence immunohistochemistry (IF) and Nissl-staining techniques to localize their chemoarchitectonic patterns.
Initial mapping shows that, consistent with previous reports, there are sparse MCH immunoreactive (ir) cell bodies at anterior levels of the hypothalamus, while at more caudal levels they are prominently found throughout the ZI and scattered across the AHN and LHAd (refer to Swanson, 2004; for explanation of abbreviations). MCH-ir axonal fibers were mostly concentrated ventromedially in the ZI, ARH, subdivisions of the TU, and ME. H/O-ir cell bodies were only present in the LHAd, ZI, and perifornical LHA at caudal hypothalamic levels. While H/O-ir fibers were found throughout the hypothalamus, they were dense in the PVi, ARH, TUsv, perifornical LHA and the internuclear regions. CalB-ir showed a high density of cell bodies within the ARH, SO, ME, TUsv, VMH, DMHa, and internuclear regions. The similarities in the density and distribution of the three (neuro)peptides mapped here indicate possible interactions among them.
While many of the peptide distributions noted have been characterized before, the high-resolution atlas-based mapping of cell bodies and/or fibers immunoreactive for MCH, H/O, and CalB in the hypothalamus is unique. These maps generated by freshman-level students will further our understanding of hypothalamic chemoarchitecture and could provide novel insights about hypothalamic structural organization.

Disclosures: **A. Martinez:** None. **V.I. Navarro:** None. **K. Arias:** None. **J. Barnett:** None. **A. Carreon:** None. **B. Castaneda:** None. **M. Flores:** None. **J. Magadan:** None. **D. Heredia:** None. **J. Hooper:** None. **T. Lopez:** None. **A. Lozano:** None. **S. Mendez:** None. **N. Mercer:** None. **A. Munoz:** None. **L. Rosario Mojica:** None. **R. Sanchez:** None. **K. Sierra:** None. **D. Sotelo:** None. **X. Stevens:** None. **A. Toccoli:** None. **Y. Verma:** None. **H. Vizcarra:** None. **A.M. Khan:** None.

Poster

683. Central Pathways Controlling Food Intake and Energy Balance

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 683.19/V7

Topic: F.10. Food Intake and Energy Balance

Support: NIH Grant GM109817
NIH Grant GM127251
NIH BUILDing SCHOLARS Program: Linked Awards RL5GM118969, TL4GM118971, and UL1GM118970

Title: High-spatial resolution atlas-based mapping of chemoarchitecture within the forebrain: Selected studies of the bed nuclei of terminal stria and the ventral tegmental area

Authors: *K. T. LORENZANA, E. J. PEREZ, K. J. GALVAN, K. A. S. BURNETT, B. E. PINALES, A. M. KHAN;
Dept. of Biol. Sci., The Univ. of Texas at El Paso, El Paso, TX

Abstract: The bed nuclei of terminal stria (BST) and the ventral tegmental area (VTA) contain neurons that participate in a variety of functions, including autonomic responses and emotional control; and the control of behaviors that involve feeding, reward and anxiety. In order to begin identifying the contributions of specific chemical signals to the array of functions served by these structures, we conducted a high-spatial resolution mapping analysis to identify the chemical phenotypes of neurons and axonal fibers in these regions. Using multi-fluorescence histochemical techniques, we labeled tissue using antibodies directed against Agouti-related peptide (AgRP), α-melanocyte stimulating hormone (αMSH), neuropeptide Y (NPY), cocaine amphetamine regulated transcript (CART), and tyrosine hydroxylase (TH). Nissl-stained tissue sections from an adjacent series were used as a reference to determine cytoarchitectonic boundaries for the fluorescently-labeled immunostaining patterns. Plane-of-section analysis was carefully performed to facilitate mapping of the chemoarchitecture within a standardized rat brain atlas (L. W. Swanson, 2018, *Brain Maps 4.0, J Comp Neurol*). We plotted the distributions of these immunoreactivities (ir) onto digital atlas templates to create maps of these diverse neuronal populations in relation to the subregions of the BST and VTA. We determined that Swanson Atlas Levels 16-23 contain distinct distributions of each chemical marker within BST subregions. The dorsomedial and ventral nuclei of the BST displayed high densities of AgRP-, NPY-, αMSH-, and CART-ir fibers. The anteromedial and anterolateral areas of the BST displayed moderate numbers of immunoreactive fibers. Areas in the BST with low immunoreactive elements included the principal and oval nuclei. TH-ir fibers were distributed sparsely within the same BST subregions displaying expression of fibers for AgRP, αMSH, NPY, and CART. Further (confocal) analysis will provide information on the putative interactions. At the level of the VTA, CART-ir neurons and fibers were evident; with many of these fibers displaying co-expression with αMSH. Together, these data contribute to our ongoing effort to create an atlas-based compendium of chemoarchitecture to aid future efforts to target specific chemical systems within functional studies of these regions.

Disclosures: K.T. Lorenzana: None. **E.J. Perez:** None. **K.J. Galvan:** None. **K.A.S. Burnett:** None. **B.E. Pinales:** None. **A.M. Khan:** None.

Poster

683. Central Pathways Controlling Food Intake and Energy Balance

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 683.20/V8

Topic: F.10. Food Intake and Energy Balance

Support: NIH Grant GM109817
NIH Grant GM127251
NIH BUILDing SCHOLARS Program: Linked Awards RL5GM118969, TL4GM118971, and UL1GM118970

Title: Distribution of neurons and/or fibers expressing cocaine and amphetamine regulated transcript, dopamine beta-hydroxylase, and alpha-melanocyte stimulating hormone within the hypothalamus: Chemoarchitectural mapping using a standardized rat brain atlas

Authors: K. A. S. BURNETT, *B. E. PINALES, E. J. PEREZ, K. T. LORENZANA, K. J. GALVAN, A. M. KHAN;
Dept. of Biol. Sci., Univ. of Texas at El Paso, El Paso, TX

Abstract: Connections to the lateral hypothalamic area (LHA) are important for feeding control. However, the contribution of several key regions that send signals to the LHA have yet to be chemoarchitecturally defined or systematically mapped within a standardized reference framework. Here, we provide a chemoarchitectural analysis of neurons and fibers that are immunopositive for cocaine amphetamine regulated transcript (CART), dopamine beta hydroxylase (DBH), and α-melanocyte stimulating hormone (αMSH) in the hypothalamus of the male rat. Using a Nissl-stained, adjacent series of tissue sections to establish cytoarchitectural boundaries, we represent the distributions of CART-, DBH-, and αMSH-immunoreactive (ir) cell bodies and/or fibers onto vector-formatted templates represented in a standardized rat brain atlas (L.W. Swanson, 2018, *Brain Maps 4.0, J Comp Neurol*). Dense CART- and DBH-ir fibers were observed within the periventricular nucleus, along the third ventricle and extending to the dorsomedial hypothalamic nucleus (DMH), and also in the LHA, encompassing areas surrounding the fornix. CART-ir cell bodies were found within the same vicinity of both fiber systems. Dense αMSH-ir fibers were observed within the boundaries of the medial preoptic nucleus, and in the paraventricular, periventricular, dorsomedial and arcuate hypothalamic nuclei. Expression of moderate to sparse immunoreactive fibers was noted within the lateral hypothalamic area. αMSH-ir fibers were also apparent, though sparse, in the suprachiasmatic, anterior and ventromedial hypothalamic nuclei. This work contributes to our ongoing effort to map the precise locations of chemoarchitectural elements within the rat hypothalamus using a high-spatial resolution series of standardized atlas templates. We anticipate that this work could provide valuable information to streamline the targeting of experimental probes to these complex systems.

Disclosures: K.A.S. Burnett: None. **B.E. Pinales:** None. **E.J. Perez:** None. **K.T. Lorenzana:** None. **K.J. Galvan:** None. **A.M. Khan:** None.

Poster

683. Central Pathways Controlling Food Intake and Energy Balance

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 683.21/V9

Topic: F.10. Food Intake and Energy Balance

Support: NSERC Discovery Grant RGPIN-2017-06272

Title: Distribution of beta-klotho mRNA within the brain

Authors: *B. S. BONO, M. J. CHEE;
Neurosci., Carleton Univ., Ottawa, ON, Canada

Abstract: Fibroblast growth factor 21 (FGF21) is an endocrine factor that facilitates energy homeostasis by promoting insulin sensitivity, glucose consumption, and the browning of white adipose tissue. FGF21 is synthesized primarily by the liver, pancreas, and adipose tissue but exerts its effects on multiple organs including the brain. Central action of FGF21 stimulates thermogenesis via the sympathetic nervous system, regulates circadian rhythm, and decreases taste preference for sucrose. However, the brain regions that support the actions of FGF21 are not clearly defined. FGF21 has a low affinity to FGF receptors and thus activation of the obligate co-receptor β-Klotho (Klb) is required for FGF21 action. In order to determine the sites of FGF21 action, we analyzed the distribution of *Klb* mRNA. We performed *in situ* hybridization using RNAscope technology to stain for *Klb* throughout the rostro-caudal axis of two male wildtype mice. We amplified *Klb* hybridization using the tyramine signal amplification system and then labelled it with Cyanine 3. *Klb* hybridization signal appeared as punctate red fluorescent "dots." In order to quantify *Klb* expression we obtained confocal photomicrographs and counted the number of dots that colocalized with 4′,6-diamidino-2-phenylindole (DAPI) stained soma. There was a widespread distribution of *Klb* throughout the brain, most notably in the hypothalamus, hippocampus, and the cerebral cortex. Within the hypothalamus, the suprachiasmatic nucleus (SCN) contained the greatest *Klb* hybridization signals (>4 dots) compared to all regions analyzed; this expression was limited to the dorsal medial part of the SCN. The periventricular nucleus, paraventricular nucleus, ventromedial nucleus, and dorsomedial nucleus had lesser but notable *Klb* hybridization (1–2 dots). Within the hippocampus *Klb* hybridization was localized to the pyramidal cell layer but had differential expression throughout the Cornu Ammonis (CA). The CA2 had the highest level of hybridization (3–4 dots), followed by CA3 (2–3 dots), and then the dentate gyrus and CA1 (1–2 dots). The hybridization of *Klb* in the cerebral cortex was heterogenous. For instance, there was selective hybridization in the cingulate cortex, motor cortex, and the retrosplenial cortex, but not in the medial prefrontal cortex (3–4 dots). In summary these findings are consistent with the known roles of FGF21. Hypothalamic *Klb* expression correlates with the known effects of FGF21 in the

regulation of energy expenditure and circadian rhythms. Meanwhile hippocampal and cortical *Klb* expression may implicate a role of FGF21 that integrates cognitive processes during feeding.

Disclosures: B.S. Bono: None. **M.J. Chee:** None.

Poster

683. Central Pathways Controlling Food Intake and Energy Balance

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 683.22/V10

Topic: F.10. Food Intake and Energy Balance

Support: NSERC Discovery Grant RGPIN-2017-06272
Queen Elizabeth Scholarship in Science and Technology II
NSERC USRA

Title: Effect of melanin concentrating hormone on neuronal excitability and synaptic input to the lateral septum

Authors: *M. A. PAYANT, D. P. SPENCER, M. J. CHEE;
Carleton Univ., Ottawa, ON, Canada

Abstract: Melanin concentrating hormone (MCH) is a neuropeptide produced exclusively by neurons in the lateral hypothalamic area and plays important roles in feeding, energy balance, and motivated behaviour. However, the target sites of MCH action are not well defined. Projections from MCH neurons are widespread throughout the brain and we found that the lateral septum (LS) has the densest accumulation of MCH nerve terminals. These terminals release glutamate to directly innervate the LS, an area also known to regulate food intake. The LS is thus a prospective area that may mediate the roles of MCH, however it is not known if or how MCH regulates LS neurons. In order to assess the role of MCH within the LS, we determined the distribution of MCH receptor (MCHR1) expression in this region and investigated the electrophysiological effects of MCH on LS neurons. In order to map the distribution of MCHR1 in the LS, we performed *in situ* hybridization for *Mchr1* mRNA using RNAscope technology. Throughout the LS, the most prevalent expression of *Mchr1* mRNA localized to the intermediate part of the LS (LSI). *Mchr1* expression emerges in the posterior region of the dorsal and ventral parts of the LS, but remained lower than the expression seen in the LSI. We prepared acute brain slices containing the LS from male or female wildtype mice and performed whole cell patch clamp recordings of LS neurons to determine the effect of MCH on cell excitability and synaptic activity. Bath application of MCH (3 µM) suppressed action potential firing and directly hyperpolarized LS neurons by 5 mV. The inhibitory effect of MCH was reversible with the washout of MCH and is consistent with the intracellular coupling of MCHR1 to G_i proteins. We then determined if MCH also inhibits GABAergic and glutamatergic inputs to the LS. MCH

application produced a reversible rightward shift in the distribution of inter-event intervals between spontaneous inhibitory postsynaptic current (sIPSC) events thus decreasing the frequency of GABAergic activity to the neuron; this corresponded with a leftward shift in the distribution of sIPSC amplitudes. Glutamatergic events at LS neurons were relatively infrequent (<0.4 Hz) and we did not detect an effect of MCH application on these excitatory inputs. In summary, the LS expresses MCHR1, and MCH can inhibit the neuronal activity and GABAergic input to LS neurons. Elucidating the mechanisms underlying MCH effects in the LS will contribute to our knowledge of this novel neurocircuit that may support the role of MCH in the regulation of energy balance and motivation.

Disclosures: **M.A. Payant:** None. **D.P. Spencer:** None. **M.J. Chee:** None.

Poster

683. Central Pathways Controlling Food Intake and Energy Balance

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 683.23/V11

Topic: F.10. Food Intake and Energy Balance

Support: the NIGMS Postdoctoral Research Associate Training (PRAT) Program NIH Grant Fi2 GM128811
The National Institute of General Medical Sciences
The National Institute of Mental Health
National Institute of Dental and Craniofacial Research

Title: A central catecholaminergic circuit driving glucoprivation-induced feeding

Authors: *S. BEAS[1,2], X. GU[3], S. RODRIGUEZ[2], O. KOITA[4], A. V. KRAVITZ[5], B. A. MATIKAINEN-ANKNEY[5], M. HOON[3], M. A. PENZO[2];
[1]Natl. Inst. of Gen. Med. Sci., Bethesda, MD; [2]Natl. Inst. of Mental Hlth., Bethesda, MD; [3]Natl. Inst. of Dent. and Craniofacial Res., Bethesda, MD; [4]Oregon Hlth. & Sci. Univ., Portland, OR; [5]Natl. Inst. of Diabetes and Digestive and Kidney Dis., Bethesda, MD

Abstract: Glucose metabolism is crucial for proper brain function. Indeed, inadequate brain glucose can result in cognitive impairments, unconsciousness and even death. Given the importance of maintaining optimal glucose levels, glucoregulatory behavioral (e.g. increased food seeking/feeding) and physiological responses (e.g. decreased insulin and increased corticosterone secretion) are in place to support glucose homeostasis. Based on previous research, catecholaminergic neurons within the ventrolateral medulla (VLM) are potently activated by glucoprivation and thought to support both behavioral and physiological responses to glucoprivic state. However, how this neuronal subpopulation contributes to these processes is unclear. Here, using a combination of fiber photometry, optogenetics, and whole cell patch-

clamp we investigated the circuit mechanism for glucoprivation-induced food seeking/intake. The results gathered from this investigation demonstrate that a forebrain projection of VLM catecholaminergic neurons drives glucoprivation-induced feeding behavior. Notably, optogenetic stimulation of these forebrain projection is sufficient to drive feeding behavior in well-fed mice. These results unveil a circuit and cellular mechanism by which VLM catecholaminergic neurons orchestrate glucoprivation-induced feeding.

Disclosures: S. Beas: None. **X. Gu:** None. **S. Rodriguez:** None. **O. Koita:** None. **A.V. Kravitz:** None. **B.A. Matikainen-Ankney:** None. **M. Hoon:** None. **M.A. Penzo:** None.

Poster

683. Central Pathways Controlling Food Intake and Energy Balance

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 683.24/V12

Topic: F.02. Behavioral Neuroendocrinology

Support: NIH Grant DA040782 (Gao)
NIH Grant DA046160 (Gao and Horvath)

Title: Linking impaired neural network oscillations in hypothalamus and hippocampus to the hypocretinergic system in high-fat diet-induced obesity in mice

Authors: M. STOILJKOVIC[1], Y. TAN[1,2], C. KELLEY[3], M. HAJOS[1], T. L. HORVATH[1], ***X.-B. GAO**[1];
[1]Yale Univ. Sch. of Med., New Haven, CT; [2]Guizhou Provincial People's Hosp., Guiyang, Guizhou, China; [3]SUNY Downstate/NYU Tandon, Brooklyn, NY

Abstract: Prolonged intake of high-fat diet (HFD) can lead to obesity but also to structural and functional brain alterations including neuronal inflammation and injury, neurotransmission changes, and certain behavioral and cognitive deficits. Accordingly, evidence suggests that brain regions such as the hypothalamus, which is involved in feeding control, and hippocampus, involved in cognitive functions, might be particularly vulnerable to HFD. In this study, we explored neural network oscillatory activity in these regions in C57BL/6 mice fed with HFD for 10-12 weeks and age-matched mice being on regular chow diet (ND). To better understand the role of hypocretin (Hcrt) neurons, which are exclusively localized in the lateral hypothalamus (LH) and widely projected throughout the brain, in HFD-induced effects we expressed stimulatory DREADD receptor hM3Dq in LH Hcrt neurons in the subset of HFD mice (HFD-DREADD). Local field potentials were recorded in vivo from LH and CA1 area of hippocampus under urethane anesthesia. In the LH, spontaneous gamma oscillation power was significantly higher in HFD mice compared to ND controls. Acute chemogenetic activation of LH Hcrt neurons in HFD-DREADD mice with clozapine-N-oxide (CNO) decreased gamma power to the

level of ND mice. On the contrary, injection of CNO in HFD mice without DREADD receptors (HFD-CNO) itself did not affect elevated gamma power. The same trend of increased spontaneous gamma oscillation in HFD and HFD-CNO comparing to ND and HFD-DREADD mice was observed in the hippocampus. However, opposite results were obtained for the power of elicited hippocampal theta oscillation induced by high-frequency brainstem stimulation. The quantitative input-output analysis between the groups showed a significant difference in theta power but not peak frequency in response to varying stimulation intensities. Post-hoc comparisons revealed a significant decrease in theta power in HFD and HFD-CNO when compared to ND and HFD-DREADD mice, although the phase-amplitude coupling between hippocampal theta and gamma elicited oscillations did not differ between the groups. These results imply that HFD has detrimental effects on Hcrt neurons, which weakened activity induces excitatory/inhibitory imbalance in hypothalamic and hippocampal neural networks thus affecting interoceptive awareness.

Disclosures: M. Stoiljkovic: None. **Y. Tan:** None. **M. Hajos:** None. **T.L. Horvath:** None. **X. Gao:** None. **C. Kelley:** None.

Poster

684. Depression: Physiology, Pharmacology, and Treatment

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 684.01/V13

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: King Fahad Medical City Research Grant 017-026

Title: Altered spatiotemporal dynamics of stimulus-evoked neural responses in clinical depression: An MEG study

Authors: V. POGHOSYAN[1], F. ALDOSARY[2], F. ALMOHAMMED[1], T. ALOTAIBI[1], B. ALQADHEEB[1], R. ALDOSARI[1];
[1]Neurophysiol., [2]Mental Hlth., King Fahad Med. City, Riyadh, Saudi Arabia

Abstract: Neurobiological underpinnings of major depressive disorder (MDD) are not yet well understood. In this ongoing exploratory study, we use magnetoencephalography (MEG) to address this issue. Here we report initial results from 15 drug-free patients with MDD and 15 matched healthy controls. MEG signals were recorded using 306-channel MEGIN system, while subjects viewed pleasant, unpleasant and neutral pictures, presented in random order. Data were analyzed based on Brainstorm (http://neuroimage.usc.edu/brainstorm), using advanced source analysis tools and rigorous statistical methods. Between-group comparison of valence-independent event-related neural activity identified an MDD-affected network of brain regions, involving predominantly right hemisphere frontal, parietal and mesial temporal areas (fig. 1).

The earliest and largest change was identified within right intraparietal sulcus (IPS), as a profound hypoactivity in patients, with an onset at 55 ms (fig. 2). Table 1 shows latencies and sequence of affected responses within the identified network. Valence-related neural activity in MDD is described elsewhere (see the abstract by Poghosyan et al. “Altered spatiotemporal dynamics of emotional neural processing in clinical depression: an MEG study”). The present report provides evidence of altered neural processing in MDD, affecting predominantly right hemisphere frontal, parietal and mesial temporal areas, largely consistent with earlier fMRI findings. Our results add the crucial timing information for these regions and reveal the precise dynamics and sequence of aberrant brain responses in MDD. Further, they stress the pivotal role of right IPS in MDD.

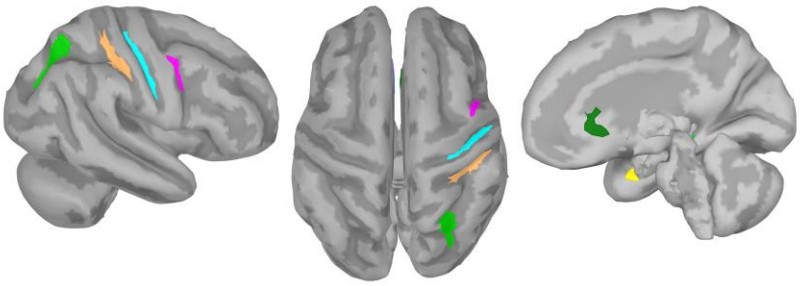

Figure 1. MDD-affected network of brain regions in visual stimulus processing. Key right hemisphere cortical areas showing differential activity between patients and controls are marked on the cortical surface. Lateral, top and medial views are shown.

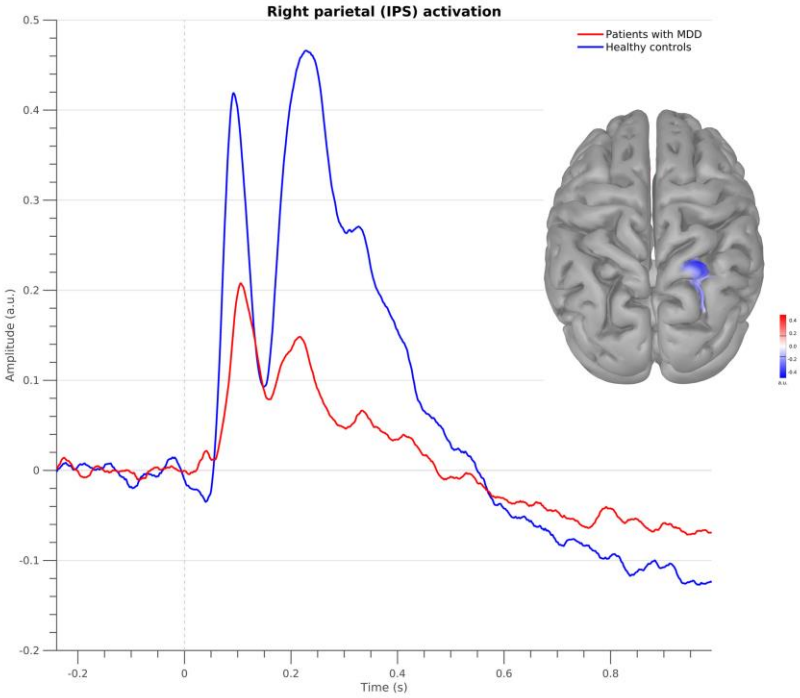

Figure 2. Right parietal (IPS) activation time course in reponse to visual stimuli in patients with MDD (red) and healthy controls (blue). The inset shows the localization of MDD-affected hypoactivation from which the region of interest was defined.

Key ROIs showing differential activity between patients and controls in visual stimulus processing

ROI name	Direction of group differences	Start time (ms)	End time (ms)	Direction of group differences	Start time (ms)	End time (ms)
Right intraparietal sulcus (**R IPS**)	C > P	55	560			
Right inf. precentral gyrus (**R inf. preCG**)	C > P	115	600			
Right central sulcus (**R CS**)	C > P	125	560			
Right postcentral gyrus (**R postCG**)	C > P	170	550			
Right mesial temporal cortex (**R MTC**,entorhinal cortex, parahippocampal gyrus etc.)	P > C	65	800			
Right rostral anterior cingulate cortex (**R rACC**)	P > C	100	650			
Left mesial temporal cortex (**L MTC**, entorhinal cortex, parahippocampal gyrus etc.)	C > P	65	145	P > C	230	575
Left rostral anterior cingulate cortex (**L rACC**)	P > C	100	620	C > P	620	1000

C > P, stronger activity in controls; P > C, stronger activity in patients

Disclosures: V. Poghosyan: None. **F. AlDosary:** None. **F. AlMohammed:** None. **T. AlOtaibi:** None. **B. AlQadheeb:** None. **R. AlDosari:** None.

Poster

684. Depression: Physiology, Pharmacology, and Treatment

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 684.02/V14

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: King Fahad Medical City Research Grant 017-026

Title: Altered spatiotemporal dynamics of emotional neural processing in clinical depression: An MEG study

Authors: V. POGHOSYAN[1], F. ALDOSARY[2], ***F. S. ALMOHAMMED**[1], T. ALOTAIBI[1], B. ALQADHEEB[1], R. ALDOSARI[1];
[1]Neurophysiol., [2]Mental Hlth., King Fahad Med. City, Riyadh, Saudi Arabia

Abstract: Major depressive disorder (MDD) is characterized by distorted emotional processing. In this ongoing exploratory study, we use magnetoencephalography (MEG) to examine neural correlates of emotional processing and its variations in MDD. Here we report initial results from 15 drug-free patients and 15 matched healthy controls. MEG signals were recorded using 306-channel MEGIN system, while subjects viewed pleasant, unpleasant and neutral pictures. Data were analyzed based on Brainstorm (http://neuroimage.usc.edu/brainstorm), using advanced source analysis tools for deep brain activity, including amygdala, and statistical methods. Group differences in valence-related patterns of neural responses were identified predominantly within bilateral prefrontal cortex, anterior temporal cortex, insular cortex, posterior lateral sulcus and amygdala (fig. 1 and table 1). The earliest and most notable difference was found in right amygdala (fig. 2 and 3): In patients, it differentiated emotional and neutral pictures in 90-140 ms and 250-450 ms time ranges, with significantly stronger response to emotional pictures. Later, from 450 ms onward, right amygdala distinguished negative from positive and neutral pictures, exhibiting sustained elevated activity in response to negative pictures. Such late-latency, negative valence-related, sustained activity was found also in right orbitofrontal, ventrolateral prefrontal and insular cortices. No such effect was evident in controls. The present report provides evidence of altered emotional neural processing in MDD, revealing the precise temporal dynamics of key brain regions often implicated in emotional processing.

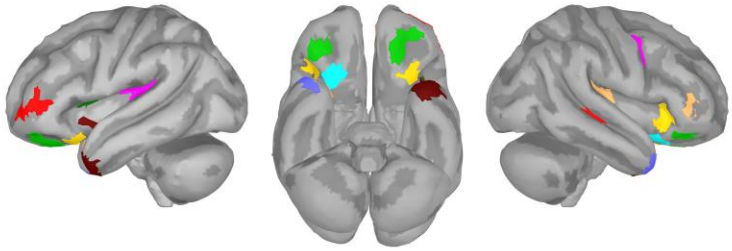

Figure 1. MDD-affected network of brain regions in emotional processing. Key cortical areas showing differential activity between patients and controls are marked on the cortical surface. Left, bottom and right views are shown, respectively.

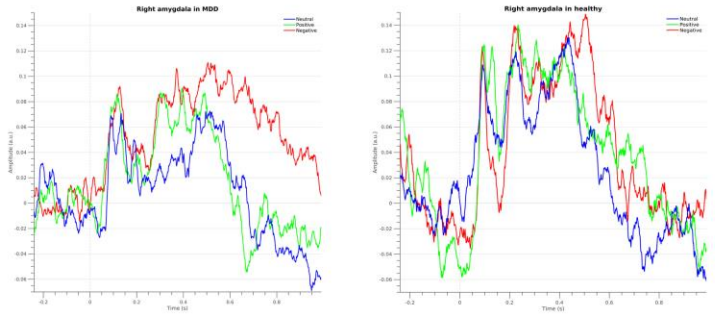

Figure 2. Right amygdala activation time course in response to neutral (blue), positive (green) and negative (red) pictures, in a) patients with MDD and b) healthy controls.

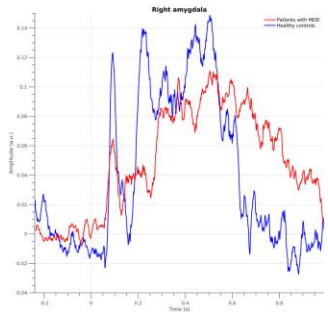

Figure 3. Right amygdala activation time course in response to negative pictures, in patients with MDD (red) and healthy controls (blue).

Key ROIs showing differential pattern of valence-related activity between patients and controls

ROI name	**Onset of differential pattern of activity (ms)**
Right amygdala	90
Right insula	95
Right orbitofrontal cortex	95
Right middle cingulate cortex	105
Right inferior prefrontal cortex	160
Left dorsolateral prefrontal cortex	90
Left middle cingulate cortex	105
Left insula	115

Disclosures: **V. Poghosyan:** None. **F. AlDosary:** None. **F.S. Almohammed:** None. **T. AlOtaibi:** None. **B. AlQadheeb:** None. **R. AlDosari:** None.

Poster

684. Depression: Physiology, Pharmacology, and Treatment

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 684.03/V15

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: NIMH Intramural Research Program

Title: The effect of ketamine on cortico-striatal circuitry in depressed and healthy individuals

Authors: *A. MKRTCHIAN[1], J. W. EVANS[1], J. P. ROISER[2], C. A. ZARATE, Jr.[1]; [1]Exptl. Therapeut. & Pathophysiology Br., Natl. Inst. of Mental Hlth., Bethesda, MD; [2]Inst. of Cognitive Neurosci., Univ. Col. London, London, United Kingdom

Abstract: A sub-anesthetic dose of ketamine can improve depressive symptoms within hours in treatment-resistant depressed (TRD) patients. These improvements occur specifically in symptom-clusters related to lack of motivation or pleasure capacity, even over and above general depressive symptoms. However, the precise neural circuits driving these effects remain unclear. Here we examine if ketamine affects cortico-striatal circuitry, which is well established in driving goal-directed behavior, in TRD patients and healthy controls.

Data were drawn from a double-blind, placebo-controlled, crossover trial of ketamine (0.5mg/kg), including 33 TRD patients and 25 healthy controls. Resting-state functional magnetic resonance imaging data were acquired at 3T, two days following ketamine and placebo infusions. Seed-based functional connectivity was examined using four seed regions in the striatum, reflecting functional subdivisions that are connected with different cortical regions involved in affective, cognitive and motor processes. Linear mixed-effects models were conducted at the group level in AFNI. Correction for multiple comparisons was achieved using an initial threshold of $p<0.005$, and a minimum cluster size of 46 voxels resulting in family-wise error-correction at $p<0.05$.

In patients, ketamine increased functional connectivity between the ventral striatum and the dorsolateral prefrontal cortex (dlPFC); the dorsal caudate and the ventrolateral PFC (vlPFC); the dorsal caudal putamen and the anterior cingulate cortex (ACC); and the ventral rostral putamen and the orbitofrontal cortex (OFC; all F-contrasts). By contrast, ketamine decreased connectivity in these circuits in healthy controls compared with placebo. Mean connectivity parameters were also examined in a control region (primary visual cortex), which did not demonstrate similar connectivity changes.

These results suggest that ketamine affects the fronto-striatal neural circuitry in cognitive and affective-associated frontal regions. However, there was a differential pattern of response beween healthy individuals and TRD patients, such that cortico-striatal functional connectivity was enhanced in patients but decreased in healthy individuals following ketamine. Our control analysis suggested that this was not a global brain pattern but instead restricted to the PFC. These findings support a homeostasis model of ketamine's neural effects that might be particularly relevant for the shift in motivational symptoms following ketamine, considering the crucial role that the cortico-striatal circuit plays in goal-directed behavior.

Disclosures: A. Mkrtchian: None. **J.W. Evans:** None. **J.P. Roiser:** None. **C.A. Zarate:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NIH.

Poster

684. Depression: Physiology, Pharmacology, and Treatment

Location: Hall A

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Program #/Poster #: 684.04/V16

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: NRF - 2016M3C7A1914448
NRF - 2017M3C7A1031331

Title: Correlation between decrease of neuronal noise and depressive symptom severity

Authors: *S. YUN, B. JEONG;
KAIST, Daejeon, Korea, Republic of

Abstract: Object: Recent studies have shown that neuronal noise is not just noise, so changes in neuronal noise in the pathologic state are also of interest. The recently developed Refined composite multiscale permutation entropy (RCMPE) overcomes the limitations of existing signal variability indicators such as Multiscale Entropy (MSE). We used RCMPE to investigate the relationship between symptom severity and neuronal noise in depression.
Methods: Resting state electroencephalography (EEG) was measured by the University of Arizona. The depressed group was selected for people with a BDI score of 12 or higher, and a total of 44 people were selected. Measurement of EEG was made with a 64 channel Neuroscan. Multi-scale (2ms~40ms) time-series data was obtained through coarse-gaining procedure and RCMPE was calculated in each epoch (2s). The epoched RCMPE was averaged according to each channel and time scale. Correlation coefficients between RCMPE and BDI scores in each group were calculated using Pearson's correlation. Multiple comparison test was performed by cluster permutation test. The cluster defining thresholds were set at 0.01. The cluster alpha level was set at p-value 0.025 and permutation n=5000.

Result: In the depressed group, the two clusters showed a significant correlation with the BDI score. The 1st cluster was located in the frontal area between 2ms and 10ms, and the cluster p-value was 0.0236. The 2nd cluster was located in the Lt. parietal area on the temporal scale of 2ms to 12ms, and the cluster p-value was 0.0244. In the Healthy control group, no significant clusters were found.
Conclusion: In the depressed group, there was a negative correlation between the severity of depressive symptoms and the neuronal noise. In particular, topologically, a decrease of neuronal noise in the frontal area and the Lt. parietal area were associated with severity of depression in depressive group.

Disclosures: S. Yun: None. **B. Jeong:** None.

Poster

684. Depression: Physiology, Pharmacology, and Treatment

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 684.05/V17

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: Fondect Regular (Conicyt), 1171313
Fondecyt Regular (Conicyt), No 1171320
CONICYT-PIA Anillo ACT1414
CONICYT-PIA Anillo ACT1416

Title: Normalization of abnormal brain activity of depressed people using a brain-computer interface system based on pattern classification of emotional brain states

Authors: *S. RUIZ[1], J. A. PEREIRA[2], A. RAY[3], M. RANA[4], P. OPAZO[1], C. BRETT[1], I. R. THAKKAR[5], R. TORRES[1], R. SITARAM[1];
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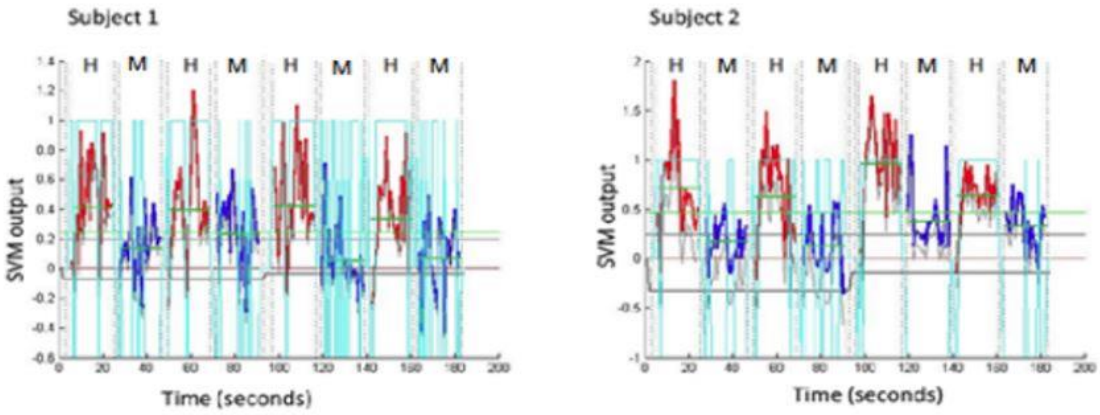
Abstract: Brain-Computer interface (BCI) systems permits to gain control of different brain signals. Most of BCI studies have been built upon the idea that a patient can learn by practice to generate a healthy brain-state. However, due to the inherent altered brain functioning, patients could have difficulties finding a healthy pattern of brain signals being guided by the feedback of their own brain activity. The two aims of the present study were: to train depressive patients to achieve a healthy emotional brain-state, aided by a BCI system asociated to a “subject-independent (or population-based) classifier” of emotional states, created from a set of EEG data coming from healthy individuals, and to explore the use of this system as a potential clinical and

neuroscientific tool.A subject-independent pattern-based classifer (SIC) of brain states (based on EEG signals and support vector machine, SVM) was created, with information coming from 19 healthy individuals during positive emotional states. This classifer was asociated to a BCI system to train 4 subjects with depressive symptoms, trained to “match” a healthy brain state. Patients participated in 3 days of BCI training. Each day consisted of 5 training runs with 4 blocks of brain-self regulation (during positive emotional imagery), interspersed with 4 blocks of rest (20s each block). Self regulation blocks were visually guided by the result of the classifier to receive the information of the similary of her brain state compared with the one provided by the classifer in real-time (updated every 1 second). Clinical changes were evaluated blinded by Beck and Hamilton scales.Patients were able to reproduce the brain patterns of the original group of healthy subjects, as reflected for classifications acuracies of the SIC (SVM-outputs) above chance [Figure 1]. Mood modifications towards the alliviation of depressive symptoms were observed on different degrees. These results represent a step forward towards the automatic recognition of brain
states in combination with Brain-Computer Interfaces, as a potential clinical and neuroscientific tool.

Figure 1. SVM output of a two representative training runs. The data samples are plotted on the x-axis against the SVM values on the y-axis. The letters ′H′ and ′M′ represent the blocks of self-inducted happines and motor imaginery respectively, separated by vertical dashed lines. The short red lines represent the mean SVM value during the condition at this time. The green line shows the overall mean of the SVM output values.



Disclosures: **S. Ruiz:** None. **J.A. Pereira:** None. **A. Ray:** None. **M. Rana:** None. **P. Opazo:** None. **C. Brett:** None. **I.R. Thakkar:** None. **R. Torres:** None. **R. Sitaram:** None.

Poster

684. Depression: Physiology, Pharmacology, and Treatment

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 684.06/V18

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: NIGMS/NIH P20 GM121312 award
NSF RII Track-2 #1539068

Title: Temporal independent EEG microstates from simultaneous EEG and fMRI measurements and implications for 'big data'

Authors: *J. H. TANG[1], H. YUAN[1], Y. CHEN[1], M. PAULUS[2], J. BODURKA[2];
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Abstract: Simultaneous electroencephalography (EEG) and functional Magnetic Resonance Imaging (fMRI) data provide a unique opportunity to measure brain spatio-temporal neural activity at a high temporal and spatial resolution [1-3]. However, EEG recorded simultaneously with fMRI contains many artefacts and is difficult to analyze. These EEG artifacts are difficult to suppress during time-consuming and labor-intensive manual preprocessing. In the era of 'big data' for neuroimaging, large EEG-fMRI datasets aim to streamline and automate EEG preprocessing and analysis [4,5]. For our preliminary analysis, 20 datasets were derived from T-1000 [6]. The manual preprocessing method involved BrainVision Analyzer 2.0 to remove Ballistic Cardiogram (BCG) and Gradient Artifacts (GA), while EEGLAB was used to denoise and perform Independent Component Analysis (ICA). The automatic correction method coded for GA, BCG artifacts and ICA reconstruction in MATLAB [4,5]. Temporal independent EEG microstates (EEG-ms) [2] were derived and compared based on two preprocessing approaches. In addition, we assessed EEG-ms associated with salience network and their differences among healthy and mood and anxiety (MA) subjects. We compared and benchmarked an automatic EEG preprocessing pipeline with manual preprocessing for the purpose to derive EEG-ms from resting state EEG-fMRI data in healthy and MA subjects. The automatic pipeline was capable to successfully extract EEG-ms. Temporal quantitative measures of EEG-ms associated with the salience network differentiated between the healthy and MA groups. Specifically, the occurrence rate of EEG-ms associated with salience network was significantly lower in the MA individuals than that in the healthy control. The measures of anxiety state (i.e. State-Trait Anxiety Inventory scores) were negatively correlated with the occurrence rate of the salience-network-associated EEG-ms ($p<0.05$). The group-level differences associated with anxiety in the salience network are in line with previous research [3]. We have confirmed the proposed feasibility of the automatic EEG preprocessing for the EEG-fMRI brain neuroimaging data to streamline and produce EEG features extraction from large data sets. Further, we independently validated

exemplar EEG features originally discovered in a different cohort with high-density EEG-fMRI measurements [2,3]. Using EEG-ms microstates, we differentiated changes between healthy and MA participants. Importantly, automated EEG-preprocessing provides a strong incentive for conducting simultaneous EEG-fMRI of the whole brain spatio-temporal neuronal activity.

Disclosures: J.H. Tang: None. **H. Yuan:** None. **Y. Chen:** None. **M. Paulus:** None. **J. Bodurka:** None.

Poster

684. Depression: Physiology, Pharmacology, and Treatment

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 684.07/V19

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Title: Neural prediction of anxiety and depression when processing negative emotion

Authors: *S. KIM[1], Y. ZOH[1], S. M. GORKA[3], K. L. PHAN[3], W.-Y. AHN[2];
[2]Dept. of Psychology, [1]Seoul Natl. Univ., Seoul, Korea, Republic of; [3]Univ. of Illinois at Chicago, Chicago, IL

Abstract: Aberrant neural activation, when processing negative emotion, is a major feature of Major Depressive Disorder (MDD) and Anxiety Disorder (AD). While existing literature suggests that there exist both common and distinct patterns of fMRI responses in MDD and AD, it is a limitation that most studies used univariate analysis (general linear modeling), and multivariate patterns among brain regions are often neglected. Here, we aimed to identify multivariate patterns of fMRI response when processing emotional stimuli that will predict individuals' level of depression and anxiety. To achieve the goal, we applied a machine learning approach (elastic net) to fMRI data from clinical populations with multiple diagnoses. Participants included 99 patients with primary diagnoses of MDD, social anxiety disorder, or generalized anxiety disorder, and additional 37 healthy controls. They completed the emotional facial matching task inside the MRI scanner. The participants' levels of depression and anxiety were measured with the Hamilton Depression Scale (HAM-D) and Hamilton Anxiety Scale (HAM-A), respectively. Preliminary results suggest that angry faces generate neural responses that are predictive of both HAM-D and HAM-A, and we found common regions predicting both HAM-D and HAM-A in the insula, the anterior cingulate cortex, and the middle temporal gyrus. These results highlight the importance of transdiagnostic and quantitative approaches in characterizing the neural underpinnings of psychiatric disorders.

Disclosures: S. Kim: None. **Y. Zoh:** None. **S.M. Gorka:** None. **K.L. Phan:** None. **W. Ahn:** None.

Poster

684. Depression: Physiology, Pharmacology, and Treatment

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 684.08/V20

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: Else Kröner Fresenius Stiftung 2014_A192

Title: Cross-sectional analysis of plasma cytokines and brain structure in untreated major depressive disorder

Authors: *G. GRYGLEWSKI[1], R. SEIGER[1], Z. KÖRNYEI[2], P. MICHENTHALER[1], L. RISCHKA[1], M. B. REED[1], L. SILBERBAUER[1], G. M. GODBERSEN[1], J. UNTERHOLZNER[1], A. KOMOROWSKI[1], É. MIKICS[3], A. DENES[2], R. LANZENBERGER[1];
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Abstract: Accumulating evidence suggests the involvement of the immune system in major depressive disorder which affects brain circuits involved in emotion processing and cognition. We analysed cross-sectional data collected from 41 patients (19 female, aged 29.6±10.6 years) suffering from an acute episode of unipolar major depression and 53 healthy controls (31 female, aged 28.3±8.8 years). Patients were free from antidepressant treatment for 3 months prior to inclusion and had a Hamilton Rating Scale for Depression ($HAM\text{-}D_{17}$) score ≥ 18. T1 weighted structural magnetic resonance imaging (MRI) was acquired on a 3T hybrid PET/MR scanner using a MPRAGE sequence (TE/TR=4.21ms/2000ms) and plasma concentrations of 20 cytokines were measured using cytometric bead arrays. MRI data was reconstructed using FreeSurfer 6.0 to obtain the volumes of bilateral amygdalae and hippocampi. Independent t-tests were used to test differences in cytokine concentrations between groups. Spearman correlation coefficients were calculated to assess the association of cytokines with volumes of brain regions. In depressed patients, higher concentrations of P-selectin (CD62P, 95%-CI=[22.6, 150.7], p=0.009) and interleukin 1 receptor, type I (CD121a, 95%-CI=[4.6, 65.8], p=0.03) were observed. Furthermore, correlations of interleukin 4 concentrations with the volumes of the bilateral amygdalae and hippocampi were found (Spearman's rho: 0.36 (right amygdala and hippocampus, p<0.01), 0.31 (left hippocampus, p=0.01), 0.29 (left amygdala, p=0.03)). This association was unaffected by correction for total intracranial volume, and persisted in the right amygdala if only the patient group was considered (Spearman's rho=0.50, p=0.02). We further analysed the associations of interleukin 4 with the volume of the subfields of the hippocampi and the nuclei of the amygdalae. Correlations were observed in the right basal nucleus, right corticoamygdaloid transition area, right cornu ammonis (CA)1, right parasubiculum, left

parasubiculum and the molecular layer and CA4 field of the left hippocampal head (all $p<0.01$). Interestingly, these correlations were higher in the patient group and absent in the group of healthy participants. These results substantiate the involvement of immune processes in the pathophysiology of depression and pinpoint the associations of specific mediators in plasma with alterations in the highly plastic gray matter structures of the hippocampoamygdalar complex.

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Poster

684. Depression: Physiology, Pharmacology, and Treatment

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 684.09/V21

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Title: Precision psychiatry: Development of methodology for personalized therapeutic brain stimulation

Authors: *R. CASH[1], L. COCCHI[2], P. FITZGERALD[3], A. ZALESKY[4];
[1]Melbourne Neuropsychiatry Ctr. & Dept. of Biomed. Engineering, The Univ. of Melbourne, Melbourne, Australia; [2]Clin. Brain Networks Group, QIMR Berghofer, Brisbane, Australia; [3]Monash Alfred Psychiatry Res. Ctr. & Epworth Healthcare, Melbourne, Australia; [4]Melbourne Neuropsychiatry Ctr., Melbourne, Australia

Abstract: Introduction: Repetitive transcranial magnetic stimulation (rTMS) of the dorsolateral prefrontal cortex (DLPFC) is a promising antidepressant therapy. We recently provided some of the strongest evidence to date that treatment response is predicted by the strength of the functional connectivity (FC) between the subgenual cingulate cortex (SGC) at the precise DLPFC stimulation site. Prospective identification of the optimal site based on brain connectivity offers a promising means to enhance rTMS clinical response. Here we address a critical gap for clinical translation of personalised rTMS and develop new methodologies to reliably pinpoint the optimal DLPFC stimulation site on a single subject basis. **Methods**: A variety of computational methods were developed based on thresholding approaches, clustering algorithms, scanning procedures and e-field modelling. The accuracy with which these could pinpoint the optimal DLPFC site (based on SGC connectivity) across repeated scans (i.e. test-retest reliability) was tested. In addition, the influence of smoothing and acquisition time on reliability estimates was evaluated. We utilised existing scan data from the healthy individuals in the human connectome project (n=1000) and a depression cohort (n=25). Test-retest reliability was defined by the median distance between coordinates identified across successive scans.

Inter-individual variation was measured as the median distance between coordinates across all individuals. **Results**: Initial results indicate substantial distortion of the SGC FC map with smoothing kernels of greater than 6mm FWHM diameter, causing shifts in the estimated optimal coordinate. While this work is still ongoing and outcomes are likely to improve, our methodology currently demonstrates that the optimal stimulation site can be reliably estimated within a distance of ~19mm across repeated scans, whilst preserving inter-individual variation. Methodologies will be compared in detail. **Discussion**: These data indicate the feasibility and reproducibility for meaningful identification of individually optimised stimulation coordinates. This methodology is critical for translation of empirical knowledge into better clinical outcomes and will facilitate research on personalised precision rTMS in cognitive & psychiatric disorders.

Disclosures: R. Cash: None. **L. Cocchi:** None. **P. Fitzgerald:** None. **A. Zalesky:** None.

Poster

684. Depression: Physiology, Pharmacology, and Treatment

Location: Hall A

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Program #/Poster #: 684.10/V22

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

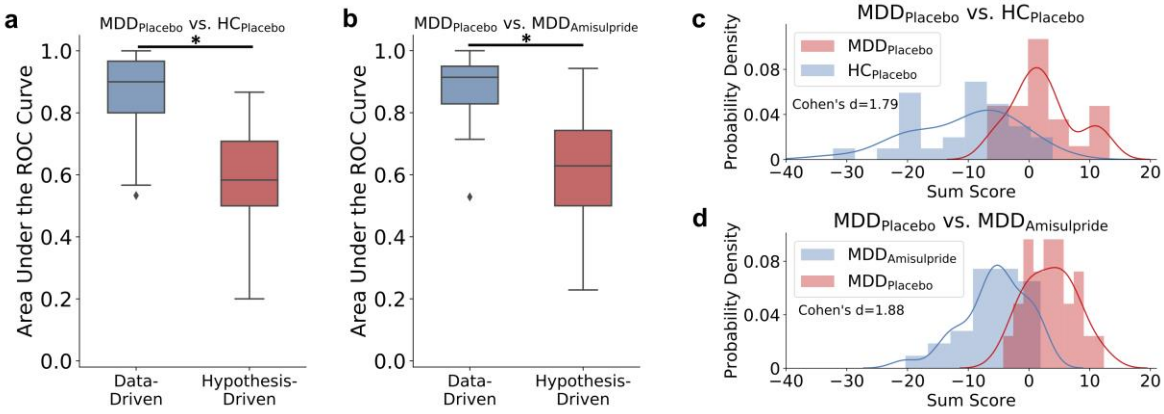
Support: This study is funded by Blackthorn Therapeutics
NIH R01 Grant MH068376
NIH R37 Grant MH068376
NIH R01 Grant MH095809

Title: Machine learning identifies large-scale reward-related activity modulated by dopaminergic enhancement in major depression

Authors: *Y. LIU[1], R. ADMON[2], E. L. BELLEAU[3,5], R. H. KAISER[6], R. CLEGG[3], M. BELTZER[3], F. GOER[3], G. VITALIANO[4,5], P. AHAMMAD[1], D. A. PIZZAGALLI[3,5]; [1]Blackthorn Therapeut., San Francisco, CA; [2]Dept. of Psychology, Univ. of Haifa, Haifa, Israel; [4]Brain Imaging Ctr., [3]McLean Hosp., Belmont, MA; [5]Dept. of Psychiatry, Harvard Med. Sch., Boston, MA; [6]Dept. of Psychology and Neurosci., Univ. of Colorado, Boulder, CO

Abstract: *Objective*: Theoretical models have emphasized systems-level abnormalities in Major Depressive Disorder (MDD). Towards unbiased yet rigorous evaluations of pathophysiological mechanisms underlying MDD, it is critically important to develop data-driven approaches that harness whole-brain data to classify MDD and evaluate possible normalizing effects of targeted interventions. Here, using an experimental therapeutics approach coupled with machine-learning we investigated the effect of a pharmacological challenge aiming to enhance dopaminergic signaling on whole-brain's response to reward-related stimuli in MDD.
Method: Using a double-blind placebo-controlled design, functional magnetic resonance imaging

(fMRI) data from 31 unmedicated MDD participants receiving a single dose of 50 mg amisulpride ($MDD_{Amisulpride}$), 26 MDD participants receiving placebo ($MDD_{Placebo}$), and 28 healthy controls receiving placebo ($HC_{Placebo}$) were analyzed. An importance-guided machine learning technique for model selection was used on whole-brain fMRI data probing reward anticipation and consumption to identify features linked to MDD ($MDD_{Placebo}$ vs. $HC_{Placebo}$) and dopaminergic enhancement ($MDD_{Amisulpride}$ vs. $MDD_{Placebo}$).
Results: Highly predictive classification models emerged that distinguished $MDD_{Placebo}$ from $HC_{Placebo}$ (AUC=0.87) and $MDD_{Placebo}$ from $MDD_{Amisulpride}$ (AUC=0.89). Although reward-related striatal activation was identified as among the most predictive features, the best models based on whole-brain features were significantly better relative to models trained using striatal features only. Examining the top features in our models indicated that, in MDD, enhanced dopaminergic signaling restored abnormal activation and connectivity in a widespread network of regions.
Conclusions: These findings provide new insights into the pharmacological mechanism of antidepressants at the system level in addressing reward processing deficits among depressed individuals.



Disclosures: **Y. Liu:** A. Employment/Salary (full or part-time):; Blackthorn Therapeutics. **R. Admon:** None. **E.L. Belleau:** None. **R.H. Kaiser:** None. **G. Vitaliano:** None. **P. Ahammad:** A. Employment/Salary (full or part-time):; Blackthorn Therapeutics. **D.A. Pizzagalli:** F. Consulting Fees (e.g., advisory boards); Blackthorn Therapeutics, Akili Interactive Labs, Boehringer Ingelheim, Posit Science, Takeda Pharmaceuticals. Other; Alkermes. **R. Clegg:** None. **M. Beltzer:** None. **F. Goer:** None.

Poster

684. Depression: Physiology, Pharmacology, and Treatment

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 684.11/V23

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: NIH Grant MH108043
IOER Funds

Title: Beneficial effects of physical activity/exercise on mood regulation

Authors: *B. POPE, L. WEGMAN-POINTS, A. ZOBEL, S. SAICHELLAPPA, L.-L. YUAN; Physiol. and Pharmacol., Des Moines Univ., Des Moines, IA

Abstract: Emerging evidence suggests physical activity/exercise exerts beneficial effects on many normal physiological and psychological processes ranging from cardiovascular function to cognition to mood regulation. Furthermore, exercise also serves as a potential protective factor to counteract the effects of stress and aging. On the basis of human and rodent studies, various cellular and molecular mechanisms have been proposed to underlie those positive influences including metabolic pathways, neurotrophic factors, and neurotransmitter systems. However, acute exercise, defined as a single bout of physical activity, has received less attention in its beneficial effects on mood regulation, yet a better understanding of acute exercise would contribute to the mechanistic studies of chronic exercise. We investigated the effects of acute exercise on the central nervous system by profiling molecular changes taking place in in brain regions responsible for mood regulation, particularly in the medial prefrontal cortex (mPFC), the most commonly reported area to undergo improvement by exercise. Rats were subject to 30 min acute treadmill running, and brain tissue was collected one-hour post-exercise. Prior to acute exercise, both control and experimental groups received 4 days of treadmill training at a low running speed followed by 4 days of rest in order to minimize potential stress impact. A phospho-antibody based, mid-throughput profiling analysis of mPFC tissue revealed a list of protein candidates that were either up-or downregulated by an acute bout of exercise. Majority of the positive hits fell into three categories, 1) synaptic markers such as postsynaptic glutamate receptors and proteins involved in presynaptic release machinery; 2) markers for Neurogenesis; and 3) signaling molecules such as protein kinases and phosphatases. Those molecular events in the mPFC induced by acute exercise showed some similarity to that of fast-acting antidepressant ketamine, raising a question whether fast-acting antidepressant ketamine may act through signaling and metabolic pathways that overlap with those activated by physical activity. Further studies are currently underway to assess the potential of harnessing the positive effects of movement to treat depression.

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Poster

684. Depression: Physiology, Pharmacology, and Treatment

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 684.12/V24

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: MH094445

Title: Characterizing the KEOPS complex in the DLPFC in depression

Authors: *M. E. ABEL[1], S. M. O'DONOVAN[1], E. BENTEA[2], K. ALGANEM[1], R. E. MCCULLUMSMITH[1];
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Abstract: Major Depressive Disorder (MDD) affects approximately 20% of the world population and is an economic burden worldwide. The treatments that are currently available have varying efficacy. 10-30% of people with MDD do not improve with antidepressant treatment, or show a partial response that is associated with side effects such as functional impairment and a high rate of relapse. A greater understanding of the underlying neurobiology of MDD is necessary to develop new, efficacious treatments.
Telomeres protect the ends of chromosomes and are essential for preserving genome stability. Previous studies have shown that subjects with MDD have shortened telomere lengths. Shortened telomere length is associated with chronic stress, a major contributing factor to the symptoms of depression. Meta-analysis has identified a positive correlation between shortened length and depression. In addition, depression severity is also significantly associated with telomere length.
The KEOPS (Kinase, Endopeptidase and Other Proteins of small Size) complex is a highly conserved eukaryotic complex involved in maintaining telomere length. The role of the KEOPS complex in MDD is yet to be elucidated. However, dysregulation of an active component of KEOPS, P53 related protein kinase (PRPK) has been identified in the DLPFC in MDD.
We hypothesize that the KEOPS complex is dysregulated in subjects with MDD and that this dysregulation leads to shortened telomere length in subjects with MDD.
We measure gene expression changes in the components of the KEOPS complex, KAE1, TP53RK (PRPK), CGI121, PCC1 and GON7 in the DLPFC of depressed subjects and healthy controls using qPCR. Changes in protein expression will be assayed by western immunoblot. Telomere length will be measured with a telomere assay. Overall, we will measure the changes in the components of the KEOPS complex in the DLPFC in MDD and healthy controls.
Key Words: postmortem, depression, (kinase) MDD, KEOPS complex, telomere length

Disclosures: M.E. Abel: None. **S.M. O'Donovan:** None. **E. Bentea:** None. **K. Alganem:** None. **R.E. McCullumsmith:** None.

Poster

684. Depression: Physiology, Pharmacology, and Treatment

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 684.13/V25

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: National Institute of Mental Health, Grant/Award Number: R01 MH102238
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Dana Foundation; Hope for Depression Research Foundation
National Institutes of Health, Grant/Award Numbers: T32 EB004314, TL1 TR000441, T32 GM007250, UH3 NS103550

Title: Model-based identification of optimal stimulation protocols for treating intractable depression with subcallosal cingulate deep brain stimulation

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Abstract: *Objective and rationale*. Deep brain stimulation (DBS) of the subcallosal cingulate (SCC) is an evolving strategy for individuals with intractable depression. Good, long-term outcomes coincides with placing the active contact within the confluence of four pathways (i.e., forceps minor (FM), cingulum bundle (CB), uncinate fasciculus, and frontal connections to the thalamus and/or striatum), inspiring a "connectomic" approach for targeting; but this model-based strategy was not deployed in SCC DBS' pivotal clinical trial, which may have contributed to suboptimal outcomes. Within the target confluence, our recent theoretical findings point to FM and the CBs being the most probable therapeutic targets, and this exploratory study's objective was to pilot a model-based strategy for optimizing stimulation protocols for activating the target pathways in three subjects.
Methods. We optimized stimulation protocols for SCC DBS using connectomic models of DBS that combined medical imaging and tractography with biophysical modeling. Out of 1065 programmable settings (i.e., electrode configurations and pulse widths), we identified three selective settings that maximally activated each pathway in isolation, and two energy-efficient settings (i.e., one per lead) that used minimal energy to activate the same proportion of pathways as the clinical setting. Subsequently, we used EEG to explore how evoked potentials generated by optimal settings differed from those evoked by the subject's therapeutic setting.
Results. Selective and energy-efficient settings differed by subject and hemisphere. FM-selective

settings produced a bilateral response with positive voltage deflections that began in the orbitofrontal cortex and propagated to the posterior cortex via the central midline, but compared to therapeutic responses, posterior features were more distributed and longer-lasting. CB-selective settings produced a lateralized response with no marked midline or posterior features. Energy-efficient settings evoked responses most similar to those of the therapeutic settings. *Conclusions.* There is likely no universal stimulation protocol for SCC DBS, and our results demonstrate there are opportunities to enhance the pathway-specificity and energy-efficiency of this therapy. Model-based design improved surgical positioning for SCC DBS, improving outcomes, and when paired with optimization, connectomic modeling can systematically identify settings that confirm target engagement and improve battery life, which may have clinical impact and simplify device programming for future clinical trials.

Disclosures: B. Howell: None. **A.C. Waters:** None. **K. Choi:** None. **A. Veerakumar:** None. **M.O. Obatusin:** None. **H.S. Mayberg:** None. **C.C. McIntyre:** None.

Poster

684. Depression: Physiology, Pharmacology, and Treatment

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 684.14/V26

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: NIH Grant UH3NS103550
Hope for Depression Research Foundation

Title: Electrophysiological features of subcallosal cingulate cortex in patients with treatment-resistant depression

Authors: *S. ALAGAPAN[1], V. TIRUVADI[1,2], M. ESLAMPANAH SENDI[1,2], A. WATERS[3], A. VEERAKUMAR[2], M. OBATUSIN[3], A. CROWELL[2], P. RIVA POSSE[2], R. J. BUTERA[1], H. S. MAYBERG[3], C. ROZELL[1];
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Abstract: Subcallosal cingulate cortex white matter (SCCwm) has been identified as an effective deep brain stimulation (DBS) target for treatment-resistant depression (TRD) [1]. Insights on electrophysiological features that are engaged by DBS, leading to symptom improvement, will enable closed-loop and adaptive stimulation strategies. We aim to identify electrophysiological markers that reflect target engagement and track treatment response using implanted pulse generators that also possess local field potential (LFP) recording capabilities (Activa PC+S, Medtronic, MN, USA). Patients generally experience a decrease in symptom severity post-surgery, briefly for a few days, followed by an increase that stabilizes by the time stimulation is

turned on. We hypothesize this decrease to be due to outlasting effects of stimulating the SCCwm during intra-operative assessments [2]. To test this hypothesis, we tracked changes in LFP spectral features during this period of no stimulation (chronic LFP). We compared the chronic LFP spectral features with those recorded right after stimulation of therapy target in an in-lab experiment (post-stimulation LFP).LFPs were acquired daily from 10 patients in the 4-week period between implantation of DBS leads and commencement of therapeutic stimulation. LFPs were acquired in differential configuration from 2 contacts on either side of stimulation contact in each hemisphere as 15 second segments every 3 - 4 hours. Power spectral densities (PSDs) were computed using a multi-taper FFT approach. Logistic regression and random forest classifiers with nested hold-one-subject-out cross-validation was used for multivariate comparison of PSD. PSDs exhibited peaks between 6 and 10 Hz in both hemispheres. Spectral power in delta and theta frequency bands decreased over the 4 weeks while power in alpha and beta bands increased. In the comparison between chronic LFP and post-stimulation LFP, we observed that the performance of the classifiers was at chance level 1 week post-surgery (AUROC = 0.54 ±0.21) while the performance was higher 4 weeks post-surgery (AUROC = 0.77 ±0.10, One-way ANOVA, $p = 0.02$), indicating that the effects of intra-operative stimulation did indeed persist beyond surgery. Additionally, we found the feature importance for beta band in both hemispheres increased with time.The results suggest activity in the beta frequency band may be a marker of symptom severity and potentially serve as a feedback signal for control of stimulation.
[1] P. Riva-Posse *et al.*, *Mol. Psychiatry*, 2018.[2] O. Smart *et al.*, *Front. Comput. Neurosci.*, 12, 2018.

Disclosures: S. Alagapan: None. **V. Tiruvadi:** None. **M. Eslampanah Sendi:** None. **A. Waters:** None. **A. Veerakumar:** None. **M. Obatusin:** None. **A. Crowell:** None. **P. Riva Posse:** None. **R.J. Butera:** None. **H.S. Mayberg:** Other; Consulting agreement with St Jude Medical (now Abbott), which has licensed intellectual property to develop SCC DBS for treatment of depression. **C. Rozell:** None.

Poster

684. Depression: Physiology, Pharmacology, and Treatment

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 684.15/V27

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: james mcdonnell understanding human cognition scholar award

Title: Recurrent neural network models of adaptive and maladaptive learning across species

Authors: *M. AFZAL[1], A. S. ANDALMAN[2], A. WATERS[1], E. CARTER[1], K. DEISSEROTH[3], H. S. MAYBERG[1], K. RAJAN[1];

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Abstract: Large-scale monitoring of activity from different brain regions and during realistic behaviors is now possible in many organisms with nervous systems of different levels of complexity, e.g., larval zebrafish, rodents, nonhuman primates, and humans. Such data provides a rich opportunity to uncover the mechanisms linking neural dynamics and behavior in both normal and disease states. These data are often high dimensional and thus challenging for traditional statistical methods. Principled theory in combination with advanced data analysis is therefore crucial to understand these data and derive mechanisms from them. Here, a new class of multi-region recurrent neural network (RNN) models is developed, constrained from the outset by data spanning multisite neural dynamics and time-varying behavior. The data-inspired multi-region RNNs are then reverse-engineered to infer brain-wide interactions and circuit mechanisms, not accessible from measurements alone. We extend previous work to multi-region RNNs based on two different datasets: 1) densely sampled, cellular-resolution imaging from over 20000 neurons in larval zebrafish as they transition to immobility after a minutes-long behavioral challenge, and 2) sparsely sampled, local field potentials (LFPs) and 256-channel electroencephalograms (EEGs) in patients undergoing DBS for depression, particularly those with concomitant motor deficits. We focus on the period between stimulation off and on in an hours-long, acute protocol. By analyzing these models, we determine whether, and which, circuit mechanisms inferred from smaller, highly sampled nervous systems (zebrafish) scale in a conserved manner to a larger, more complex, and sparsely sampled nervous system (human patients), as well as mechanisms that are divergent. To do this, we first analyze the full multi-region RNN dynamics and the essential low-dimensional features of those population dynamics extracted through state-space analyses, and compare them with analogous measures from data. Second, we analyze the connectivity matrices of the multi-region RNN models fit to data and infer the within- and across-region directed interactions responsible for observed dynamics and behavior. This approach provides a novel and viable alternative for the inference of directed interactions linking neural activity and behavior from different types of data, outperforming correlation-based analyses and also valuable for large brains beyond the scope of connectomics. This approach of building and analyzing data-inspired multi-region RNN models can be used to infer brain-wide circuit mechanisms mediating both adaptive and maladaptive states.

Disclosures: M. Afzal: None. **A.S. Andalman:** None. **A. Waters:** None. **E. Carter:** None. **K. Deisseroth:** None. **H.S. Mayberg:** None. **K. Rajan:** None.

Poster

684. Depression: Physiology, Pharmacology, and Treatment

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 684.16/V28

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: Davee Family Foundation, Chicago

Title: Reinforcement learning makes distinct contributions to predict anhedonia in adults with depression after behavioral activation therapy

Authors: *J. K. GOLLAN[1], T. KAHNT[2], G. ABITANTE[1], J. DEARCANGELIS[1], Q. J. HUYS[3];
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Abstract: Anhedonia may explain treatment resistance to behavioral psychotherapies. Anhedonia is explained by diminished reward sensitivity and impaired reinforcement learning, sub-constructs of the positive valence system domain of NIMH's Research Domain Criteria (RDoC; Insel et al., 2010). The behavioral properties of reinforcement learning and their status as predictors of therapy response are not well characterized. This experimental prospective, longitudinal study aimed to identify behavioral features of reinforcement learning linked with anhedonia in participants with depression and test how reinforcement learning predicts anhedonia severity after nine weeks of behavioral activation psychotherapy. Our approach was to measure Pavlovian and instrumental learning using an orthogonalized go/no-go task (Guitart-Masip et al., 2012b) and build computational models from this behavioral data. The task separates action from valence and allows us to collect data on learning performance. Adults (n=13) were enrolled, with scores $\geq$ 24 on the Inventory of Depressive Symptomatology, Self-Report (IDS-SR)(Rush et al., 1986) and depression diagnoses on the Mini-International Neuropsychiatric Interview (MINI 7.0.2)(Sheehan et al., 1998). Anhedonia was measured using items 19 and 21 on the IDS-SR. Using ANOVAS to compare learning accuracy, i.e., mean percentage of correct responses, results reveal preferential learning to seek reward (go to win) and withhold from loss (no-go to avoid). Task performance was well explained by a computational model, which includes a parameter for associative reinforcement learning (Rescorla-Wagner component), Pavlovian 'go' bias, Pavlovian (go to win) bias, Pavlovian (no-go to avoid loss) bias. Importantly, reinforcement learning at baseline predicted anhedonia status at end of treatment. These results advance computational approaches to define reinforcement learning that may develop targeted treatments for anhedonia.

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Poster

684. Depression: Physiology, Pharmacology, and Treatment

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 684.17/V29

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: UCSD Pace Grant
Majda Grant

Title: Oscillatory mechanisms of electroconvulsive therapy (ECT) for major depressive disorder (MDD)

Authors: *S. E. SMITH[1], V. MA[2,7], M. JACOBSON[9], D. PRINTZ[3,8], B. VOYTEK[1,4,5,6], M. SOLTANI[3,10];
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Abstract: Patients with psychotic and mood disorders, including Major Depressive Disorder (MDD), are typically treated with therapy and medication. In cases of otherwise treatment-resistant MDD, electroconvulsive therapy (ECT) can be highly efficacious. However, despite its efficacy, the neural mechanism(s) by which ECT results in beneficial outcomes for MDD has not yet been identified. MDD has been attributed to states of pathological hemispheric imbalance in slow frequency power, with abnormally-elevated alpha (8-12 Hz) oscillation power often localized to left frontal cortical regions (Henriques & Davidson, 1990).
Here, we evaluated the electrophysiological signatures of the effects of ECT on neural oscillations in the theta (3-8 Hz) and alpha (8-12Hz) bands in a unique dataset of clinical MDD patients receiving ECT treatment. In this study, resting-state electroencephalography (EEG) data and clinical ratings (MADRS, QIDS, C-SSRS) were collected from MDD patients intermittently over a 12-session ECT treatment. Data was collected before and after the first, fourth, eighth, and twelfth ECT sessions, to permit analysis of the short-term effects within a single session, and long-term effects over the course of treatment. In addition to assessing the feasibility of this collection regime, we characterize these data in the frequency domain using measures of oscillatory power and aperiodic activity.
Preliminary results show that there are hemispheric differences in slow frequency oscillatory power in MDD patients that are altered by ECT at a single-treatment scale. Over the course of treatment, the size of this hemispheric effect is greater for late sessions than early sessions. In more exploratory analyses, we evaluated oscillatory dynamics in the time domain. We propose that MDD might be characterized by pathologically overcoupled neural firing in frontal cortical

regions, with ECT acting to disrupt overcoupling by introducing high-frequency activity into the neuronal network (McIntyre et al., 2004). In the time domain, we quantify this phenomenon using measures of oscillatory waveform shape and find that at a short-term scale, ECT produces a smoothing effect on sharply-peaked slow-frequency oscillations, similar to the proposed action by which deep brain stimulation aids in ameliorating the motor symptoms of Parkinson's disease.

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Poster

684. Depression: Physiology, Pharmacology, and Treatment

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 684.18/V30

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: Caltech Innovation Initiative
Della Martin Foundation
GM123582
HHMI

Title: Genetically encoded biosensors for rapidly acting antidepressants (RAADs) inside neurons

Authors: *K. BERA[1], A. KAMAJAYA[1], A. L. NICHOLS[1], A. V. SHIVANGE[1,2], P. M. BORDEN[2], B. N. COHEN[1], A. K. MUTHUSAMY[1], J. H. JEON[1], T. CHIN[1], J. S. MARVIN[2], C. H. KIM[1], J. H. WANG[1], P. DESHPANDE[1], L. L. LOOGER[2], H. A. LESTER[1];
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Abstract: Rapidly acting antidepressants (RAADs) partially relieve depression in < 1 day, then continue this relief for several days. This onset is 10- to 100-fold folder faster than serotonin and norepinephrine reuptake inhibitors (SSRIs and SNRIs). Some RAADs are ketamine enantiomers (R-Ket/S-Ket), metabolites [(2R, 6R)-HNK/(2S, 6S)-HNK], or analogs such as radafaxine. Other RAADs, such as scopolamine (Scop) is best known as a muscarinic antagonist and structurally unrelated to ketamine. The mechanism(s) of RAAD action are largely unknown at levels ranging from the molecular target, the signaling pathway, the cell types, or the circuits. It is important to detect and quantify the RAADs inside subcellular regions of living neurons.
Therefore, we develop the "**i**ntensity-based **RAAD**-**S**e**n**sing **F**luorescent **R**eporter" [iRAADSnFR] genetically encoded biosensor family for RAADs. This biosensor family structurally resemble a previously published nicotine biosensor: a fusion between a mutated periplasmic binding protein OpuBC, interdomain likers, and circularly permuted GFP. Mutants are tested with computational docking models, site-saturation mutagenesis, high-throughput fluorescence screens on bacterial lysates, and fluorescence measurements with purified proteins.

We have mutated residues at the binding site, for sensitivity to RAADs. In solution, iS-KetSnFR responds to S-Ket with EC_{50} of ~ 7 μM, and with maximal fluorescence increases ($\Delta F/F_0$) of ~ 3.8; iR-KetSnFR displays EC_{50} = ~ 22 μM and $\Delta F/F_0$ = 2.5; iScopSnFR displays EC_{50} = ~ 7 μM and $\Delta F/F_0$ = 3.5.
We add additional sequences that target the sensors either to the plasma membrane (PM) or to the endoplasmic reticulum (ER). Fluorescence microscopy shows that, at the low μM concentrations appropriate to the antidepressant action, S-ketamine enters and leave the endoplasmic reticulum within a few seconds and attains extracellular levels. We hope to expand the family to sense other RAADs and within other organelles.
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Poster

684. Depression: Physiology, Pharmacology, and Treatment

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 684.19/V31

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Title: Involvement of serotonin system in antidepressant like effects of quercetin 4'-O-glucoside in mouse model of unpredictable chronic mild stress induced depression

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Abstract: Depression is a common neuropsychiatric disorder. The available pharmacotherapy is ineffective for a substantial proportion of patients and has numerous side effects. Therefore, finding safer drugs for the management of depression is of paramount importance. The present study was aimed to evaluate the anti-depressant like effects of quercetin 4'-O-glucoside (QG) in mouse model of unpredictable chronic mild stress (UCMS) induced depression. Animals were subjected to various stress paradigms to induce depression like behaviour and were treated with QG for 21 days. Behavioural tests (forced swim test, sucrose preference test and open field test) as well as brain oxidative stress, monoamine oxidase A (MAO-A) and serotonin levels were determined to measure the anti-depressant like effects of QG. Treatment of UCMS- exposed mice with QG (10 and 20 mg/kg) improved UCMS induced behaviour anomalies and restored brain biochemical parameters (oxidative stress, MAO-A activity and serotonin levels). QG was

found effective in treating stress induced depression in animals via prevention of brain oxidative stress and restoring serotonin levels by inhibiting MAO-A activity. Thus, QG could be developed as a potential antidepressant drug.

Disclosures: V. Singh: None. **G. Chauhan:** None. **R. Shri:** None.

Poster

684. Depression: Physiology, Pharmacology, and Treatment

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 684.20/V32

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: NIH Grant R01 MH106865
NIH Grant P30 CA030199

Title: *In vitro* and *in vivo* characterization of group II mGlu receptor negative allosteric modulators as an alternative to ketamine for depression

Authors: D. J. SHEFFLER[1], M. B. BICAKCI[2], A. ANTWAN[2], N. PRAKASH[2], E. M. STANDARD[1], G. VELICELEBI[1], R. A. GADIENT[1], J. H. HUTCHINSON[1], D. R. PANICKAR[1], A. S. LIMPERT[1], N. D. P. COSFORD[1], *A. DER-AVAKIAN[2];
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Abstract: The noncompetitive N-methyl-D-aspartate (NMDA) glutamate receptor antagonist ketamine produces rapid antidepressant effects in patients with major depressive disorder (MDD), which has led to the recent FDA approval of intranasal (S)-ketamine (Spravato, Esketamine) for the treatment of patients with treatment-resistant depression (TRD) in conjunction with an oral anti-depressant. Group II metabotropic glutamate receptor ($mGlu_{2/3}$) antagonists produce many of the same downstream molecular and preclinical behavioral effects as ketamine, suggesting that $mGlu_{2/3}$ may be targeted for antidepressant treatment without producing the undesirable effects of ketamine. However, a recent Phase II clinical trial with decoglurant (RG1578, RO4995819), a non-selective $mGlu_{2/3}$ negative allosteric modulator (NAM), failed to show efficacy in depression as an adjunctive to selective serotonin reuptake inhibitors (SSRIs). In order to better understand the factors that may have contributed to this clinical trial failure, we evaluated the *in vitro* pharmacological and *in vivo* pharmacokinetic, neurophysiological, and behavioral properties of ketamine, decoglurant, and new $mGlu_{2/3}$-selective NAMs in male Wistar rats. Ketamine suppressed frontal slow-wave delta (0-4 Hz) oscillations, enhanced frontal high-frequency gamma (30-100 Hz) oscillations, and decreased immobility in the forced swim test (FST) both immediately and one week after drug administration. Conversely, decoglurant failed to produce the same frontal EEG effects as

ketamine and failed to produce a persistent antidepressant-like effect in the FST. Moreover, the plasma concentration of decoglurant remained elevated near peak levels for at least 24 h after drug administration. Compared to decoglurant, new $mGlu_{2/3}$-selective NAMs showed greater potency for $mGlu_{2/3}$, greater plasma and brain concentrations after systemic administration, and much more rapid plasma clearance. The new $mGlu_{2/3}$-selective NAMs also produced similar frontal EEG effects and persistent antidepressant-like effects in the FST as compared to ketamine. Thus, decoglurant failed to produce ketamine-like pharmacokinetic, neurophysiological and behavioral effects in rats, which may partly explain its lack of efficacy in depression. Moreover, our results suggest that targeting $mGlu_{2/3}$ holds promise for the development of effective, fast-acting antidepressant treatments.

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Poster

684. Depression: Physiology, Pharmacology, and Treatment

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 684.21/V33

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: FND-148423
MOP-125985

Title: Antidepressant effect of ketamine and (2R,6R)-hydroxynorketamine requires activation of cap-dependent mRNA translation initiation

Authors: *A. AGUILAR VALLES[1], E. MATTA CAMACHO[1], A. SKALEKA[2], M. ESLAMIZADE[2], D. DE GREGORIO[3], G. GOBBI[3], J.-C. LACAILLE[4], N. SONENBERG[2]; [1]Neurosci., Carleton Univ., Ottawa, ON, Canada; [2]Biochem., [3]Psychiatry, McGill Univ., Montreal, QC, Canada; [4]Univ. De Montreal, Montreal, QC, Canada

Abstract: BACKGROUND AND AIM: The fast-acting antidepressant drug ketamine and its metabolite (2R, 6R)-hydroxynorketamine (HNK) activate the mammalian target of rapamycin (mTOR) signaling pathway, which is required for the antidepressant effect of ketamine. mTOR regulates many cellular functions, including mRNA translation (also known as protein synthesis) through phosphorylation and inactivation of the eukaryotic initiation factor 4E (eIF4E) binding proteins (4E-BPs), leading to the activation of eIF4E and mRNA translation initiation. There are two alternative hypotheses on the cellular targets of ketamine, one suggesting that it directly targets excitatory neurons while another suggests that it indirectly activates these neurons by

inactivating inhibitory interneurons. We sought to determine whether 4E-BPs were required for the antidepressant effect of ketamine and HNK, and whether this pathway is activated in excitatory or inhibitory neurons. METHODS: To determine whether the 4E-BP/eIF4E axis is required for the antidepressant effect of ketamine and HNK, *Eif4ebp1* or *Eif4ebp2* knockout (KO) mice were treated with ketamine (IP, 10 mg/kg) or HNK (IP, 20 mg/kg) and their antidepressant effect (1 h) was determined in the forced swim test (FST) and novelty suppressed feeding (NSF). To determine whether 4E-BPs are required in a specific cell type, we used conditional *Eif4ebp1* or *Eif4ebp2* KO mice in excitatory (Camk2a positive) or inhibitory (Gad2 positive) neurons treated with either ketamine, HNK or fluoxetine (IP, 3 mg/kg). RESULTS: Neither drug affected the immobility in the FST of *Eif4ebp1*$^{-/-}$ or *Eif4ebp2*$^{-/-}$ mice, but, as expected, they reduced it in wildtype mice. In addition, the effect of ketamine on NSF (reduced latency to feed in a new environment) was absent in *Eif4ebp2*$^{-/-}$ and *Eif4ebp1*$^{-/-}$ mice. Mice lacking either *Eif4ebp1* or *Eif4ebp2* in Camk2a+ cells, were resistant to the antidepressant effects of ketamine and HNK, but responded normally to an acute injection fluoxetine. Conditional KO mice in Gad2+ cells were also resistant to the effects of ketamine, HNK and fluoxetine. Furthermore, *Eif4ebp2-/-* mice in Gad2+ cells displayed reduced immobility in the FST without any antidepressant treatment, suggesting a more preponderant role for 4E-BP2 in Gad2+ neurons in the response to antidepressant drugs. CONCLUSIONS: Overall, these results indicate that activation of cap-dependent translation is required in both excitatory and inhibitory neurons for the antidepressant effect of ketamine and HNK.

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Poster

684. Depression: Physiology, Pharmacology, and Treatment

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 684.22/V34

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: NIH GM-123582
HHMI

Title: Development of an optimized biosensor for the visualization of the selective serotonin reuptake inhibitor fluoxetine in the endoplasmic reticulum of live cells

Authors: *L. LUEBBERT[1,2], A. L. NICHOLS[1], P. M. BORDEN[3], A. V. SHIVANGE[1,3], J. H. WANG[1], A. K. MUTHUSAMY[1], J. S. MARVIN[3], L. L. LOOGER[3], H. A. LESTER[1,3]; [1]Biol. and Biol. Engin., Caltech, Pasadena, CA; [2]Inst. of Biol., Leiden Univ., Leiden, Netherlands; [3]Janelia Res. Campus, Howard Hughes Med. Inst., Ashburn, VA

Abstract: Major depressive disorder (MDD), more commonly known as depression, is a severe mood disorder and one of the most common illnesses worldwide. Depression is often treated with selective serotonin reuptake inhibitors (SSRIs), which lead to the elevation of extracellular serotonin concentrations. That SSRIs bind to the serotonin transporter (SERT) on the plasma membrane (PM) is indisputable. However, SSRIs typically require 2-6 weeks before a response to treatment can be observed, and the processes that occur during this delay remain elusive. We wish to test the hypothesis that SSRI-SERT interactions within organelles play a role, especially within the endoplasmic reticulum (ER) and *cis*-Golgi. As a first step, one must directly test, quantify, and temporally resolve the entry of SSRIs into organelles. We are developing and applying genetically encoded fluorescent biosensors to study the subcellular pharmacokinetics of SSRIs. OpuBC, a monomeric bacterial periplasmic binding protein (PBP), has previously been mutated to bind nicotine at a site between two domains. We insert circularly permuted "superfolder" GFP (cpGFP), flanked by several residue linkers, near the OpuBC interdomain hinge regions. By applying directed evolution to optimize the sensing of drugs, we have achieved the goal of $\Delta F/F_0 \approx 1$ at 1 μM for the fluoxetine-biosensor pair. We call this "**i**ntensity-based **Fluoxetine**-**S**e**n**sing **F**luorescent **R**eporter" (iFluoxetineSnFR). Targeting and retention sequences direct the constructs to the ER or the PM of mammalian clonal lines and cultured neurons. Live-cell video imaging shows that, after we jump [fluoxetine] (increase or decrease) near cells, the drug appears in the ER within < 10 s but takes up to 10 times longer to leave. Responses are robust, even at the steady state [fluoxetine] in the brain of a patient. These results resemble those for our existing biosensor iEscitalopramSnFR. The two SSRIs enter the lumen of the ER at concentrations similar to those detected on the extracellular surface of the plasma membrane, seconds after the SSRI enters the extracellular space. These experiments provide first evidence for the existence and relevance of SSRI inside-out drug action. It may be possible to develop other iDrugSnFRs for other SSRIs and for other organelles. We hope that further application of these tools will encourage investigators to study the initial steps in the pathway of SSRI intracellular pharmacokinetics, allowing elucidation of the role "inside-out" neuropharmacology plays in therapy for major depressive disorder.

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Poster

684. Depression: Physiology, Pharmacology, and Treatment

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 684.23/V35

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: Pennsylvania State Department grant (Project 10: 420491-04400-02) to Dr. Nune Darbinian
NIH grant R01HD069238 to Dr. Laura Goetzl
PA Shriners Center Grant to Dr. Michael Selzer (MS).

Title: Effects of *in utero* EtOH exposure on biomarkers of depression and anxiety: pDING and the serotonin-dopamine pathway

Authors: *N. DARBINIAN[1], A. DARBINYAN[3], N. MERABOVA[1], G. TATEVOSIAN[1], S. AMINI[4], M. F. MORRISON[2], L. GOETZL[5], M. E. SELZER[1];
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Abstract: Introduction: Children with fetal alcohol spectrum disorder (FASD) exhibit cognitive, behavioral, and other neuropsychological problems, and are at higher risk of developing depression. Many women who used alcohol (EtOH) during pregnancy also suffer from comorbid depression, and both EtOH abuse and depression in the mother might influence the fetal development of metabolic pathways implicated in childhood depression, *i.e.*, the serotonergic (5-HT) and dopaminergic (DA) pathways. In order to determine whether EtOH-exposed fetal brains have biochemical abnormalities predictive of depression, we have used an available biobank of fetal brain tissues. Molecular mechanisms of EtOH neurotoxicity are relatively unexplored in human fetal brain; we interrogated the role of the serotonergic and dopaminergic systems. Serotonergic signal transmission may be a target for therapies to reduce FAS. Previously we reported a neuroprotective role against EtOH toxicity for pDING phosphatase (from medicinal plant St. John's wort). Now we interrogate the roles of endogenous pDING, serotonin (5-HT) transporter (SERT) and 5-HT receptor in the neurotoxicity mediated by EtOH.
Methods: Fetal brains were collected according IRB approved protocol. The EtOH exposed group (N=6) was compared with controls matched for gestational age, fetal gender. pDING levels were assessed in total brain, synaptosomes, and blood. Transcriptomic microarrays were applied to human cells induced by human DING protein. mRNA was quantified by qRT-PCR. Expression of 84 human genes associated with DA and 5-HT pathways, and biomarkers of depressive disorders (BDNF, GDNF) in fetal tissues were analyzed.
Results: EtOH exposure upregulated DA (D3 and D5) and 5-HT receptors (HTRB, HTR5A and HTR6) ~ 5-fold, while HTR4 was down-regulated 4-fold. EtOH increased DA transporter gene expression 2-80 fold, and down-regulated 5-HT transporter (SERT) gene expression. EtOH exposure reduced also pDING 5.2-fold in blood. Transcriptomics profiles revealed several upstream regulators, including 5-HT1A that was inhibited >100-fold by stress conditions, while pDING upregulated 5-HT1A 5-fold.
Conclusions: pDING is expressed in human brain and blood. pDING increased survival of EtOH-exposed cells and rescues the expression of HTR1A, which is strongly suppressed by stress conditions. pDING binds to SERT in human brain cells. The findings suggest potential

mechanisms for the increased rates of FAS in children of women who experience EtOH use and/or depression during pregnancy, and an important neuroprotective role for pDING in FASD.

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Poster

685. Mechanisms Underlying Depression and Anxiety

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 685.01/V36

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: Centre for Collaborative Drug Research; Neuroscience Catalyst Grant

Title: Small conductance calcium-activated potassium channels (SKCs) as novel targets for the development of antidepressants

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Abstract: Background: The antidepressant effects of ketamine and scopolamine (SCP) have recently been described. Despite divergent upstream pharmacological action, recent evidence suggests a downstream convergence point involving small conductance calcium-activated potassium channels (SKCs), which directly regulate neuronal activity and plasticity.
Methods: Fisher344 rats (n=5-6/group) underwent chronic unpredictable stress (CUS), and the effects of SCP and SCP+EBIO on behaviours were assessed. Brain-wide [^{125}I]apamin autoradiography was performed on CUS rats. SK3 knockout mice (WT=10, Hom=12) underwent behavioural testing. Three novel SKC antagonists were assessed in forced swim test (FST) following intracerebroventricular (ic.v.) infusion in Sprague Dawley rats (n=7-8/group). Results were corrected for multiple comparisons where appropriate.
Results: SCP (4 µg/kg, i.v.) reversed CUS-induced reduction of sucrose preference (P=0.003), and CUS-induced prolongation of feeding latency in the novelty-supressed feeding test (P=0.001). Co-administration of the SKC positive modulator EBIO (4 mg/kg, i.v.) abrogated the effects of SCP. CUS increased [^{125}I]apamin binding of SKCs in the CA1 (P=0.04) and prelimbic cortex (P=0.006). SK3 knockout did not produce effects in the elevated plus maze (EPM), but produced a trend towards decreased hyponeophagia in the novelty-induced hypophagia test (NIHT) (p=0.07), and reduced passive behaviour in the FST (P=0.048). All three novel SKC antagonists (10 ng, ic.v.) reduced passive behaviour in the FST (P<0.001).
Conclusion: Small molecules targeting SKCs offer a promising new avenue for the development

of antidepressants, which may circumvent the addiction liability and adverse effects associated with ketamine and scopolamine.

Disclosures: **M.G. Nashed:** None. **F.R. Bambico:** None. **I. Greig:** None. **D. Nguyen:** None. **H. Lau:** None. **J. Zhang:** None. **D. Oleinichenko:** None. **M. Billyard:** None. **J.N. Nobrega:** None.

Poster

685. Mechanisms Underlying Depression and Anxiety

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 685.02/V37

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Title: Activating transcription factor 4(ATF4)-dependent activation of the human tryptophan hydroxylase 2 gene is mediated through binding to a CCAAT/enhancer-binding protein(C/EBP)-ATF composite site in its promoter

Authors: *H. MATSUI[1], **Y. NAWA**[2], H. KANEKO[2], M. TSUBONOYA[2], T. HIROI[2], R. TAKAHASHI[3];
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Abstract: Tryptophan hydroxylase 2(TPH2) plays a critical role in the regulation of 5-HT neurotransmission and is thus a promising therapeutic target for the treatment of neuropsychiatric disorders. The mechanism by which the human TPH2 (hTPH2) gene expression is activated still remains an open question. Activating transcription factor 4 (ATF4), a member of CREB/ATF transcription factor family of basic-region leucine zipper proteins, has been implicated in integrated stress response, synaptic plasticity, learning and memory, circadian rhythm, and behavior. ATF4 can form a homodimer, and heterodimers with CCAAT/enhancer-binding proteins (C/EBPs). ATF4-C/EBP heterodimers bind to DNA sequences called C/EBP-ATF composite site to regulate target gene expression. Bioinformatics analysis (JASPAR database) revealed one potential ATF4 binding site near the transcription start site of the hTPH2 gene (-53/-46, 5'-TTGCATCA-3') that is identical to the consensus C/EBP-ATF composite site. However, functions of this composite site still remain undetermined. In this study, we examined how the hTPH2 promoter activity changes by ATF4 and C/EBPs. A 2-kb promoter region of the hTPH2 gene (-1850/+141) was cloned into pGL4-Basic and then, its 5'-untranslated region (+10/+121; a region containing potential repression elements) was deleted to yield TPH2-100. Promoter activities were assessed by transfections into RN46A cells**,** a *cell* line derived from rat raphe neurons. Quantitative real-time RT-PCR analysis revealed the expression of *Atf2*, *Atf3*, *Atf4*, *Cebpa*, *Cebpb*, *Cebpg*, *Cebpd* and *Cebpe* genes in RN46A cells. Overexpression studies

demonstrated that among ATFs tested, ATF4 was the most potent in activating the hTPH2 promoter. This activation was further enhanced by co-expression of each of the five C/EBPs. Curiously, C/EBPG which lacks all known activation domains also further enhanced the effects of ATF4. The C/EBP-ATF composite site mutations negated the effects of ATF4. A dominant negative ATF4 blocked the effects of ATF4. Functional analysis of N-terminal and internal deletion mutants indicated that ATF4 (aa 1-124) is critical for activation. Moreover, co-expression of endogenous inhibitor proteins, tribbles pseudokinase 3 or taxilin γ attenuated the effects of ATF4. Finally, we found that the treatment with BDNF activated the hTPH2 promoter. BDNF has been reported to increase ATF4 levels. Thus, we speculated that BDNF activates the hTPH2 promoter, possibly via modulation of ATF4 functions. Altogether, these results imply that ATF4 plays a pivotal role in regulating the hTPH2 gene expression, and itself undergoes complex regulation at multiple levels.

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Poster

685. Mechanisms Underlying Depression and Anxiety

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 685.03/V38

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: MOST 107-2320-B-006-014

Title: Inhibition of K_{ATP}channel activity in brown fat reduces high fat diet-induced depression

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Abstract: Clinical researches indicate the highly correlation between obesity and depression. Depressed patients show symptoms such as anhedonia, which caused by dysregulation of mesolimbic dopamine (DA) system that is the projections of dopaminergic (DAnergic) neurons from the ventral tagmental area to the nucleus accumbens (NAc). Several studies indicate that ATP sensitive potassium channels (K_{ATP}) regulate the firing rate of DAnergic neurons. To ask if ATP-sensitive potassium (K_{ATP}) channels act as a metabolic sensor that link metabolic disorders to depression in the mesolimibic DA system, we established high fat diet (HFD)-fed obese mice model. These mice displayed type II diabetic characteristics and importantly depressive symptoms evaluated by sucrose preference test and forced-swim test. The analysis of catecholamine was shown lower levels of serotonin and DAnergic activities in the NAc of HFD than Chow-fed mice. Previous report indicated the activity of brown adipose tissue (BAT) might

be related to mood control. Hence, HFD induced depression mice were implanted by mini-osmic pump containing K_{ATP}channel blocker (glibenclamide) into the interscapular BAT. Our results showed two weeks of glibenclamide treatment improves glucose homeostasis, insulin sensitivity, the blood triglyceride concentration as well as reduces depressive symptoms. Additionally, the NAc of HFD with glibenclaminde infusion presents higher amount serotonin and DAnergic activity as compared to HFD mice which further support the behavioral assessments. Collectively, our data suggest that inhibition of K_{ATP}channel activity in the BAT not only improves metabolic abnormalities but also depressive symptoms.

Disclosures: Y. Kuo: None. **P. Chen:** None.

Poster

685. Mechanisms Underlying Depression and Anxiety

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 685.04/V39

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Title: Characterization of NV-5138, the first selective brain mTORC1 activator

Authors: *E. GIAIME, S. SENGUPTA, S. HAHM, G. P. VLASUK, E. SAIAH;
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Abstract: The mechanistic target of rapamycin complex 1 (mTORC1) has been linked to several important chronic medical conditions many of which are associated with advancing age. A variety of inputs including the amino acid leucine are required for full mTORC1 activation. The cytoplasmic proteins Sestrin1 and Sestrin2 specifically bind to the multiprotein complex GATOR2 and communicate leucine sufficiency to the mTORC1 pathway activation complex. Here we present *in situ* hybridization data showing the specific expression of Sestrin1 and Sestrin2 mRNA in neurons. We also present data showing that NV-5138 activates mTORC1 both *in vitro* and *in vivo*. NV-5138 transiently activates mTORC1 in several peripheral tissues. In contrast to orally administered leucine, NV-5138 uniquely activates mTORC1 in different regions of the brain. Finally, we show that a transient activation of mTORC1 in neurons can induce synaptic protein synthesis as well as spine formation in prefrontal cortex and hippocampus up to three days after dosing. NV-5138 is the first selective orally available mTORC1 activator targeting an amino acid sensor that is brain penetrant and will permit the exploration in areas of unmet medical need including neuropsychiatric conditions and cognition which have been linked to the activation status of mTORC1.

Disclosures: E. Giaime: None. **S. Sengupta:** None. **S. Hahm:** None. **G.P. Vlasuk:** None. **E. Saiah:** None.

Poster

685. Mechanisms Underlying Depression and Anxiety

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 685.05/V40

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: JSPS KAKENHI Grant 18H02756
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JSPS KAKENHI Grant 18K07620
GSK Japan Research Grant 2016

Title: Distribution of multiple lysophosphatidic acid receptors in adult mouse brain

Authors: *N. KAJITANI[1], M. OKADA-TSUCHIOKA[1], H. ABE[1,2], W. OMORI[1,3,4], K. ITAGAKI[1,4], A. MACHINO[1,3], M. TAKEBAYASHI[1,5];
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Abstract: Background: Lysophosphatidic acid (LPA) is a bioactive phospholipid that acts as an extracellular signaling molecule through six different G-protein-coupled receptors (LPA1-6). LPA has many roles in the central nervous system that influence brain development, function, and behavior. In this study, we examined the distribution of all LPA receptors in adult mouse brain. Among LPA receptors, LPA1 is crucial for LPA-induced learning and emotional behavior and an antidepressant effect (Kajitani et al. 2016), indicating that LPA1 may be a potential therapeutic target for neuropsychiatric disorders. However, the cellular localization of LPA1 is not completely understood. Identification of LPA1 expressing cells is essential for drug discovery research. We evaluated the cellular localization of LPA1 in the brain using LPA1 heterozygous mice that integrate a lacZ reporter-tagged deletion allele. **Method:** Adult wild type C57BL/6J and LPA1 heterozygous mice were used in this study. All animal experiments were approved by the animal research ethics committee of NHO Kure Medical Center. Total RNA was extracted from nine brain regions (olfactory bulb, frontal cortex, striatum, hippocampus, thalamus, hypothalamus, mid brain, hind brain and cerebellum). The mRNA expression changes were examined by real-time PCR. Cellular localization of LacZ in LPA1 heterozygous mice brain was evaluated by double fluorescent immunostaining of antibodies against β-galactosidase (LacZ) and each cell markers (CD31, GFAP, Iba1, NeuN, Olig2 and S100β). **Results:** The mRNA expression of all LPA receptors was detected in adult mouse brain. LPA1, 2, 3, 5 and 6 mRNAs were abundantly expressed in the brain stem (hypothalamus, mid or hind brain). LPA4 mRNA was abundantly expressed in the olfactory bulb. In LPA1 heterozygous mice, mRNA

expression of LPA1 was strongly correlated with that of LacZ, indicating that LacZ can be alternatively used to examine LPA1 cellular localization. Fluorescent immunostaining revealed that the majority of LacZ-positive cells were Olig2-positive oligodendrocytes. Most S100β-positive ependymal cells expressed LacZ. The remaining LacZ-positive cells were GFAP-positive astrocytes and CD31-positive vascular endothelial cells. Neuron and microglia hardly expressed LacZ. **Conclusion:** Almost all LPA receptors were abundantly expressed in the brain stem. Especially in LPA1, oligodendrocytes could be involved in the distribution of LPA1 in the brain. Astrocytes, ependymal cells and vascular endothelial cells also expressed LPA1. These findings could be useful in the development of drugs targeting LPA1.

Disclosures: N. Kajitani: None. **M. Okada-Tsuchioka:** None. **H. Abe:** None. **W. Omori:** None. **K. Itagaki:** None. **A. Machino:** None. **M. Takebayashi:** None.

Poster

685. Mechanisms Underlying Depression and Anxiety

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 685.06/V41

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Title: Psychoactive properties of BNN27 in both sexes - A novel neurosteroid derivate

Authors: *M. G. SOTIROPOULOS[1], N. KOKRAS[1], C. DIOLI[1], R. PARAVATOU[1], I. CHARALAMPOPOULOS[2], A. G. GRAVANIS[2], C. DALLA[1];
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Abstract: Dehydroepiandrosterone (DHEA), a potent neuroactive neurosteroid, is synthetized in the brain, as well as in peripheral tissues and glands, like the adrenals. Neurosteroids and DHEA in particular, play a role in neurodegeneration and neural protection, but they are metabolized in androgens, estrogens or other active metabolites. A synthetic analogue of DHEA, named BNN27 ((20R)-3β,21-dihydroxy-17R,20-epoxy-5-pregnene), has been developed. Although the neurotrophic actions of BNN27 have been studied, its potential anxiolytic or antidepressant properties have not been investigated. Male and female adult Wistar rats were treated with BNN27 (10, 30, 90 mg/kg, i.p.) or vehicle (DMSO 100%) and were subjected to a series of behavioral tests. Horizontal and vertical activity, and time spent in the center of the arena were measured in the open field. Total number of transitions and per cent of time spent into the illuminated compartment were measured in the Light/Dark Box. Time spent and entries in the open arms were measured in the Elevated Plus Maze. Immobility, swimming, climbing and head shake behaviors were measured in the two-day Forced Swim Test (FST). Specifically, rats were subjected to a 15min pretest FST session, thereafter all rats received three injections of BNN27 or vehicle at 1, 19, 23 hrs after the pretest session and one hour later they were subjected to the

second 5min FST test session. Three weeks later, all rats had again one single injection of either BNN27 or vehicle, were killed, hippocampus and prefrontal cortex were collected for biogenic monoamine and aminoacid assays using HPLC-ED, and trunk blood was collected for hormone measurements. Our results showed that at 30min post-injection, BNN27 has a marked impact on spontaneous motor activity of male and female rats. Specifically, both male and female rats displayed lower horizontal and vertical activity when injected with progressively higher doses of BNN27. The highest BNN dose resulted in a clear suppression of motor activity in the open field. The statistical analysis, using a two-way ANOVA, revealed that BNN27 increases the levels of glutamine in the area of the hippocampus, irrespectively of the dosage and the sex of the animals. Furthermore, the levels of glutamate in the areas of the hippocampus and the prefrontal cortex were higher in males than in females. BNN27 treatment seems to influence the levels of glutamine and thus indirectly, the glutamatergic system in the hippocampus. This finding may be linked with the possible capacity of BNN27 to improve cognitive function in neurodegenerative disorders. Our results further show that BNN27 has psychotropic properties in male and female rats.

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Poster

685. Mechanisms Underlying Depression and Anxiety

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 685.07/V42

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Title: *In vivo* anxiolytic and antidepressant activity of LCGA-17, a new peptide modulator of GABAergic system

Authors: *A. MALYSHEV, I. DORONIN, V. PAVSHINTCEV, V. GEDZUN, I. SUKHANOVA, E. RAZUMKINA, M. LOVAT, A. KUCHUMOV, G. BABKIN;
Lactocore, Inc., Plymouth, MI

Abstract: Background: New concepts of pharmacotherapy in psychiatry highlight increasing potential for peptides in treating mood disorders. LCGA-17 is a novel tetrapeptide discovered using docking procedures from proprietary peptide library and characterized as potential GABA-A receptor positive allosteric modulator. The GABAergic system plays an important role in normal functioning of corticolimbic circuits and regulation of hippocampal neurogenesis and neural maturation, which are now established as cellular substrates of many treatments. LCGA-17 could provide prominent anxiolytic and antidepressant effect by enhancing GABA-A receptors activity.
Objective: Investigate dose-dependent LCGA-17 efficacy in depressive/anxiety models in

comparison with benzodiazepine, and the role of GABA-A receptor in mediating the peptide's activity.
Methods: Three doses of the LCGA-17 (1, 10, 20 mg/kg) were studied after a single i.p. injection in BALB/C mice (n=13 per group) using elevated plus maze (EPM) and forced swim (FS) tests, with diazepam (0.75 mg/kg) as a positive control. The most efficient dose was chosen for co-administration with bicuculline (5 mg/kg), a competitive GABA-A receptor antagonist, to be compared with the peptide alone in a new set of animals using the same behavioral methods.
Results: EPM test revealed a significant increase in time on open arms after 20 mg/kg dose injection of LCGA-17 and improvement in complex "anxiety index" parameter in all 3 doses of the peptide comparing to control group. Anxiolytic-like activity was dose-dependent and comparable to diazepam. But unlike diazepam, LCGA-17 also showed an ability to decrease behavioral despair in FS test by significantly reducing immobility time at all 3 peptide doses and increasing climbing time at 20 mg/kg. EPM and FS tests were subsequently used to compare the efficacy of the peptide alone (at 20 mg/kg) and in combination with bicuculline. It has been observed that bicuculline completely abolished peptide's effects while the peptide alone had reproducibly shown high activity in both tests, pointing to a strong connection of the peptide's activity with GABA-A receptor.
Conclusion: Novel peptide LCGA-17 showed dose-dependent anxiolytic-like and antidepressant-like activity in vivo, with no reduction in locomotor activity, or any other common psychotomimetic side effect. Bicuculline-dependent type of activity suggests LCGA-17 is likely a GABAergic system modulator. Further experiments using chronic stress models are in progress to develop this promising peptide as a potential treatment of mood disorders.

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Poster

685. Mechanisms Underlying Depression and Anxiety

Location: Hall A

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Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: NIH/NIGMS T32-GM008181 (to LMR)
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NIH/NIMH R01-MH086828 (to SMT)
NIH/NIMH R01-MH107615 (to TDG)
Harrington Project for Discovery and Development Scholar Innovator Award (to TDG)

U.S. Department of Veterans Affairs Merit Award 1I01BX004062 (to TDG)

Title: (*2R,6R*)-hydroxynorketamine acts through a synapse-specific presynaptic mechanism to rapidly potentiate hippocampal glutamatergic transmission

Authors: *L. M. RIGGS[1], Y. ARACAVA[2], P. ZANOS[3], J. FISCHELL[4], E. X. ALBUQUERQUE[5], E. F. R. PEREIRA[5], S. M. THOMPSON[6], T. D. GOULD[7];
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Abstract: Preclinical studies indicate that (*2R,6R*)-hydroxynorketamine (HNK) retains the rapid and sustained antidepressant-like actions of ketamine, but is spared its dissociative-like properties and abuse potential. While (*2R,6R*)-HNK is thought to exert its antidepressant-like effects by potentiating α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR)-mediated synaptic transmission, its acute mechanism of action is unknown. Here, the acute synaptic effects of (*2R,6R*)-HNK were examined by recording field excitatory postsynaptic potentials (fEPSPs) and miniature excitatory postsynaptic currents (mEPSCs) in rat hippocampal slices. (*2R,6R*)-HNK bath application caused a rapid and persistent potentiation of AMPAR-mediated Schaffer collateral (SC)-CA1 fEPSPs in slices derived from male and female rats. The (*2R,6R*)-HNK-induced potentiation occurred independent of *N*-methyl-D-aspartate receptor (NMDAR) activity, was accompanied by a concentration-dependent decrease in paired pulse ratios, was occluded by raising glutamate release probability, and was blocked by presynaptic calcium channel inhibition. Additionally, in the presence of tetrodotoxin, (*2R,6R*)-HNK increased the frequency, but not amplitude, of mEPSC events, confirming a presynaptic site of action that is independent of glutamatergic network disinhibition. A dual extracellular recording configuration revealed that the presynaptic effects of (*2R,6R*)-HNK were synapse-selective, occurring in CA1-projecting SC terminals, but not in CA1-projecting temporoammonic terminals. Overall, we found that (*2R,6R*)-HNK enhances excitatory synaptic transmission in the hippocampus through a concentration-dependent, NMDAR-independent, and synapse-selective increase in glutamate release probability with no direct actions on AMPAR function. The current study provides novel insight regarding (*2R,6R*)-HNK's acute mechanism of action, and reveals that non-canonical presynaptic forms of synaptic plasticity can be engaged by compounds with rapid-acting antidepressant potential. These findings represent an important step toward identifying novel antidepressant drug mechanisms that may possess superior efficacy, safety, and tolerability than those currently available.

Disclosures: L.M. Riggs: None. **Y. Aracava:** None. **P. Zanos:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Co-inventor on a patent application for the use of (2R,6R)-hydroxynorketamine in the treatment of depression, anxiety, anhedonia, suicidal ideation, and posttraumatic stress disorders.. **J. Fischell:** None. **E.X. Albuquerque:** None. **E.F.R. Pereira:** None. **S.M. Thompson:** None. **T.D. Gould:** B. Contracted Research/Research Grant (principal investigator

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Poster

685. Mechanisms Underlying Depression and Anxiety

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 685.09/V44

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: F.I.R. 2018 Universita' degli Studi di Cagliari

Title: Crosstalk between lysophosphatidic acid and cannabinoid receptor signalling in the regulation of antidepressant activation of MAP kinases in hippocampal neurons

Authors: *M. C. OLIANAS[1], S. DEDONI[2], P. ONALI[3];
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Abstract: Accumulating evidence indicates that lysophosphatidic acid (LPA) signalling participates in the regulation of neuroprotection and emotional behaviour. Moreover, we have previously reported that in neuronal and glial cells activation of the LPA_1 receptor mediates MAP kinase activation and pro-survival effects of different classes of antidepressants. The cannabinoid system has also been implicated in the pathogenesis of depression and anxiety through the modulation of multiple neurotransmitter pathways. However, there is little information on whether lysophospatidic acid and cannabinoid systems interact in the regulation of neuronal responses to antidepressants. In the present study we report that in HT22 mouse hippocampal neurons the endocannabinoid anandamide stimulated ERK1/2 phosphorylation, which was blocked by the selective CB_1 receptor antagonist rimonabant. The stimulatory effect of anandamide was mimicked by the cannabinoid receptor agonist WIN55,212-2. Both LPA and the tricyclic antidepressant amitriptyline induced a rapid increase of ERK1/2 phosphorylation , which was blocked by LPA_1 receptor antagonists but insensitive to rimonabant. The exposure of HT22 hippocampal cells to either anandamide or WIN55,212-2 potentiated the stimulation of ERK1/2 induced by either LPA or amitriptyline. The potentiation was prevented by cell pre-treatment with rimonabant. These data provide the first evidence for the occurrence in hippocampal neurons of a functional interaction between endogenously expressed CB_1 and LPA_1

receptors in the control of intracellular signalling. This interaction appears to set the gain of MAP kinase activation in response to endogenous lipids and antidepressants.

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

Poster

685. Mechanisms Underlying Depression and Anxiety

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 685.10/V45

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Title: Demonstration of high affinity, reversible JNJ-42226314 binding by monoacylglycerol lipase in brain homogenates and via autoradiography using [^{3}H]SAR-127303

Authors: *S. W. SUTTON, B. LORD, T. W. LOVENBERG, P. BONAVENTURE; Janssen Res. & Development, L.L.C., San Diego, CA

Abstract: Cannabis Sativa has been used for many generations to treat a variety of ailments including pain and depression. However, tetrahydrocannabinols and other cannabinoids are long lived agonists that have undesirable effects such as memory impairment and hyperphagia. Plant cannabinoids engage 2 cannabinoid receptors (CB1R and CB2R), which have endogenous cannabinoid ligands in mammals (2-arachidonoyl glycerol and anandamide). Monoacylglycerol lipase (MGLL; Navia-Poldanius et al, 2012) is the key serine hydrolase catabolizing 2-arachidonoyl glycerol (2-AG), a full agonist of both cannabinoid receptors. MGLL inhibitors offer a strategy to transiently increase local levels of the endocannabinoid 2-AG by inhibiting its degradation, optimally avoiding the undesirable cannabinoid effects. SAR-127303, a selective covalent inhibitor of MGLL and ABHD6, has been shown to be a suitable tracer for imaging MGLL in the brain (Wang et al., 2016). We have used [^{3}H]SAR-127303 in enzyme binding assays to describe the high affinity and reversible binding of MGLL inhibitor JNJ-42226314. When using this tracer for in vitro binding one can show compounds' affinity and selectivity with regard to serine hydrolase ABHD6. The relative amount of MGLL binding competed by selective MGLL inhibitors as opposed to selective ABHD6 inhibitors confirms an excess of MGLL binding sites compared to ABHD6 sites in native brain tissue. The small fraction of binding from ABHD6 sites can also be seen in binding of this tracer using samples from MGLL knockout mouse brain tissue. Jump dilution with a tracer solution further shows the reversibility of JNJ-42226314 and its K_{off}. In vitro autoradiography experiments using native rodent, simian and human brain samples further show the brain distribution of MGLL.

Disclosures: S.W. Sutton: A. Employment/Salary (full or part-time):; Janssen Research & Development. **B. Lord:** A. Employment/Salary (full or part-time):; Janssen Research & Development. **T.W. Lovenberg:** A. Employment/Salary (full or part-time):; Janssen Research &

Development. **P. Bonaventure:** A. Employment/Salary (full or part-time):; Janssen Research & Development.

Poster

685. Mechanisms Underlying Depression and Anxiety

Location: Hall A

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Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: NIH Grant MH070727 (to L.M.M)
NIH Grant MH066198 (to E.T.K)
NARSAD YI Grant (to K.S)

Title: An instructive role for eukaryotic elongation factor 2 kinase in rapid antidepressant action

Authors: *K. SUZUKI, E. T. KAVALALI, L. M. MONTEGGIA;
Dept. of Pharmacology, Vanderbilt Brain Institute, Vanderbilt Univ., Nashville, TN

Abstract: Major depressive disorder is one of the most prevalent mental illnesses. Traditional antidepressants, which target the monoamine system, are commonly for the treatment of depression but typically take several weeks to exert a clinical effect, with a sizable fraction of the patient population failing to respond to treatment. There has been a major unmet need for the development of pharmacological therapies that can quickly and effectively alleviate symptoms associated with depression. Ketamine is a noncompetitive glutamatergic N-methyl-D-aspartate receptor (NMDAR) antagonist with rapid and sustained antidepressant efficacy for patients with treatment-resistant major depressive disorder. We previously showed that ketamine blocks NMDARs activated by spontaneous glutamate release that couple to eukaryotic elongation factor 2 kinase (eEF2K) signaling, which is essential for the rapid antidepressant action of ketamine in mouse models. When eEF2K phosphorylates its only known target, eukaryotic elongation factor 2 (eEF2), it impairs ribosomal translocation and slows the elongation phase of protein synthesis. Conversely, when eEF2K is inhibited the result is desupression of protein translation. Our hypothesis is that ketamine block of resting NMDAR activity in hippocampus suppresses eEF2K activity and regulates protein synthesis including brain-derived neurotrophic factor (BDNF) and α-amino-3-hydroxy-5-methylisoxazole-4-propinic acid receptors (AMPARs) to trigger a novel form of homeostatic plasticity that is necessary for rapid antidepressant effects. While our work proposes a specific intracellular signaling pathway necessary for rapid antidepressant action, there is little known regarding eEF2K in neurons. We examined eEF2 phosphorylation in hippocampal neurons with respect to specific localization of eEF2K in neuronal subcompartments. We observed high levels of phosphorylated eEF2 in dendrites and spines suggesting eEF2K functions at postsynaptic sites. In addition, to elucidate the impact of eEF2K inhibition on synaptic function, we performed whole cell voltage patch clamp experiments in

hippocampal neurons. Data will be presented showing that eEF2K plays a key role in setting synaptic efficacy which may provide critical insight into the molecular mechanisms important for rapid antidepressant action.

Disclosures: K. Suzuki: None. **E.T. Kavalali:** None. **L.M. Monteggia:** None.

Poster

685. Mechanisms Underlying Depression and Anxiety

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 685.12/W1

Topic: G.05. Anxiety Disorders

Support: R01MH105528

Title: Sex differences in the development of anxiodepressive-like behavior in mice with chronic pain

Authors: *A. M. CARDENAS, E. DIMITROV;
RFUMS, North Chicago, IL

Abstract: Gender differences in pain perception and response to analgesics are well established. The prevalence of chronic pain is higher among women and women are more likely to report widespread pain. However, studies in both, humans and rodents, suggest that females show increased resilience to the development of pain-associated behavioral phenotype. Women in pain clinics have higher physical activity levels and experience less mood disturbances than men. Females do not develop place-conditioned hypersensitivity, while males are readily conditioned by pain experience. Female rodents are less susceptible to develop chronic pain after stress and do not show contextual memory impairment after prolonged periods of pain. The neurotransmitter norepinephrine (NE) is an essential modulator of both pain and mood, and the sexually dimorphic locus ceruleus (LC) is the main source of NE to the forebrain. NE is also a factor for maintenance of the hippocampal neurogenesis, which is vital not only for memory processing, but also for the modulation of anxiety and stress response. We investigated the possible contribution of LC activity to the sex differences in the development of pain phenotype in mice. Mice of both sexes were subjected to neuropathic pain for 45 days. The male mice showed decreased thermal and mechanical thresholds, increased anxiodepressive-like behavior and suppressed hippocampal neurogenesis as measured by the reduced number of doublecortin (DCX) neurons in the hippocampus. The thermal and mechanical thresholds decreased in female mice as well, but the females did not manifest any heightened anxiodepressive-like behavior or changes in DCX expression even after 45 days of pain. We also evaluated the protein levels of dopamine-β-hydroxylase (DBH) in tissue samples from the pons in mice with and without pain. Increased protein levels of DBH were found in females with pain, but not in male mice with

pain. Next, we used a chemogenetic approach to inhibit the LC projections to the ventral hippocampus in female mice with chronic pain. Clozapine N-oxide (CNO) was added to the drinking water of mice in which the projection neurons from LC to hippocampus were transfected by inhibitory AAV-DREADD-Gi virus. The experimental group developed anxiodepressive-like behavior after only 14 days of CNO treatment. The CNO treated group also showed significant decrease of hippocampal DCX expression. Together, the results of our experiments show that the resilience of female mice to the development of pain-associated anxiodepressive-like behavior relies on intact hippocampal neurogenesis, which is very likely supported by increased norepinephrine release from an overactive LC.

Disclosures: A.M. Cardenas: None. **E. Dimitrov:** None.

Poster

685. Mechanisms Underlying Depression and Anxiety

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 685.13/W2

Topic: G.07. Other Psychiatric Disorders

Support: Grant-in-Aid for Scientific Research (C) 19K07192

Title: Effects of serotonin1A receptor agonist on doxorubicin and cyclophosphamide-induced anxiety-like behavior in rats

Authors: *Y. KITAMURA[1], Y. NAKAMURA[2], Y. SUMIYOSHI[2], N. NAITO[2], Y. WADA[2], I. MIYAZAKI[3], M. ASANUMA[3], T. SENDO[1];
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Abstract: We previously reported that combination treatment with doxorubicin and cyclophosphamide (chemotherapy) produced anxiety-like behavior and significantly increased the frequency of (±)-DOI (a serotonin $(5\text{-HT})_{2A}$ receptor agonist)-induced wet-dog shakes in rats. Chemotherapy-induced anxiety-like behavior is mediated by the hyperfunctioning of the 5-HT_{2A} receptor subtype. On the other hand, several studies have suggested that there are functional interactions between 5-HT_{2A} receptors and 5-HT_{1A} receptors. In the present study, we focused on the effects of a 5-HT_{1A} receptor agonist on doxorubicin and cyclophosphamide-induced anxiety-like behavior in rats. [METHODS] Rats were intraperitoneally injected with doxorubicin (5 mg/kg) and cyclophosphamide (50 mg/kg) once a week for 2 weeks. We assessed anxiety-like behavior using the light-dark test. We also evaluated the frequencies of DOI-induced wet-dog shakes (5-HT_{2A} receptor function) and the 8-OH-DPAT-induced flat body posture (5-HT_{1A} receptor function). [RESULTS] Combination treatment with doxorubicin and cyclophosphamide significantly increased the number of DOI-induced wet-dog shakes, but did not affect the

frequency of the 8-OH-DPAT-induced flat body posture. The number of DOI-induced wet-dog shakes was significantly decreased by 8-OH-DPAT treatment. Anxiety-like behavior was significantly inhibited by mirtazapine, a 5-HT_{2A} receptor antagonist/5-HT_{1A} receptor agonist, and tandospirone, a partial 5-HT_{1A} receptor agonist, but not fluoxetine, a selective serotonin reuptake inhibitor. [DISCUSSION and CONCLUSION] These results suggest that 5-HT_{1A} receptor agonists could be used to inhibit doxorubicin and cyclophosphamide-induced anxiety-like behavior.

Disclosures: Y. Kitamura: None. **Y. Nakamura:** None. **Y. Sumiyoshi:** None. **N. Naito:** None. **Y. Wada:** None. **I. Miyazaki:** None. **M. Asanuma:** None. **T. Sendo:** None.

Poster

685. Mechanisms Underlying Depression and Anxiety

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 685.14/W3

Topic: G.05. Anxiety Disorders

Support: 1R15 DA044500-01A1
R25NS08068

Title: Effects of chronic and acute inhibition of cannabinoid CB2 receptor on anxiety levels and oxytocin activity

Authors: L. RODRÍGUEZ, P. MUNOZ, A. RAMOS, V. ENCARNACION, E. OLMEDO, F. GONZALEZ, W. NORZÉ, *C. S. MALDONADO-VLAAR;
Biol., Univ. Puerto Rico, San Juan, PR

Abstract: Oxytocin (OT) has been tested as a potential therapeutic agent in the treatment of various behaviors related to cocaine addiction. Previous work in our laboratory demonstrated that OT has anxiolytic effects and the ability to reduce cue-induced cocaine seeking behavior. Many studies revealed a cross-talk between the endocannabinoid system and the OT system. Our objective was to assess: (1) behavioral effects of chronic and acute inhibition of the CB2 receptor (AM630) in adult male Sprague-Dawley rats, (2) changes produced in the expression of CB2, TRPV1 and OT receptors within the amygdala, median raphe nucleus and hypothalamus. We expect that chronic treatment with AM630 will increase anxiety behavior and acute administration will have an anxiolytic effect. A separate group of animals received twice daily injections of AM630 (3mg/kg i.p.) or vehicle for 5 days. On the 6^{th} day they were tested on the elevated plus maze (EPM). In addition, another group of animals received a single dose of AM630 (3mg/kg i.p.) or vehicle before testing on the EPM. Preliminary results show that when administered chronically systemic blockade of CB2 receptor had a tendency to increase anxiety behavior in male animals. Further biochemical studies will examine cross talk between OT and

the endocannabinoid system as mediators of possible mechanisms responsible for regulating anxiety behavior involving OT.

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Poster

685. Mechanisms Underlying Depression and Anxiety

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 685.15/W4

Topic: G.07. Other Psychiatric Disorders

Support: Host-Pathogen CoBRE Pilot Grant P20GM113123
IDeA Network of Biomedical Research Excellence Grant P20GM103442
Vice President for Research and Economic Development Seed Grant P20GM103442

Title: Class II human leukocyte antigen expression influences behavioral manifestations of mild food allergy in mice

Authors: *D. L. GERMUNDSON, N. A. SMITH, K. NAGAMOTO-COMBS;
Pathology, Univ. of North Dakota Sch. of Med. and Hlth. Sci., Grand Forks, ND

Abstract: Food allergy has been implicated in triggering or exacerbating symptoms of anxiety, depression, attention-deficit hyperactivity disorder, and autism. However, food allergy as a cause of behavioral manifestations has been debated due to inconsistencies in human cohort studies. A factor of such inconsistencies may be variations in class II human leukocyte antigen (HLA-II), which is essential in antigen recognition and presentation for adaptive immunity. HLA-II is highly polymorphic, and it is well-established that specific HLA-II haplotypes increase susceptibilities to various diseases. As HLA-II variants have unique affinities to an antigen, we hypothesized that behavioral manifestations of food allergy would depend on the HLA-II variant expressed. To test this hypothesis, we used three strains of transgenic mice expressing an allelic variant of HLA-II, DR3, DR15, or DQ8. We previously demonstrated that sensitization of C57BL/6 mice to cow's milk whey proteins resulted in anxiety-like behavior without anaphylaxis. Based on this mouse model, we sensitized 4-week-old male and female mice to a major cow's milk allergen, beta-lactoglobulin (BLG), for 5 weeks followed by a BLG challenge. Clinical symptoms, such as itching and swelling, were monitored, and changes in body temperature were recorded at 30 min post-challenge. Sensitized DR3 mice showed moderate clinical responses with perioral redness and swelling, while DQ8 and DR15 mice exhibited occasional ear scratching. One day post-challenge, locomotion, anxiety-like behavior, and spatial memory were tested with open-field activity monitoring and cross maze test. No significant

behavioral changes were observed in sensitized DR3 and DQ8 mice. In contrast, BLG-sensitized DR15 mice displayed behavioral alterations in a sex-dependent manner. The mobility of sensitized male mice decreased compared to their sham counterparts, while sensitized females showed decreased spatial memory. This data establishes that variations in HLA-II differentially influence both physical and behavioral manifestations of non-anaphylactic food allergy. More importantly, our findings support a screening strategy to identify individuals with increased susceptibility to behavioral manifestations of mild or undiagnosed food allergy.

Disclosures: D.L. Germundson: None. **N.A. Smith:** None. **K. Nagamoto-Combs:** None.

Poster

685. Mechanisms Underlying Depression and Anxiety

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 685.16/W5

Topic: G.05. Anxiety Disorders

Title: Anxiolytic effects of full-spectrum cannabidiol-rich hemp extracts in mice

Authors: J. WAGNER[1], R. ARVILA[1], M. BROOKS[1], H. WEBSTER[1], K. REID[1], F. MCGUINNESS[1], F. GAVIN[1], T. HARYU[2], B. PREDOVICH[2], ***J. S. KAPLAN**[1]; [1]Western Washington Univ., Bellingham, WA; [2]Prelabs, LLC, Lehigh Acres, FL

Abstract: Cannabidiol (CBD) is a non-intoxicating cannabinoid that has been shown to have anxiolytic properties. There is a vast number of CBD products available to potential users, yet many pre-clinical empirical assessments of CBD's efficacy are limited by the use of isolated or synthetically-derived CBD, cannabis-derived CBD, or only assess acute exposure. Synthetic and isolated forms of CBD are practically non-existent in the current marketplace, and many individuals cannot legally access cannabis-derived CBD. Consequently, many are turning to hemp-based extracts for chronic treatment of anxiety. Here, we tested the dose-dependent anxiolytic effects of a full-spectrum CBD oil from a commercially-available hemp source in mice using the elevated plus maze assay. We observed that after one week of twice daily i.p. injections of 5 mg/kg of CBD in hemp oil, mice showed reduced anxiety-like behavior compared to vehicle-treated mice as measured by the ratio of time spent in the open arms compared to the closed arms. These anxiolytic effects were lost at higher doses of 20 mg/kg and 100 mg/kg, consistent with previous studies showing an inverted-U dose-response curve for CBD's anxiolytic properties. Our findings support CBD's anxiolytic benefits at low-to-moderate doses and confirm that they persist after repeated exposures of a full-spectrum hemp oil. Our follow-up experiments will assess different full spectrum hemp-derived CBD oils with varying minor cannabinoid and terpene compositions. These comparisons will provide important insight into the roles of terpenes and other cannabinoids in modulating the therapeutic efficacy of cannabis-based treatment of anxiety. Additionally, we will present our immunohistochemistry results

where we assessed the impact of hemp oil exposure on cannabinoid type I receptor expression profiles. Together, our work demonstrates the importance of dose, even from full-spectrum hemp extracts, in CBD's anxiolytic properties and they shed light on the role of terpenes and minor cannabinoids in these anxiolytic effects.

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Poster

685. Mechanisms Underlying Depression and Anxiety

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 685.17/W6

Topic: G.05. Anxiety Disorders

Support: JPSP KAKENHI Grant Number JP15K18865
JPSP KAKENHI Grant Number JP17K15458

Title: Anxiolytic properties of Matcha in mice: Contribution of dopamine D1 receptor- and serotonin 5-HT_{1A} receptor-mediated mechanisms

Authors: *Y. KURAUCHI[1], H. PRASAD DEVKOTA[2], K. HORI[2], Y. NISHIHARA[1], T. SEKI[1], H. KATSUKI[1];
[1]Dept Chemico-Pharmacol Sci, Grad Sch. Pham Sci, Kumamoto Univ., Kumamoto, Japan; [2]Dept Med. Botany, Grad Sch. Pham Sci, Kumamoto Univ., Kumamoto, Japan

Abstract: Matcha tea is a traditional drink in Japan. In recent years, the term Matcha is becoming popular worldwide, because it is also used as a dietary supplement or flavoring ingredient in snacks. Matcha is the finely ground powder of specially cultivated tea plant leaves (*Camellia sinensis*), and is thought to be beneficial for brain functions; however, only a few scientific studies have shown the effects of Matcha tea powder on psychiatric behavior. Here, we evaluate the anxiolytic activity of Matcha tea powder in mice, using the elevated plus maze test. Oral administration of Matcha tea powder and ethanol extract (CSE) of Matcha tea powder exerted anxiolytic effects. Among the fractions of CSE, the ethyl acetate and hexane fractions (CSEE and CSEH, respectively) exerted anxiolytic effects. Notably, the water fraction of CSE (CSEW) synergistically enhanced the anxiolytic effects of CSEE, although CSEW itself did not show anxiolytic properties. Moreover, SCH23390, a dopamine D1 receptor blocker, and WAY100135, an antagonist of the serotonin (5-hydroxytryptamine: 5-$HT)_{1A}$ receptor, prevented Matcha tea powder and CSEE from exerting their anxiolytic effects. These results suggest that Matcha tea powder exerts anxiolytic effect through the activation of the dopaminergic and serotonergic systems.

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Poster

685. Mechanisms Underlying Depression and Anxiety

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 685.18/W7

Topic: G.05. Anxiety Disorders

Support: Defense Advanced Research Projects Agency SUBNETS contract number W911NF-14-2-0043
National Science Foundation Graduate Research Fellowship

Title: Neurotherapeutic effects of closed-loop stimulation in an NHP model of anxiety

Authors: S. R. SANTACRUZ[1], ***E. L. ZIPPI**[2], J. M. CARMENA[2,3];
[1]Biomed. Engin., Univ. of Texas at Austin, Austin, TX; [2]Helen Wills Neurosci. Inst., [3]Electrical Engin. and Computer Sci., Univ. of California, Berkeley, Berkeley, CA

Abstract: The prefrontal cortex is known to be involved in emotional regulation. In order to demonstrate a functional link between mood state and neural state, we used a proxy for an acute anxiety animal model in the nonhuman primate (NHP). Two NHP subjects were trained in an eight-target center-out task which consisted of three blocks. During the first block, baseline physiology and behavior was established. At the beginning of the second block, beta-carbolines, a type of benzodiazepine inverse agonist, were administered to induce an acute anxiety-like state. Finally, in the third block a treatment was administered to the subjects in the form of either closed-loop stimulation or midazolam, a known anxiolytic drug in the class of benzodiazepines. Using biomarkers of mood state changes discovered during this behavior, we designed closed-loop microstimulation protocols to mediate these changes and restore the subjects to a baseline, non-anxious state. We applied unilateral microstimulation to prefrontal cortical sites to modulate the response evoked from the beta-carbolines administered in the second block. We found that microstimulation was able to restore neural features to baseline levels and generate a profound anxiolytic physiological response.

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Poster

685. Mechanisms Underlying Depression and Anxiety

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Program #/Poster #: 685.19/W8

Topic: G.05. Anxiety Disorders

Support: CAPES
CNPq

Title: Cannabidiol effects on defensive responses and compulsive-like behaviors in rats considering the influence of sex and estral cycle

Authors: *D. FABRIS[1], K. GENARO[2], W. A. PRADO[3], J. S. CRIPPA[3], A. R. DE OLIVEIRA[1];
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Abstract: The endocannabinoid signaling system (eCBs) regulates various physiological processes and is considered a potential pharmaceutical target for modulating emotional responses. Cannabidiol (CBD), a phytocannabinoid, enhances the action of eCBs and has an anxiolytic effect in several animal models. Although there are important differences in prevalence, severity and symptomatology in the expression of emotional disorders between men and women, preclinical research is performed predominantly in males. Few studies consider the influence of sex and the impact of fluctuations of female gonadal hormones on the expression of emotions and the effects of drugs used in the treatment of mental disorders. The present study evaluated the effects of CBD on defensive and compulsive-like behaviors in rats, considering the influence of sex and estrous cycle phases. Male and female (proestrus and late diestrus) Wistar rats (n=6-11) received intraperitoneal administration of CBD at doses of 0.0, 0.3, 3.0 or 30 mg/kg. In the sequence, distinct groups had their behavioral responses analyzed in the elevated plus-maze (EPM), open field, marble burying, nestlet shredding and spontaneous alternation tests. Males that received 3.0 mg/kg CBD showed increased number (1-way ANOVA, $F(3,33)=3.27$; $p<0.05$) and duration ($F(3,33)=3.04$; $p<0.05$) of visits to the open arms of the EPM, indicative of an anxiolytic effect. No significant effect was observed for any of the other tests. Females receiving 0.3 mg/kg CBD during late diestrus, but not during proestrus, showed the same increase in the exploratory response of the open arms of the EPM (number of visits: $F(3,29)=3.45$; $p<0.05$; duration: $F(3,29)=4.03$; $p<0.05$). Again, no significant effect was observed for the other tests. The results indicate that sensitivity to CBD seems to be dependent on the type of defensive/compulsive response assessed and differ according to gender and phase of the estrous cycle.

Disclosures: **D. Fabris:** None. **K. Genaro:** None. **W.A. Prado:** None. **J.S. Crippa:** None. **A.R. de Oliveira:** None.

Poster

685. Mechanisms Underlying Depression and Anxiety

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 685.20/W9

Topic: G.07. Other Psychiatric Disorders

Support: NIH Grant P20GM113123
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Title: Anxiety-like behavior is differentially induced in C57BL/6J and BALB/cJ mice as a form of non-anaphylactic response to cow's milk allergy

Authors: ***N. A. SMITH**, D. L. GERMUNDSON, K. NAGAMOTO-COMBS;
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Abstract: Neuropsychiatric disorders such as depression, attention deficit hyperactivity disorder, and autism spectrum disorder are a major public health concern. Though a large proportion of research focuses on development of behavior modulating pharmaceuticals, the complex etiology underlying these disorders requires further investigation. It is well-documented that the immune system influences behavior. For example, food allergy is often reported to be comorbid with various neuropsychiatric disorders. However, this observation is not universal to all allergic individuals. We therefore hypothesized that some individuals are predisposed to behavioral manifestation of food allergy due to specific biases in their immune responses. Because the type of T helper cell (Th) activated upon allergen exposure is a major determinant of hypersensitivity reactions, we used two strains of mice with distinct Th1- or Th2-biased responses and assessed whether allergen sensitization would induce differential behavioral responses upon allergen challenge. Starting at 4-weeks of age, Th1-biased C57BL/6J and Th2-biased BALB/cJ male and female mice were sensitized with a major cow's milk allergen, β-Lactoglobulin (BLG), for 5 weeks. Sex- and strain-matched sham-treated mice were used as controls. On the 6th week, all mice were challenged with BLG, and their symptom score and body temperature were recorded at 30 min post-challenge. In BALB/cJ mice, sensitized male and female scored higher in our symptom scale and showed greater degrees of hypothermia compared to their respective sham groups. One day after the challenge, male BALB/c mice additionally showed decreased activity and increased anxiety-like behavior with open field activity monitoring and elevated zero maze test, respectively. Sensitized male C57BL/6J mice also displayed anxiety-like behavior despite showing no observable signs of anaphylaxis upon challenge, indicating that allergy-induced behavioral changes can manifest without anaphylaxis. Females did not show behavioral changes, demonstrating a sex-specific response to the allergen challenge. These results suggest that sex

and genetic background of an individual can differentially affect behavioral changes caused by food allergy.

Disclosures: **N.A. Smith:** None. **D.L. Germundson:** None. **K. Nagamoto-Combs:** None.

Poster

685. Mechanisms Underlying Depression and Anxiety

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 685.21/W10

Topic: G.05. Anxiety Disorders

Title: Therapeutic potential of a single administration of the anticonvulsivant pregabalin in extinguishing contextual aversive memory and inducing anxiolytic-like responses in diabetic animals

Authors: *A. P. FARIAS WALTRICK, A. H. B. DE LIMA SILVA, J. MENEZES ZANOVELI;
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Abstract: Diabetes mellitus (DM) is a chronic metabolic disorder highly associated with several psychopathologies such as anxiety disorders and stress-related disorders (*i.e.* the post-traumatic stress disorder). A major challenge for patients suffering from DM and their comorbidities is treatment, as there is a high prevalence of patients resistant and/or refractory to first-line medications. Thus, evidence suggests that anticonvulsant drugs such as pregabalin may be a good alternative in those cases. Pregabalin acts by selectively binding to the α2δ subunit of calcium-dependent voltage channels. The channel undergoes a conformational change that reduces the influx of calcium at the nerve terminals, decreasing, for example, the release of excitatory neurotransmitters such as glutamate. There are almost no studies investigating cognitive impairments related to fear anxiety in diabetic (DBT) rats. Therefore, the present study aimed to investigate the effect of pregabalin (0, 30 and 100 mg/kg, i.p.) on the freezing time in normoglycemic (NGL) and DBT rats submitted to the contextual fear conditioning protocol. The freezing time was evaluated in 3 sessions (S1, S2, and S3) without unconditioned stimulus presentation, with S2 occurring 24 hours after S1 and S3 occurring a week after S2. Shortly after S3, the animals were also submitted to the elevated plus maze test to evaluate anxiety parameters and/or sensitization of fear response. Our data show that DBT animals have greater difficulty in extinguishing a contextual aversive memory (S2), which is longer (S3) in relation to NGL. In addition, DBT animals presented an increased anxiety-like response than NGLs. Interestingly, we verified that a single injection of the drug was able to accelerate the extinction of aversive memory and to induce the anxiolytic-like effect. All these effects present a long-lasting duration (7 days after pregabalin injection). Finally, the data showed the importance of studying the pathophysiology of this overconsolidation of enduring aversive memory associated with

increased anxiety in DBT rats, and the importance of studies on new alternative treatments. To conclude, pregabalin seems to have therapeutic potential for such cases of more pronounced aversive responses associated with aversive memory.

Disclosures: A.P. Farias Waltrick: None. **A.H.B. de Lima Silva:** None. **J. Menezes Zanoveli:** None.

Poster

685. Mechanisms Underlying Depression and Anxiety

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Program #/Poster #: 685.22/W11

Topic: G.07. Other Psychiatric Disorders

Support: R01 MH109475
R01 MH104227

Title: Different types of stress affect rodent's performance in attentional set-shifting task

Authors: *S. MA, Y. ZUO;
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Abstract: As the pace of modern life accelerates, stress becomes more and more prevalent. Many studies have shown that stress can lead to various mental and physical health conditions and is a risk factor for many psychiatric disorders such as depression, anxiety, sleep disorders and post-traumatic stress disorder. Among different brain areas, the prefrontal cortex (PFC) is the most sensitive to the stress exposure. The PFC is responsible for cognitive and executive functions. In rodents, PFC consists of two major subregions: medial prefrontal cortex (mPFC) and orbital frontal cortex (OFC). To evaluate PFC-mediated cognitive flexibility - a core executive function, we used attentional set-shifting task (AST). Previous lesion experiments show mPFC is responsible for extradimensional shift (EDS), which requires the subject to alter their response strategy and focus on previously irrelevant information to solve the new set of problems. On the other side, OFC is responsible for reversal, which requires the subject to change their response to previous non-rewarded information. In this study, we subjected mice to two modes of stress common in our daily life: restraint stress (RS, 2h of physical restraint repeated daily) and unpredictable stress (US, daily exposure to varying mild stressors). Our work finds that mice undergoing RS before AST exhibit impairment of EDS only; while mice subjected to US were impaired in both reversal and EDS. We are currently studying how distinct brain circuits are affected by different modes of stress to lead to altered mPFC and OFC functions.

Disclosures: S. Ma: None. **Y. Zuo:** None.

Poster

686. Psychiatric Disorder: Rodent Models

Location: Hall A

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Topic: G.07. Other Psychiatric Disorders

Support: Simons Foundation Autism Research Initiative (291584)
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Title: Robust and replicable measurement for prepulse inhibition of the acoustic startle response

Authors: E. A. MILLER[1], D. B. KASTNER[2], M. N. GRZYBOWSKI[3], M. R. DWINELL[3], A. M. GEURTS[3], *L. M. FRANK[4];
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Abstract: Measuring animal behavior in the context of experimental manipulation is critical for modeling and understanding neuro-psychiatric disease. Prepulse inhibition of the acoustic startle response (PPI) is a behavioral paradigm used extensively for this purpose, but the results of PPI studies are often inconsistent. As a result, the utility of this metric remains uncertain. Here we deconstruct the phenomenon of PPI. We first confirm several limitations of the traditional PPI metric, including that the underlying startle response has a non-Gaussian distribution and that the traditional PPI metric changes with different stimulus conditions. We then develop a novel model that reveals PPI to be a combination of the previously appreciated scaling of the startle response, as well as a scaling of sound perception. Using our model, we find no evidence for differences in PPI in a rat model of Fragile-X Syndrome (FXS) compared to wild-type controls. These results in the rat provide a reliable methodology that could be used to clarify inconsistent PPI results in mice and humans. In addition, we find robust differences between wild-type male and female rats. Our model allows us to understand the nature of these differences, and we find that both the startle-scaling and sound-scaling components of PPI are a function of the baseline startle response. Males and females differ specifically in the startle-scaling, but not the sound-scaling, component of PPI. These findings establish a robust experimental and analytical approach that has the potential to provide a consistent biomarker of brain function.

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Poster

686. Psychiatric Disorder: Rodent Models

Location: Hall A

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Title: Ethologically based behavioural and neurochemical characterisation of mice with loss of dysbindin-1A

Authors: *C. M. O'TUATHAIGH[1], L. DESBONNET[3], C. PAYNE[4], E. PETIT[4], R. COX[4], S. LOFTUS[2], G. CLARKE[2], O. TIGHE[4], S. WILSON[5], B. P. KIRBY[4], T. DINAN[2], J. L. WADDINGTON[6];
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Abstract: Dysbindin-1 is implicated in several domains implicated in schizophrenia including cognition, glutamate and dopamine neurotransmission. Selective knockout of dysbindin-1A (dys-1A$^{-/-}$), the most abundant and widely expressed isoform in the brain, is associated with working memory deficits. Using an ethologically based approach, the following behavioural phenotypes were examined in dys-1A$^{-/-}$ mice: exploratory activity, social interaction, anxiety, problem-solving ability. The ethogram of initial exploration in dys-1A$^{-/-}$mice was characterised by increased sniffing and rearing seated behaviour; over subsequent habituation, sniffing and rearing to wall were increased, with reduced stillness behaviour. In a test of dyadic social interaction with an unfamiliar C57Bl6 in a novel environment, male dys-1A$^{-/-}$mice showed increase latency to engage in investigative social behaviour relative to wildtype mice. No genotypic differences were observed in frequency of agonistic behaviours. Marble burying behaviour was unaffected in dys-1A$^{-/-}$ mice. Using the puzzle box test to measure general problem-solving performance, no effect of genotype was observed across nine trials of increasing complexity. Levels of monoamines and their metabolites were measured in the striatum, hippocampus, and prefrontal cortex using high-performance liquid chromatography [HPLC] with electrochemical detection. Dys-1A$^{-/-}$ demonstrated a marginal increase in dopamine

levels in the hippocampus, and lower levels of 5-HT in ratio to its metabolite (5-HIAA) in the prefrontal cortex. These studies elaborate the behavioural phenotype of dys-1A$^{-/-}$ mice, revealing genotype-related differences in non-social and social exploratory behaviours and habituation of exploration in a novel environment, as well as subtle changes in dopamine and 5-HT activity in schizophrenia-relevant brain areas.

Disclosures: C.M. O'Tuathaigh: None. **L. Desbonnet:** None. **C. Payne:** None. **E. Petit:** None. **R. Cox:** None. **S. Loftus:** None. **G. Clarke:** None. **O. Tighe:** None. **S. Wilson:** A. Employment/Salary (full or part-time):; GlaxoSmithKline. **B.P. Kirby:** None. **T. Dinan:** None. **J.L. Waddington:** None.

Poster

686. Psychiatric Disorder: Rodent Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 686.03/W14

Topic: G.07. Other Psychiatric Disorders

Title: Binge eating disorder - Role of accumbal cocaine- and amphetamine-regulated transcript and orexin as well as impulsivity traits in a rat model

Authors: *J. S. SCHULLER, M. KOCH;
Neuropharm., Univ. Bremen, Bremen, Germany

Abstract: Binge eating disorder (BED) is the most prevalent eating disorder affecting approximately 2-5 % of the adult population and is often associated with obesity. Furthermore, it is often co-morbid with anxiety, mood or substance abuse disorder. BED is characterized by compulsive episodes of excessive consumption of highly palatable food (binges) together with strong feelings of guilt and loss of control. [1]
BED is conceptualized as an impulsive/compulsive disorder with altered reward sensitivity and food-related attentional biases. [2] In the current study we not only investigate possible correlations between BED and impulsivity in rats but also the neuronal basis of BED using an animal model of the disease. Basis of the experimental set-up is the hypothesis that eating disorders including BED result from disturbances in neural circuits underlying impulse control and reward processing.
The involvement of the nucleus accumbens (NAc) in impulse control and in pathological feeding behavior have been studied extensively both in animals and humans. [3] However, the underlying neurotransmitter systems still need to be further elucidated. Several neuropeptides (e.g. the group of orexins or cocaine- and amphetamine-regulated transcript (CART)) and neurotransmitters (e.g. dopamine) which are involved in the natural feeding behavior are candidates to play an important role in BED.
We here investigate the role of two neuropeptides in a rat model of BED considering impulsivity

traits. For this purpose, male Lister Hooded rats were screened for impulsivity using a well-established impulse control paradigm (5-choice serial reaction time task) and subsequently tested in a paradigm for BED (limited access model). Preliminary findings suggest that antagonizing the orexin 1-receptor in the NAc shell region differentially affects the binge eating behavior in high-impulsive rats compared to both low-impulsive and control animals, while CART-antibodies did not reveal such effects. These findings suggest orexin dysregulation being involved in BED.

1. Hutson, P. H., Balodis, I. M. & Potenza, M. N. Binge-eating disorder: Clinical and therapeutic advances. *Pharmacol. Ther.* 182, 15-27 (2018).
2. Kessler, R. M., Hutson, P. H., Herman, B. K. & Potenza, M. N. The neurobiological basis of binge-eating disorder. *Neurosci. Biobehav. Rev.* 63, 223-238 (2016).
3. Basar, K. *et al.* Nucleus accumbens and impulsivity. *Prog. Neurobiol.* 92, 533-557 (2010).

Disclosures: J.S. Schuller: None. **M. Koch:** None.

Poster

686. Psychiatric Disorder: Rodent Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 686.04/W15

Topic: G.07. Other Psychiatric Disorders

Title: Cortical serotonergic dysregulation in Gunn rat: A model for congenital hyperbilirubinemia

Authors: *A. OH-NISHI[1], S. MIURA[2], K. TSUCHIE[2], R. ARAUCHI[2], T. MIYAOKA[2], M. INAGAKI[2];
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Abstract: [Introduction]It has been reported that Jaundice or neonatal hyperbilirubinemia increase the risk of Attention Deficit Hyperactivity Disorder (ADHD) (Wei 2015), although the molecular mechanisms are not yet well understood. Several reports show the Gunn rat, which is an animal model of congenital Jaundice, has hyperactivity similar to ADHD (Hayashida 2009, Tsuchie 2013, Stanford 2015). It is well understood that cortical serotonin have important role for cognitive functions including attention. In this study, we investigated cortical serotonin neurotransmission in the Gunn rat.[Methods]The amounts of serotonin and its metabolites in the cortical region of the Gunn rats were measured by high performance liquid chromatograph, furthermore, serotonergic neurons in the dorsal raphe nucleus were visualized by immunohistochemistry. The hyperactivity in the Gunn rats were confirmed by open field test.[Results]There were significantly higher serotonin and its metabolite at the frontal cortex and hippocampus in the Gunn rats compared to the control rats. The immunohistochemistry showed

that the number of TPH positive cells was increasing in dorsal raphe nucleus of Gunn rats. Moreover, we demonstrated that serotonergic neuronal intervention improves a behavioral abnormality in the Gunn rats.[Conclusion]The serotonergic dysfunctions in the cortical regions seem to play an important role in neonatal hyeprbilirubinaemia associated abnormal behaviors. Our study suggests that intervention with abnormal serotonergic transmission may improve symptom of neonatal hyeprbilirubinaemia associated ADHD.

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Poster

686. Psychiatric Disorder: Rodent Models

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Support: Fondation de France (00066511)
Agence Nationale de la Recherche (ANR13 SAMA001401)
INSERM
Grenoble Alpes University

Title: Role of microRNAs in impulsive behavior in rats: Implication for impulse control disorders associated with Parkinson's disease

Authors: *T. DUFOURD, D. MALLET, C. CARCENAC, S. BOULET, S. CARNICELLA; Grenoble Inst. of Neurosciences - INSERM U1216, Grenoble, France

Abstract: Parkinson’s disease (PD) has long been considered as a pure motor disorder. However, a plethora of non-motor manifestations may occur, ranging from apathy to impulse control disorders (ICDs), and are now considered as disabling as the motor symptoms. These neuropsychiatric disorders are two major comorbid syndromes of PD, and dopamine replacement therapy used to treat the motor symptoms is often associated with ICDs, that include pathological gambling, hypersexuality and compulsive shopping. These behavioral addictions, occurring in 10 to 14 % of PD patients under dopaminergic medications, completely mask the overall motor benefits of the treatment. Unfortunately, it remains unknown why only a portion of these patients will develop these symptoms and thereby, relevant and efficient management of this syndrome is lacking. Recently, several studies have linked dysregulations of microRNAs with PD or psychiatric disorders. These molecules are small non coding RNA playing a pivotal role in the translation of RNA messenger into proteins. However, no one has investigated yet the implication of these molecules in the neuropsychiatric symptoms associated with PD. We therefore investigate the potential implication of microRNAs in the development of ICDs. Some

factors of vulnerability to develop those ICDs have been identified, such as impulsivity trait and dopaminergic treatment use. We used here a behavioral approach with a delay discounting task, a task that allow to assess a form of impulsivity tightly linked to ICDs. After separating rats according to their impulsivity level, we then assessed the effect of pramipexole, a dopaminergic treatment known to induce ICDs in PD patients, in the development of impulsive behavior and looked at microRNA expression profile. Finally, by using high-throughput microRNA sequencing, we identified in tissues of selected brain regions and in plasma from rats, specific microRNAs associated with impulsivity traits and modified by a dopaminergic treatment. A causal validation is ongoing to disentangle the implication of these microRNAs in the development of impulsivity, by using an overexpressing strategy in order to mimic the dysregulations induced by pramipexole in the striatum and assess the effect of this molecular manipulation on the behavior of rodents according to their impulsive level. These findings may lead to the identification of potential new biomarkers that could be useful for the identification of patients under medication vulnerable to ICDs. Also, the microRNAs identified will be good candidates for the development of innovative therapeutic strategies, leading to a better caretaking of these patients.

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Poster

686. Psychiatric Disorder: Rodent Models

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Program #/Poster #: 686.06/W17

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Support: NSERC
CIHR
Mitacs

Title: Prenatal tetrahydrocannabinol exposure causes strong reductions in omega-3 fatty acid levels in mesocorticolimbic brain circuits: Implications for increased neuropsychiatric vulnerability

Authors: *T. D. JUNG[1], M. CHANG KIT[1], K. YEUNG[1], D. HARDY[1], W. J. RUSHLOW[2], S. R. LAVIOLETTE[1];
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Abstract: Acute or chronic exposure to tetrahydrocannabinol (THC), the primary psychotropic component of cannabis, is known to induce schizophrenia-like symptoms in humans and other animals. The developing brain is particularly sensitive to the effects of THC. While adolescent

exposure to THC has been shown to increase the risk of schizophrenia, little is known about how pre-natal THC exposure may impact brain development and neuropsychiatric risk. This is particularly concerning given that increasing numbers of pregnant women are consuming cannabis to alleviate pregnancy-related symptoms. Dysregulated dopamine (DA) signaling is strongly implicated in schizophrenia. Interestingly, omega-3 fatty acid supplementation has been shown to improve schizophrenia symptoms and delay schizophrenia onset. In addition, schizophrenia has been linked to decreased omega-3 fatty acid levels in neurons. Considering that omega-3 deficiency is linked to aberrant dopaminergic signalling, we hypothesized that pre-natal exposure to THC might alter levels of omega-3 fatty acids in schizophrenia-related neural circuits, including the nucleus accumbens (NAc), prefrontal cortex (PFC), and hippocampus (HIPP). Accordingly, we examined the levels of docosahexaenoic acid (DHA), an essential omega-3 fatty acid that is abundant in the brain, following prenatal exposure to THC. In this study, pregnant Sprague Dawley rats received daily intraperitoneal THC or vehicle injections from gestational day 6 to 22. The brains of pups were collected and frozen at 3 weeks and 6 months of age. Matrix-assisted laser desorption/ionization (MALDI) imaging mass spectrometry (IMS) was used to obtain the DHA peak intensities in the PFC (prelimbic and infralimbic), NAc and HIPP (ventral subiculum and CA1). Remarkably, our findings reveal for the first time, a substantial loss of DHA in the observed brain regions of THC treated rats, demonstrating that prenatal THC exposure can strongly reduce omega-3 fatty acid levels in neural regions implicated in schizophrenia. These findings are also the first evidence to suggest that chronic prenatal THC exposure can increase vulnerability to a schizophrenia-related phenotype by functional modulation of neural omega-3 fatty acid expression.

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Poster

686. Psychiatric Disorder: Rodent Models

Location: Hall A

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Program #/Poster #: 686.07/W18

Topic: G.07. Other Psychiatric Disorders

Support: 2018YS01R

Title: Cocaine drives schizophrenia-like behaviors via reduced neuronal activity in the nucleus accumbens

Authors: *S. HAM[1], H.-I. IM[2];
[1]Korea Inst. of Sci. and Technol., Seoul, Korea, Republic of; [2]Ctr. For Neurosci., Korea Inst. of Sci. & Technol., Seoul, Korea, Republic of

Abstract: Schizophrenia (SCZ) is a complicated disorder with abnormal symptoms in various categories: positive, negative, and cognitive symptoms. Although specific cause of SCZ has been not elucidated until now, many researchers have believed that genetic factors are involved in these symptoms based on numerous genomic studies. However, development of SCZ-like behaviors also can be provoked by a number of environmental factors at adulthood. As one of environmental stimuli, some drugs such as cocaine can induce schizophrenic behaviors. Despite of obvious SCZ-like symptoms by these drugs, drug-induced SCZ models have been mainly studied about reliability and validity as an animal model of SCZ. The purpose of this study is to make a cocaine-induced schizophrenia (CIS) model with reliability and validity, and to explore important genes of CIS. First, we used cocaine to induce schizophrenic symptoms into young adult C57BL/6 male mice, which is a dopamine reuptake inhibitor. We successfully established CIS mouse model with three categories of symptoms. Subsequently we checked whole brain changes with immunostaining of neuronal activity related protein, ribosomal protein S6. Interestingly we found that reduced intensity of that through whole brain, and we observed that most altered region was nucleus accumbens, where neurons receive major dopaminergic inputs from substantia nigra and ventral tegmental area. In addition, we observed decreased number of spike within nucleus accumbens with microelectrode array. Finally, to study the effects of the environmental factor on schizophrenia, by performing RNA sequencing, we found that expression changes of several genes in the nucleus accumbens of the CIS model. These findings suggest that SCZ-like behaviors induced by cocaine may be mediated via reduced neuronal activity of neurons within nucleus accumbens. This brain dysfunction maybe resulted from changes of genes such as miR-5126, miR-3473g, LCAM2, and ZAR1L. As a result, this new model is reliable and valid as a SCZ model, and the neurological change could be used in the study of SCZ in the future.

Disclosures: **S. Ham:** None. **H. Im:** None.

Poster

686. Psychiatric Disorder: Rodent Models

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Title: Neuroprotective effect of low field magnetic stimulation in cuprizone-induced demyelinated mice

Authors: *Z. SUN, Z. ZHANG, Y. HE, J. YANG;
Beijing Anding Hosp., Beijing, China

Abstract: Myelination of axons by oligodendrocytes is essential for proper physiological function, and white matter and myelin sheath integrity are disrupted in schizophrenia. To date, non-invasive magnetic brain stimulation is a promising new therapeutic approach in neuropsychiatric diseases. In particular, deep-brain reachable low field magnetic stimulation (DMS), could alleviate cognitive impairment and depressive-like behaviors in animal models. In this study, we sought to assess the effects of DMS on myelin sheath damage and schizophrenia-like behaviors in the cuprizone-induced demyelination mouse model. Mice were fed cuprizone (copper ion chelating agent, 0.2% w/w mixed with food) for 6 weeks to induce demyelination. During these 6 weeks, mice were stimulated with either sham, high-frequency (HFS, gamma Hz) DMS for 20 minutes or quetiapine (a common kind of antipsychotics) each day. Behavioral tests were conducted 24 h after the final DMS session. The expression of oligoastrocyte was examined by immunohistochemistry and the expression of neuregulin-1/ErbB4 in the prefrontal cortex was measured with Western blotting. Six weeks of HFS and quetiapine significantly alleviated schizophrenia-like behaviors in cuprizone mice, including improved nesting, social interaction and sensorimotor gating. In addition, both HFS and quetiapine repaired the myelin sheath and increased the expression of PDGFR α (marker of oligodendrocyte precursor cells). However, no significant difference was found in the therapeutic effect between HFS and quetiapine. Furthermore, the expression of neuregulin-1 and its receptor ErbB4, in the prefrontal cortex of demyelinated mice. Our findings showed that DMS is a potential effective neuromodulation technique for the treatment of schizophrenia, and indicated the neuroprotective effect of DMS on oligoastrocyte. The mechanism underlying these therapeutic effects might involve the neuregulin-1/ErbB4 signaling.

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Poster

686. Psychiatric Disorder: Rodent Models

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Topic: G.07. Other Psychiatric Disorders

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Title: Age-dependent effects of dentate gyrus inhibition on hippocampal pathology and psychosis-like behaviors in mice

Authors: *D. SCOTT[1], C. A. TAMMINGA[2];
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Abstract: Although psychosis is the defining and the most recognizable symptom domain in schizophrenia, the biological mechanisms underlying psychosis remains unknown. Analysis of post-mortem human brain and *in vivo* human imaging studies in schizophrenia have detected abnormalities within hippocampal subfields: decreased GluN1 within the dentate gyrus (DG), along with increased synaptic plasticity markers in CA3 and increased *in vivo* basal activity within CA3/CA1 which correlates with psychosis severity. We have previously demonstrated in mice that CA3 hyperactivity is sufficient to induce psychosis-like behaviors. However, the mechanism underlying the induction of this hippocampal hyperactivity remains unclear. We hypothesize that decreasing DG granule cell activity in mice would result in a replication of both the brain pathology associated with psychosis, i.e., increased basal activity and synaptic markers in CA3, and a psychosis-like behavioral phenotype. Moreover, as psychosis tends to emerge during adolescence, we believe adolescent, as opposed to adult mice, will be particularly susceptible to the hippocampal dysfunction. To address this, we infused male adult and adolescent C57BL6/J mice (n >6/group) with AAVs containing either DREADDs or a control virus to specifically inhibit DG granule cells. Following surgery, we chronically treated mice with the DREADD ligand Compound 21, assessed basal activity in the hippocampal subfields through expression of cFos, measured synaptic markers with Western blotting, and performed behavioral analysis, utilizing paradigms associated with a psychosis-like phenotype in mice: prepulse inhibition, fear conditioning, and social memory. Scientific rigor was ensured by repeating each experiment in multiple cohorts of mice, and analyses were performed using automated methodology when possible, to eliminate experimental bias. Results suggest that decreasing DG activity increases hippocampal activity regardless of age, but adolescent mice show molecular alterations at the MF-CA3 synapse, as well as a psychosis-like behavioral phenotype. These results suggest a critical period during which DG dysfunction can cause pathological and behavioral effects suggestive of psychiatric illness.

Disclosures: D. Scott: None. **C.A. Tamminga:** None.

Poster

686. Psychiatric Disorder: Rodent Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 686.10/W21

Topic: G.07. Other Psychiatric Disorders

Support: Institutional funds (psychiatry department, Sherbrooke University)

Title: Possible mild mitochondrial uncoupling and normal leak activity, with increased striatal complex I-II oxygen consumption in males in a murine, juvenile, two hit model of schizophrenia

Authors: O. HUBERT[1], C. MAURICE-GELINAS[1], P. SARRET[3], ***S. GRIGNON**[2]; [1]Pharmacology/Physiology & Psychiatry, [2]Psychiatry & Pharmacology/Physiology, Univ. De

Sherbrooke, Sherbrooke, QC, Canada; [3]Pharmacology/Physiology, Philippe Sarret, Sherbrooke, QC, Canada

Abstract: Schizophrenia is a chronic disorder involving among others, mitochondrial abnormalities. We have previously shown an increase in complex I and complex II-induced respiratory activity (IRA) in a murine, juvenile, two hit (maternal immune activation + adolescent restraint stress) model of schizophrenia (THMS). To gain further mechanistic insight, we present here the results of the concomitant determination of ATP levels and the expression levels of proteins relevant to mitochondrial function, including uncoupling proteins (UCP) 2 and 4. The tryptophan metabolite and NMDAR antagonist, kynurenic acid, provides an interesting connection between inflammatory/oxidative status and neurochemical function and is increased in schizophrenia. Hence, we also report on the effects of 1 methyl-DL-tryptophan (1MT), an inhibitor of the kynurenine rate-limiting indoleamine 2,3-dioxygenase. Methods Mitochondrial O_2 consumption and ATP production were measured from mitochondria isolated from the striatum with MitoXpress and Invitrogen kits, respectively. Control or THMS mice were treated with vehicle or 1MT. Leak activity (glutamate-malate (G-M) + succinate (S) + ADP + oligomycin), complex I (G-M + ADP) and complex II (G-M+ S + rotenone + ADP) IRA and ATP production were measured. Results In line with our previous results, we confirmed *an increase in complex I+II IRA in the THMS male striatum (+46%; p<0.05)*. ATP production was not significantly different in the THMS. *The ATP/ (O_2 consumption) ratio for complex I+II IRA was decreased by 34.2% (p=0.02) in THMS mice*. 1MT was devoid of significant effects in the male striatum under our conditions, on O_2 consumption and ATP production. Complex I+II IRA and ATP production in the presence of oligomycin (leak activity) did not differ between the two groups. OXPHOS proteins, UCP2 and UCP4 levels were unchanged. Discussion We confirmed a robust increase in complex I-II IRA in the striatum in male THMS mice, without a parallel increase in ATP production, which is compatible with the pattern of "mild uncoupling" elicited, among others, by UCP proteins; however, UCP2 and UCP4 levels were unchanged. Further work addressing other proteins involved in mitochondrial uncoupling (UCP5, ANT) and the post-translational modulation of UCPs, might provide further mechanistical insights.

Disclosures: O. Hubert: None. **C. Maurice-Gelinas:** None. **P. Sarret:** None. **S. Grignon:** 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, HLS pharmaceuticals.

Poster

686. Psychiatric Disorder: Rodent Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 686.11/W22

Topic: G.07. Other Psychiatric Disorders

Title: Chronic psychosocial stress during pregnancy affects maternal behavior and neuroendocrine function and modulates hypothalamic CRH signaling pathway

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Abstract: Postpartum depression (PPD) affects up to 20% of women and exerts adverse consequences on mother and child. Stress and abnormalities in neuroendocrine function have been associated with PPD. Here, we measured effects of chronic psychosocial stress during pregnancy (CGS) on maternal behavior and postpartum hypothalamic-pituitary-adrenal (HPA) axis regulation. From gestational day 6.5 to 17.5, pregnant C57Bl/6 female mice were exposed to a novel chronic stress paradigm consisting of variable psychosocial stressors and were assessed from postpartum day 2 to 7 for behavioral alterations as well as circadian and acute stress associated glucocorticoid (CORT) response. mRNA changes in molecular regulators of the HPA axis were measured in 1 mm punches of the hypothalamic paraventricular nucleus (PVN) via qPCR. Offspring were also assessed for behavioral changes at postnatal day 28. After undergoing CGS during pregnancy, mice exhibited deficits in maternal care, a depressive-like phenotype, and anxiety. Abnormalities in the activity of the maternal HPA axis were measured as seen by a flattening of the circadian rhythm of CORT secretion, CORT hypersecretion following 20 minutes of restraint stress, and increased adrenal gland weights. These changes were associated with an upregulation of PVN corticotropin releasing hormone (CRH) mRNA and decreased CRH receptor 1 compared to non-stressed control dams, while vasopressin and oxytocin levels remained undisturbed. Furthermore, PVN glucocorticoid receptor (GR) and progesterone receptor (PR) mRNA were downregulated, and FKBP5 mRNA, a co-chaperone known to negatively orchestrate GR/PR transcriptional activity, was increased during the peripartum period. Behavioral alterations were also observed in CGS female offspring only, including a decrease in time spent immobile and in frequency of immobility episodes in the forced swim test, suggesting an impulsivity-like phenotype. These results implicate maternal hypothalamic changes in GR/PR signaling pathway as putative regulators of postpartum changes in CRH after stress and in maternal affective dysregulation. They further suggest sex-specific differences in alterations in neurodevelopment after exposure to elevated maternal CORT levels due to CGS. Transcriptional profiles in brain regions known to play essential roles in mood regulation are currently being generated in order to gain better insight into the neurobiological pathways that become dysregulated following CGS. Furthermore, sex-specific differences in placental metabolism and fetal exposure to CORT are being investigated.

Disclosures: **S. Zoubovsky:** None. **S. Hoseus:** None. **L. Muglia:** None. **J. Schulkin:** None.

Poster

686. Psychiatric Disorder: Rodent Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 686.12/W23

Topic: G.07. Other Psychiatric Disorders

Title: Olanzapine and clozapine differentially influence behavior in GluN1 DG-specific KO mice

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Abstract: Psychosis, a predominant symptom domain of schizophrenia, has been characterized in human *in vivo* imaging and post-mortem studies by decreased hippocampal GluN1 expression in dentate gyrus (DG), CA3 subfield hyperactivity and increased synaptic plasticity markers. Thorny excrescences (TE) constituting the mossy fiber-CA3 synaptic connections have been deemed a tunable gain control of excitatory input and were found increased in post-mortem studies. We hypothesize that drug treatment may reverse the CA3 subfield hyperactivity and abnormal TE morphology, which could lead to reversal of psychosis-like behavioral phenotypes. In order to test that, we administered clozapine and olanzapine to male GluN1 DG-specific knock-out (at least 4 months old) mice. As a measurable output, we looked at the morphology of TEs and performed a battery of behavioral tests with N>8/group. The behavioral test battery consisted of open field test, object location and recognition memory, social recognition memory, pre-pulse inhibition, contextual and cued fear conditioning. Golgi-Cox staining or AAV-GFP infusion was used to analyze the morphology of TEs and measure their total area. We have found that clozapine and olanzapine have different influence on behaviors listed above. These experiments, which are still ongoing, will provide a broad perspective regarding the antipsychotic mechanism underlying current pharmacotherapies and may suggest novel targets for emerging drugs.

Disclosures: F. Dybowski: None. **C.A. Tamminga:** None.

Poster

686. Psychiatric Disorder: Rodent Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 686.13/W24

Topic: G.07. Other Psychiatric Disorders

Support: NIH/NIAAA R01 AA022448

Title: Novel insights into purinergic P2X4-dopamine D2 receptor interaction in regulation of sensorimotor gating and underlying signaling molecules: A potential mechanism underlying psychiatric disorders

Authors: *S. KHOJA[1], L. ASATRYAN[2], M. W. JAKOWEC[3], D. L. DAVIES[4];
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Abstract: Sensorimotor gating is the process of filtering out trivial sensory information from salient ones in order to efficiently navigate in a stimulus-laden environment. Sensorimotor gating deficits have been linked to psychiatric disorders characterized by cognitive deficits including schizophrenia, bipolar disorder and autism. Current anti-psychotics have shown limited effectiveness in treating patients with cognitive deficits. Considering that sensorimotor gating deficiencies could be a predisposing factor to poor cognitive functioning, elucidation of mechanisms of sensorimotor gating could lead to identification of novel drug targets for treatment of cognitive deficits. To this end, we have reported a role for purinergic P2X4 receptors (P2X4Rs) in sensorimotor gating using prepulse inhibition (PPI) of acoustic startle reflex as an operational measure. P2X4Rs are ion channels gated by adenosine-5'-triphosphate (ATP) in the brain. Positive modulation of P2X4Rs by ivermectin (IVM) induced deficits in PPI in a P2X4R-dependent manner. Additionally, P2X4R knockout (KO) mice exhibited PPI deficits that were restored upon dopamine (DA) D2 receptor antagonism, supporting a role for DA D2 receptors in P2X4R-mediated PPI disruption. However, unrecognized compensatory changes induced by gene deficiency may undermine this novel interaction. To pharmacologically investigate the P2X4-D2 interaction, we tested the effects of the D2 receptor antagonist, raclopride (3 mg/kg) and the D2 agonist, quinpirole (0.1mg/kg) in regulation of IVM-mediated effects on PPI. From a mechanistic standpoint, we tested the effects of raclopride on phosphorylation of signaling proteins underlying PPI regulation including dopamine and cyclic-AMP regulated phosphoprotein of 32kDa (DARPP-32), Ca^{2+}/calmodulin kinase II (CaMKII) and neuronal nitric oxide synthase (nNOS) in the ventral striatum, a critical brain region underlying PPI function. We found that raclopride significantly reversed IVM-mediated PPI disruption whereas quinpirole synergistically augmented the PPI disruptive effects of IVM. At the molecular level, raclopride significantly blocked IVM-mediated increase in DARPP-32 phosphorylation and decrease in CaMKII phosphorylation, thus providing a mechanistic explanation for changes at the behavioral level. Collectively, these findings suggest that P2X4Rs- D2 receptor interaction is important for normal PPI functioning and that disruption of this interaction could lead to gating deficits which can result in fragmentation of cognitive behavior.

Disclosures: S. Khoja: None. **L. Asatryan:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Dr. Liana Asatryan is an inventor on patent for use of IVM for treatment of alcohol use

diosrders. **M.W. Jakowec:** None. **D.L. Davies:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Dr. Daryl L. Davies is an inventor on patent for use of IVM for treatment of alcohol use diosrders.

Poster

686. Psychiatric Disorder: Rodent Models

Location: Hall A

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the Springbank Foundation (YHC),
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Title: Modulation of brain networks by continuous theta burst stimulation in Mal de Debarquement syndrome

Authors: *Y. CHEN[1], D. GLEGHORN[3], B. DOUDICAN[3], Y.-H. CHA[3], L. DING[2], H. YUAN[4];
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Abstract: Repetitive transcranial magnetic stimulation (rTMS) has been increasingly explored in treating many neuropsychiatric conditions. However, the response is heterogeneous across patients, mainly due to limited understanding about the mechanisms of rTMS. Our research has been focusing on optimizing rTMS treatment for a balance disorder called Mal de Debarquement Syndrome (MdDS), a motion perception disorder caused by entrainment to background oscillating motion. Our previous work based on functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) have both revealed the important role of the default mode network (DMN) related to treatment responses. Using prior fMRI and EEG data that suggested targeting of the posterior DMN, we used a rapid form of rTMS called continuous theta burst stimulation (cTBS) as a potentially more efficient method to desynchronize the posterior DMN. Targets included the occipital cortex, cerebellar vermis, and lateral cerebellar hemispheres. In this study, independent component analysis (ICA) was run on concatenated clean EEG sources. The derived EEG connectivity maps were then compared with the clinical score changes after cTBS. As a result, the DMN was identified in the EEG connectivity maps of the participants (n = 24). We confirmed that a decrease of symptoms in positive responders was associated with a decrease in connectivity within the DMN as measured by EEG. Furthermore, baseline

connectivity was negatively correlated with symptom changes in positive responders in both the left and right parietal lobules (i.e., higher baseline connectivity, better clinical response). Our results confirmed the significant contribution of DMN nodes in MdDS and TMS treatment mechanisms. Moreover, the cTBS protocol applied in this study took much less time and yielded larger treatment magnitudes than a prior 1Hz-10Hz rTMS protocol over the dorsolateral prefrontal cortex. This study suggests that baseline brain imaging with EEG holds promise in the development of more effective stimulation protocols for patients.

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Poster

686. Psychiatric Disorder: Rodent Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 686.15/W26

Topic: G.07. Other Psychiatric Disorders

Support: NIGMS, NIH T34 GM008074

Title: The effect of traumatic brain injury on p300 amplitudes in impulsive vs. non impulsive antisocial personality disorder

Authors: *A. PEREZ CORTEZ[1], R. A. SCHUG[2];
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Abstract: A predominant symptom of antisocial personality disorder (ASPD) is impulsivity, frequently associated with deleterious effects upon individuals and society. Reactive crime as a result of impulsive and reckless behavior has been identified as a large portion of convictions for people with ASPD. Few attempts have been made to validate diagnostic measures with more objective data from methodologies such as neuropsychological and electroencephalography (EEG) measures. Impulsive behavior may be attributed to impairments in the orbitofrontal region and measured using electrodes FP1 and FP2. Moreover, it may be that not all individuals with ASPD display impulsivity, raising the question of possible impulsive variants marked by deficits in orbitofrontal functioning as indicated by reduced performance on neuropsychological and EEG measures. The present study sought to identify a potential impulsive subtype of ASPD (ASPD-I) and substantiate traditional diagnostic measures with neuropsychological performance data. Adult males (n = 60) recruited from a large-city rescue mission were evaluated for ASPD using the Structured Clinical Interview for DSM-5 Personality Disorders (SCID-5-PD). To empirically assess for impulsive behaviors, a composite z-score of combined scores from Porteus Maze Test, Iowa Gambling Task, and a Go/No-Go Task was computed and used to assign

participant cases into quartiles, transforming a continuous variable into categorical as a way to evaluate a range within our sample. A 2 (ASPD: Absent, Present) x4 (Quartile groups for Impulsivity) between-subjects ANCOVA was used to examine average amplitudes at frontal lobe sites while controlling for number of past traumatic brain injuries (TBI). Main effects for ASPD and impulsivity were found on several electrode sites, while the simple effect of impulsivity for the ASPD present condition supported our hypothesis for physiological variance in impulsivity within ASPD. In some electrode sites, a curvilinear relationship was found where the most impulsive people in the sample were not found to be different from controls, but those in the middle two groups were significantly different from controls. Because TBI was a significant covariate for only one electrode site, it may not have influenced brain activity as an anatomical barrier despite previous literature suggesting otherwise. Understanding the variability within this disorder may assist in identifying a more functional form of ASPD that has been overlooked in previous research. Future research should explore psychosocial factors that influence magnitude differences of impulsive presence.

Disclosures: A. Perez Cortez: None. **R.A. Schug:** None.

Poster

687. Other Psychiatric Disorders

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 687.01/W27

Topic: G.07. Other Psychiatric Disorders

Title: miR-19b is increased in peripheral blood of schizophenic patients and affects proliferation and survival of hippocampal neural progenitor cells

Authors: *S. BOKU[1], T. HORAI[2], S. OKAZAKI[2], I. OTSUKA[2], K. MOURI[2], A. HISHIMOTO[2];
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Abstract: MicroRNAs (miRNAs) have been investigated in neurodevelopmental and psychiatric disorders including schizophrenia (SZ). Previous studies showed miRNAs dysregulation in postmortem brain tissues and peripheral blood of SZ patients. These suggest that miRNAs may play a role in the pathophysiology of SZ and that miRNAs may be a potential biomarker of SZ. Previous studies also showed that miRNAs regulate neurogenesis and that neurogenesis is involved in the pathophysiology of SZ. In addition, a recent study showed that miR-19a and 19b, which are enriched in neural progenitor cells (NPC) in adult hippocampus, are increased in human NPC derived from induced pluripotent stem cell (iPSC) derived from SZ patients. However, it remains unclear whether the expression of miR-19a and 19b are altered in peripheral blood of SZ patients and how miR-19a and 19b affects neurogenesis. To elucidate them, first we examined the levels of miR-19a and 19b in peripheral blood of SZ patients with quantitative RT-

PCR and showed that the level of miR-19b, but not miR-19a, was significantly higher in peripheral blood of SZ patients than that of healthy controls. Next, we examined the involvement of miR-19b in proliferation and survival of mouse neonatal mice hippocampus-derived NPC with BrdU assay and TUNEL assay. The knockdown of miR-19b significantly increased both proliferation and survival of neonatal mice hippocampus-derived NPC. These results suggest that the level of miR-19b in peripheral blood can be a potential biomarker of schizophrenia and that the higher level of miR-19b may increase vulnerability of SZ via attenuating proliferation and/or survival of hippocampal NPC.

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Poster

687. Other Psychiatric Disorders

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 687.02/W28

Topic: G.07. Other Psychiatric Disorders

Support: 5251831121

Title: A genetics-first approach to understanding mechanisms of psychiatric disorders: subcortical alterations in 22q11.2 deletion syndrome and convergence with idiopathic neuropsychiatric illness

Authors: *C. R. K. CHING[1], P. M. THOMPSON[2], C. E. BEARDEN[3], E. 22Q11.2 DELETION SYNDROME WORKING GROUP[4];
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Abstract: Strong biological markers of psychiatric disorders have not yet been identified. A genetics-first approach that starts with a known etiology may provide insights disrupted biological pathways contributing to complex psychiatric phenotypes, guiding better nosology and future treatments. 22q11.2 deletion syndrome (22q11DS) is among the strongest genetic risk factors for schizophrenia. One in four 22q11DS patients develop schizophrenia, and 60% meet criteria for a neuropsychiatric disorder including autism, anxiety, mood disorders, and/or ADHD. Here we present the largest study of subcortical structure in 22q11DS, comparing patterns of effects across the largest harmonized psychiatric neuroimaging studies ever conducted.

T1-weighted brain MRI scans were acquired at 14 scan sites (22q11DS=533, HC=330), including a subset of matched 22q11DS subjects with psychotic disorder (22q+Psy=64) and without (22q-Psy=64). Gross volume (FreeSurfer 5.3) and two shape metrics quantifying local thickness and surface area were computed bilaterally for the hippocampus, amygdala, thalamus, caudate, putamen, pallidum, and accumbens. Multiple linear regressions were fit for all measures, adjusting for age, age^2, sex, scan site, and intracranial volume, and corrected for multiple comparisons. Spearman rank correlations of effect sizes were used to compare subcortical effects across psychiatric disorders.

The 22q11DS group showed significant alterations in most subcortical structures, with shape analysis revealing complex subfield changes. 22q+Psy subjects generally had lower volumes compared with 22q-Psy. 22q+Psy effects significantly overlapped with alterations in several neuropsychiatric disorders including schizophrenia, major depression, bipolar, and obsessive compulsive disorder (Figure 1).

The significant convergence of effects with other large-scale psychiatric studies, including generally larger effect sizes in 22q11DS and 22q+Psy, lends further support to a genetics-first approach as a powerful avenue to studying mechanisms of psychiatric illness.

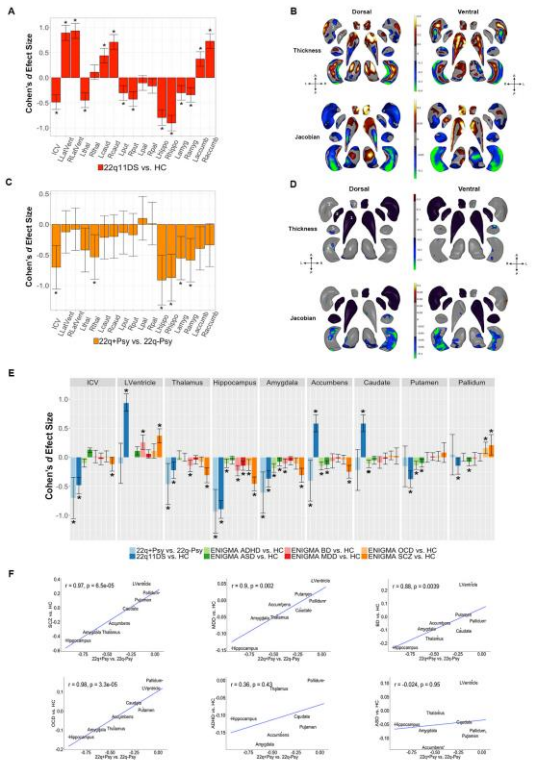

Figure 1. A. Cohen's *d* effect sizes (with 95% confidence intervals) plotted for 22q11DS vs. HC gross volumetric comparison. An asterisk (*) indicates significant group difference after correction for multiple comparisons. FDR corrected P-values<0.05 were considered significant. Models were adjusted for age, age*age, sex, ICV, and scan site. Abbreviations: *L/R*, left/right; *LatVent*, lateral ventricle; *thal*, thalamus; *caud*, caudate; *put*, putamen; *pal*, pallidum; *hippo*, hippocampus; *amyg*, amygdala; *accumb*, accumbens; *ICV*, intracranial volume. **B.** 22q11DS vs. HC shape analysis with regression coefficients plotted in regions passing correction for multiple comparisons (FDR q<0.05). Blue/green colors indicate negative coefficients, or regions of lower thickness (i.e., local radial distance) or Jacobian (i.e., local surface area contraction) measures in 22q11DS compared to HC. Red/yellow colors indicate positive coefficients, or regions of greater thickness or Jacobian values in 22q11DS comared to HC. The top row includes local thickness results; the bottom row includes Jacobian (surface area dilation/contraction) results. Dorsal and ventral views of the structures are provided: A, anterior; P, posterior; L, left; R, right. 1. Caudate; 2. Putamen; 3. Globus Pallidus; 4. Hippocampus; 5. Amygdala; 6. Thalamus; 7. Nucleus Accumbens. Gray regions indicate areas of no significant difference after correction for multiple comparisons. **C.** Cohen's *d* effect sizes (with 95% confidence intervals) plotted for 22q+Psy vs. 22q-Psy gross volumetric comparison. Asterisk (*) indicates significant group difference after correction for multiple comparisons. Models were adjusted for age, age*age, sex, and scan site. **D.** Shape analysis comparing 22q+Psy vs. 22q-Psy with regression coefficient values plotted in regions passing correction for multiple comparisons (q<0.05) with same color scheme as in part B. Black structures are those for which no vertexwise test was significant after correction for multiple comparisons. **E.** Gross volume case-control Cohen's *d* effect size estimates from the ENIGMA schizophrenia (N=4,568; van Erp 2016), major depressive disorder (N=8,927; Schmaal 2016), bipolar disorder (N=4,304; Hibar 2016), obsessive compulsive disorder (N=2,967; Boedhoe 2016), autism spectrum disorders (N=3,222; van Rooij 2018), and attention deficit hyperactivity disorder (N=3242; Hoogman 2017) Working Group Studies, which all used harmonized processing and analysis methods to the current 22q11DS study. Significant case-control differences are indicated by (*), including 95% confidence intervals from original study publication. Note that the ENIGMA ADHD group did not assess lateral ventricle volume in their subcortical study. **F.** Spearman rank correlations between 22q+Psy vs. 22q-Psy gross volume effect size estimates and those from other ENIGMA working groups (8 ROIs: lateral ventricle, amygdala, hippocampus, thalamus, caudate, putamen, pallidum, and nucleus accumbens). Significant correlations were found between 22q+Psy and the ENIGMA schizophrenia, major depressive disorder, bipolar disorder, and obsessive compulsive disorder Working Group Studies.

Disclosures: C.R.K. Ching: None. **P.M. Thompson:** None. **C.E. Bearden:** None. **E. 22q11.2 Deletion Syndrome Working Group:** None.

Poster

687. Other Psychiatric Disorders

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Program #/Poster #: 687.03/W29

Topic: G.07. Other Psychiatric Disorders

Support: IITP 2017-0-00432
NRF-2015M3C7A1065049

Title: Brain response on game craving according to personal preference for games

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Abstract: Nowadays, Internet gaming disorder (IGD) is very popular issues especially for adolescents. The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) published by the American Psychiatric Association in 2013 says that IGD is a condition for further study. Recent studies have demonstrated that neurofeedback training helps addiction patients to improve mental health and control cravings. Accordingly, the effective way to induce craving is very important for the study on game craving. However, most of previous studies did not consider subjects' preference of games presented as stimuli that could affect to craving response. In this study, we hypothesized that there will be difference of brain activity between preferred and non-preferred gameplay videos when subjects are exposed to the videos. We compared self-reported craving score and electroencephalogram (EEG) pattern between preferred and non-preferred gameplay video for both IGD and healthy control (HC) groups. We recruited a total of 62 adolescent/late-adolescent males (age: 19.31 +- 2.51 years) participate in our experiment. All participants were classified into IGD and HC group according to the score of Korea version of Young's Internet addiction test (Y-IAT-K) (Young et al.,1998; Kim et al., 2003). The IGD group were 21 young adults (Y-IAT-K score > 60) and the HC group were 20 young adults (Y-IAT-K score < 40). We measured EEG of all participants while they were watching preferred and non-preferred gameplay videos. After each videos were over, they conducted self-assessment to report the level of game craving. Craving scores for preferred gameplay videos were significantly higher than non-preferred gameplay video in the IGD, but not in the HC. For the brain activity, the IGD group for preferred gameplay video exhibited significantly increased relative delta power and decreased alpha/beta power on anterior and posterior area of the brain compared to non-preferred gameplay video. However, there was no change on the same band and area in the HC group. Previous studies discussed that increase of

low frequency band power of EEG and decrease of high frequency band power in anterior and posterior areas was relevant to craving (Liu et al., 1998; Kim et al., 2003; Reid et al., 2006). In this study, we found that the preference of games presented as stimuli has a strong influence on both self-reported craving score and EEG pattern. These results indicate that that preferred games could be stimuli to elicit game craving more effectively than non-preferred games in the IGD group.

Disclosures: J. Ha: None. **L. Kim:** None.

Poster

687. Other Psychiatric Disorders

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Topic: G.07. Other Psychiatric Disorders

Support: Grant 81571755

Title: Attention-deficit/hyperactivity disorder (ADHD) is a brain disorder marked by an ongoing pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development in order to explore abnormal brain functional connectivity (FC) and network property in ADHD, we calculated FC, global and local network efficiency and compared group differences between 30 ADHD boys and 30 age-matched healthy control using functional near-infrared spectroscopy imaging. We found significant differences between the two groups and we also found the differences were negatively correlated with inattention and hyperactivity/impulsivity symptoms in ADHD

Authors: *M. WANG[1], Y. TAN[2], Q. QIAN[2], H. NIU[1];
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Abstract: Attention-deficit/hyperactivity disorder (ADHD) is a brain disorder marked by an ongoing pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development. As an emerging portable and non-invasive technology, functional near-infrared spectroscopy (fNIRS) has been applied to a number of brain neuroimaging studies, but little is known whether brain differences between ADHD and healthy control (HC) can be found by resting-state fNIRS imaging. The aims of the present study were to explore: 1) whether there are differences between ADHD and HC in brain functional connectivity (FC) and network efficiency. 2) whether there is relationship between the brain FC and network efficiency and clinical characteristics in ADHD. In the present study, we calculated FC, global and local network efficiency based on binary brain networks and compared group differences between 30

ADHD boys and 30 age-matched HC using network-based statistics. We found that the mean FC pattern of ADHD children exhibited lower values than that of HC and more specifically, ADHD showed decreased FC values in almost all brain functional networks, especially in frontoparietal and visual network. At network level, global efficiency of ADHD was significantly lower than that of HC while at nodal level, some nodes were found to have increased nodal efficiency but some were just the opposite in ADHD group. We also found that the changes of FC values negatively correlated with the inattention and hyperactivity/impulsivity symptoms in ADHD ($p<0.05$), suggesting the occurrence and development of disease is accompanied by a reduction in brain FC. These results may benefit a lot for finding biomarkers for ADHD children, and fNIRS may become an assistant for ADHD diagnosis.

Disclosures: **M. Wang:** None. **Y. Tan:** None. **Q. Qian:** None. **H. Niu:** None.

Poster

687. Other Psychiatric Disorders

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 687.05/W31

Topic: G.07. Other Psychiatric Disorders

Support: NSW Ministry of Health, Office of Health and Medical Research
National Health and Medical Research Council Australia Principal Research Fellowship 1117079

Title: Elevation of complement pathway-related transcripts in midbrain in schizophrenia cases who display cytokine-related high inflammation profiles

Authors: T. D. PURVES-TYSON[1,2], ***D. A. ROTHMOND**[1], K. ROBINSON[1], C. SHANNON WEICKERT[1,2];
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Abstract: Introduction: Neuroinflammation contributes to the pathophysiology of schizophrenia and the complement system has been implicated. In ~50% of people with schizophrenia, pro-inflammatory cytokine transcripts are elevated in postmortem midbrain. It is unknown whether molecular measures of the complement system are changed near dopamine cell bodies in the midbrain in schizophrenia. We hypothesised that gene expression of complement initiator C1qA, effectors C3 and C4, and regulators decay-accelerating factor (DAF/CD55) and MAC-IP (membrane attack complex-inhibitory protein /CD59), will be elevated in the midbrain in schizophrenia cases exhibiting high inflammation. Methods: C1qA, C3, C4, DAF and MAC-IP mRNAs were examined by qRT-PCR in the midbrain from 28 schizophrenia cases and 29 healthy controls. Three diagnosis/inflammatory subgroups (controls/low inflammation

schizophrenia/low inflammation, schizophrenia/high inflammation) were previously defined using cluster analysis of pro-inflammatory transcripts. Student's t-tests or ANCOVA, with demographic variables as covariates when required, were used to detect diagnostic differences and differences between inflammation/diagnosis subgroups. Spearman's correlations were used to determine relationships between illness duration, antipsychotics, immune cell gene expression and complement gene expression. Results: C1qA, C3, C4 and MAC-IP mRNAs were increased between 37%-107% in the schizophrenia/high inflammation subgroup compared to both low inflammation subgroups ($F>5.51$, $p<0.05$), while DAF mRNA was unchanged ($p>0.05$). No transcript correlated with illness duration but C1qA, C3 and C4 mRNA positively correlated with daily CPZ equivalents ($Rho>0.44$, $p<0.05$). Complement gene expression was strongly and positively correlated with gene expression of markers of microglia (AIF), astrocytes (GFAP) and macrophages (CD163) in schizophrenia cases. Conclusions: Increased complement cascade synthesis may be a component of the state of increased inflammation in some schizophrenia cases and contribute to midbrain pathophysiology. Increased complement transcripts correlate with glial cells, including microglia and astrocytes, and one immune cell marker for macrophages. Increased MAC-IP supports that resident neurons or cells in midbrain may be attempting to protect themselves against increased complement activity. While the role of antipsychotics in complement activation cannot be ruled out, the increased antipsychotics in those patients with higher inflammation and complement could also indicate a more symptomatic patient requiring higher treatment doses.

Disclosures: T.D. Purves-Tyson: None. **D.A. Rothmond:** None. **K. Robinson:** None. **C. Shannon Weickert:** None.

Poster

687. Other Psychiatric Disorders

Location: Hall A

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Program #/Poster #: 687.06/W32

Topic: G.07. Other Psychiatric Disorders

Title: Transcranial direct current stimulation reduced food craving and nucleus accumbens response to high calorie food cues among individuals with obesity

Authors: M. LEE[1], K. LEE[2], J.-C. KIM[1], H.-M. BAEK[3], *H. CHOI[1];
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Abstract: Previous studies have reported that individuals with obesity tend to be more sensitive to reward stimuli such as high calories foods. Obese people also show greater reward-related circuit response to food pictures because they may be more rewarded by food cues. Transcranial

direct current stimulation (tDCS) is a neuromodulation technique that shown to be effective to reduce food craving and consumption. The present study aimed to investigate the tDCS effects on neural and behavioral response involved in eating. Method: Fourteen obese adults participated in this study (4 female, BMI=29.63±1.16, age=29.53±12.65). This study employed a single-blind sham-controlled within subjects crossover design in which all participants received real and sham tDCS. An intersession interval was at least two weeks for avoiding any carryover effects due to stimulation. Visual analogue scales (1-10 score) related to food craving were measured before and after tDCS session, respectively. All participants were scanned while they were viewing 100(50 high-calories food/50 low-calories food) picture stimuli during an fMRI assessment. ROI analysis was conducted using a pre-determined region of interest (ROI), especially the nucleus accumbens(NAcc) implicated in reward and motivation processing. Parameter estimates of the high vs. low contrast image were extracted from the NAcc ROI. Paired t-tests on behavioral ratings (e.g., fullness) and neural activation (i.e., NAcc response to high-calories vs low-calories food pictures) were used to compare the real vs. sham tDCS sessions. Results:There were statistically significant differences in the fullness score ($t(10)=2.246$, $p<0.05$) between real and sham stimulation. Food preference score for high calorie-food that acquired in scanner was not different between real and sham tDCS condition($t(13)=-1.309$, p=,213). RoI analysis revealed that left accumbens area activity for high-calories food is greater after the sham tDCS session than real session ($t(12)=-2.555$, $p=.025$). However, there was statistical correlation with right NAcc activation and food preference rating for each of food cues($r=.592$, $p<.05$). Conclusion: Brain stimulation with tDCS modulated eating behaviors and NAcc activation. Our study implies that the brain stimulation with tDCS represents a promising option for treating obesity in humans by modulation of neural circuits associated with reward and motivation in response to food cues.

Disclosures: **M. Lee:** None. **K. Lee:** None. **J. Kim:** None. **H. Baek:** None. **H. Choi:** None.

Poster

687. Other Psychiatric Disorders

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Program #/Poster #: 687.07/W33

Topic: G.07. Other Psychiatric Disorders

Support: Charles Bullard Fellowship in Forest Research

Title: Forests and brain health: Emerging benefits

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Abstract: Forests are essential. They emerged more than 300 million years ago and are incredibly resilient - they have recovered from catastrophic volcanic eruptions, ice ages, and meteor strikes. Forests offer exercise, solace, medicines and biodiversity; new species, potentially the source of new medicines, are still being discovered. Furthermore, natural climate solutions are essential in mitigating climate change and the biggest potential for additional negative carbon emissions lies in forest-based sequestration. To this end, proforestation is a purposeful policy that maximizes natural climate solutions by growing existing forests to take full advantage of many ecosystem values - biological carbon sequestration, flood resilience, biodiversity, and health - including brain health. Unlike more common forest-based strategies to combat climate change, i.e. afforestation and reforestation, proforestation does not require significant additional land, time, money or labor to yield immediate and lasting benefits to the planet and to people. The brain health benefits of proforestation are expected to increase significantly in the coming decades, and the National Health Service has a motto “growing forests for health.” With this in mind, the positive impact of forests on brain health cannot be overlooked: we face increasing costs for disorders ranging from Alzheimer’s disease to addiction. Lifestyle modifications are effective and successful, and forests offer co-benefits of exercise, mindfulness, stress reduction and more - naturally. Here we review recent quantitative research on benefits in healthy people and special populations, such as U.S. veterans and at risk teens, and identify strategies for combining proforestation with brain health benefits in communities across the country. In the U.S. one option is the Old Growth Forest Network, a national network of more than 90 protected native forests in 22 states. Future research should focus on gaps in understanding and on identifying more intact protected forests across the landscape to optimize forest-based brain health benefits and benefit current and future generations.

Disclosures: S.A. Masino: None.

Poster

687. Other Psychiatric Disorders

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Program #/Poster #: 687.08/W34

Topic: G.07. Other Psychiatric Disorders

Support: National Institute of Mental Health (1U01MH108148-01 L.H.)
Dean's Challenge Award from the Accelerating Innovation and Discovery in Medicine Program of the University of Maryland School of Medicine (S.A.A., L.H.)
UMB/UMCP Center for Health-related Informatics and Bioimaging (S.A.A.)
Intramural Research Program of the National Institute of Mental Health (F.J.M)

Title: Molecular, cellular, neurodevelopmental, neuroimaging, and neurocognitive consequences of rare variants in the schizophrenia risk gene SETD1A

Authors: *R. OSHONE[1], M. CORTES-GUTIERREZ[1], A. CASELLA[2], E. HUMPHRIES[3], C. COLANTUONI[1,4], S. DETERA-WADLEIGH[5], T. POLLIN[6,7], B. MITCHELL[6,7], A. SHULDINER[6], F. MCMAHON[5], L. HONG[8,9], S. AMENT[1,8,9];
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Abstract: Despite progress from large genome-wide association study (GWAS) consortia, common risk variants for schizophrenia (SCZ) have proven difficult to follow up for biological and clinical translation, primarily due to their small effects. The discovery of rare variants with large effects on neuropsychiatric disease risk has gained momentum through sequencing studies. The first gene implicated and replicated by exome sequencing in SCZ is a chromatin remodeling gene called SET Domain Containing 1A (*SETD1A*). Many distinct rare loss-of-function and missense variants in *SETD1A* collectively confer substantial risk for SCZ. SETD1A is a histone methyltransferase, responsible for methylation of lysine 4 on the histone 3 tail (H3K4me3), an important marker of active promoters and enhancers. However, the mechanisms by which *SETD1A* variants lead to SCZ risk are unknown. Here, we integrated multiple cutting-edge technologies to trace molecular, cellular, neurodevelopmental, neuroimaging, and neurocognitive consequences of rare *SETD1A* variants. Our analyses of publicly available and newly generated RNA-seq and single-cell RNA-seq data from the developing and adult human cortex revealed that *SETD1A* is most highly expressed during mid-fetal brain development, specifically in radial glia, the neural stem cells (NSCs) that give rise to cortical excitatory neurons (ENs). CRISPR/Cas9 knockout of *SETD1A* in human embryonic stem cells (hESCs) revealed increased apoptosis and decreased proliferation. RNA-seq analysis of *SETD1A* knockout hESC-derived NSCs revealed that *SETD1A* is required for the expression of a gene module that *in vivo* is expressed in proliferative NSCs early in brain development. We hypothesized that *SETD1A* variants cause decreased proliferation of radial glia *in vivo*, which would result in reduced numbers of cortical ENs. Consistent with the hypothesis, data from the UK Biobank and Amish Connectome Project revealed that protein-coding variants in *SETD1A* are associated with decreased cortical thickness, a well-known deficit in SCZ cases, as well as deficits in cognition. Overall, our results suggest a critical role for *SETD1A* in the development of the human cortex and support a causal path from gene to brain to behavior underlying SCZ risk.

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Poster

687. Other Psychiatric Disorders

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Topic: G.07. Other Psychiatric Disorders

Support: NIH Grant MH099393
NIH Grant MH104673

Title: Alteration in resting-state functional connectivity of the anterior cingulate cortex in individuals with greater lifetime history of aggression

Authors: M. GOTRA[1], *S. KEEDY[2], J. WREN-JARVIS[2], R. LEE[2], E. F. COCCARO[3]; [1]Psychology, Rosalind Franklin Univ. of Med. and Sci., North Chicago, IL; [3]Psychiatry and Behavioral Neurosci., [2]Univ. of Chicago, Chicago, IL

Abstract: Background: Aggression and impulsivity have been associated with structural and neurochemical properties of the anterior cingulate cortex (ACC), as well as the amygdala and orbito-frontal cortex. However, no prior work has assessed functional connectivity of these brain areas at rest in relation to aggression. In the present study, we aimed to address this gap, beginning with a focus on the ACC, a node of the default mode network, the most robustly identifiable network in resting state functional magnetic resonance imaging (fMRI) studies. **Methods:** Resting state fMRI and structural T1 weighted images were collected on subjects who were also assessed with the Lifetime History of Aggression (LHA) scale, a commonly used measure of trait aggression. Subjects included those diagnosed with intermittent explosive disorder (IED; n=22) and healthy controls (n=23), allowing for a wide range of LHA scores for the analysis. Mean age was 34.8 years (59% female) for the IED group and 29.6 years (52% female) for healthy controls. Following standard preprocessing, seed-based connectivity maps, with ACC as the seed, were calculated using the CONN toolbox. Regression analyses were conducted using these connectivity maps and scores from the LHA, controlling for age and sex. Significant results were identified at $p < 0.0125$, corrected for multiple comparisons. **Results:** Greater LHA scores were associated with significantly reduced connectivity between the ACC and several other brain regions (no increased connectivity was identified). These regions included the posterior cingulate cortex (PCC), precuneus, a cluster at the left temporo-parietal-occipital junction (angular gyrus, superior occipital cortex, posterior supramarginal gyrus), and the left thalamus. **Conclusion:** Participants with more life history of aggression had weaker connectivity between the ACC and brain regions responsible for sensory and social processing.

Additionally, greater aggression was associated with weaker connectivity in the ACC to the PCC and precuneus, key components of the default mode network. These results suggest that increased lifetime aggression, which characterizes those diagnosed with IED, is associated with dysfunction in key networks associated with stimuli saliency and self-relevant processing, in line with prior studies and expanding the body of knowledge to include alterations detectable in the resting state.

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Poster

687. Other Psychiatric Disorders

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 687.10/W36

Topic: G.07. Other Psychiatric Disorders

Title: Sensitivity, biases and multisensory integration in the visual and haptic perception of elliptical shapes in patients with anorexia nervosa

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Abstract: A key feature of Anorexia Nervosa (AN) is a distorted perception of the body shape. Recent studies on Eating Disorders (EDs) showed that AN patients exhibit various sensory and perceptual deficits in the visual and tactile modalities. In this study, we investigated visuo-haptic integration in AN patients using Helbig and Banks (2007)'s paradigm, which allows one to assess the weight given to each sensory modality and whether the two sensory modalities are integrated optimally. The study included three groups of participants: a Healthy Control (HC) group (N=18), a restricting type AN group (N=10), and an intermediate group of individuals with body concerns (assessed with the Body Shape Questionnaire) showing psychological features commonly associated with ED (assessed with the Eating Disorders Inventory 2), with normal BMI and no diagnosis. The stimuli consisted in high-relief ellipses with variable axes lengths. For each participant, we measured the Point of Subjective Equality (PSE), i.e. the eccentricity of the ellipses that were perceived as circular, and the discrimination threshold (DL) between vertically and horizontally elongated ellipses in a haptic condition, a visual condition and three bimodal conditions where the visual and haptic cues could be consistent or not. We found that AN patients discriminated elliptical shapes less precisely than the other groups and that they perceived ellipses as more horizontally elongated than the HCs with the intermediate

group in the middle. Our results confirm that haptic and visual information is optimally integrated in the control group. For the two other groups, the evidence is compatible with the optimal integration and best modality hypotheses. The increase DLs provide support for the idea that the restricted diet of individuals might impair normal function of peripheral sensory apparatus but they do not explain the observed biases when judging the shape of the ellipses. To our knowledge, this is the first study that demonstrates a bias in the perception of the shapes that do not represent body parts in AN.

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Poster

687. Other Psychiatric Disorders

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Program #/Poster #: 687.11/W37

Topic: G.07. Other Psychiatric Disorders

Support: NARSAD Grant 2389142

Title: Neural correlates of emotion regulation in adults with ADHD

Authors: *J. J. CAPELLA[1], Y. HUNG[1], S. D. HOULIHAN[1], R. HOAGLAND[1], M. UCHIDA[2], S. GAILLARD[1], J. D. GABRIELI[1], J. BIEDERMAN[2];
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Abstract: Attention-Deficit/Hyperactivity Disorder (ADHD) is a lifelong neurobehavioral disorder conventionally characterized by inattentive, hyperactive, and impulsive behaviors. One symptom set, poor emotion regulation (ER), an executive function deficit in regulating negative emotions, has received increasing attention in recent ADHD research. Deficits in ER can lead to significant impairments in the ability to handle daily life stress, resulting in irritability, low frustration tolerance, and emotional outbursts. However, little is known about the neural mechanism and behavioral manifestation of ER in ADHD, particularly for adults. Using multi-modal neuroimaging methods and rigorous behavioral assessments, we aim to provide a neural profile of ER in adults with ADHD. Specifically, we explored the relationship between ER, working memory, and mindfulness in 33 adults with ADHD and healthy age-matched controls. Participants (mean age = 28.0, *SD*=6.9) completed measurements of working memory (CANTAB Spatial Working Memory Task) and mindfulness (Cognitive and Affective Mindfulness Scale, Mindful Attention Awareness Scale, and others). In a functional magnetic resonance imaging (fMRI) session, participants were instructed to actively alter their perception of negative stimuli from the IAPS image set. We obtained functional (fMRI and resting fMRI) and structural (T1 and diffusion tensor imaging) data to provide a full neural profile of ER in

ADHD. Pilot publications and preliminary results indicate activation in the medial and lateral prefrontal cortex (including the anterior cingulate cortex) during reappraisal, as well as an attenuated amygdala response. We hypothesize that this amygdala downregulation is attenuated in participants with ADHD, and other regions may be recruited as compensatory mechanisms. Characterizing the neural response to emotional reappraisal strategies can lead to a better understanding of emotion regulation and its relationship with other functional impairments associated with ADHD. By providing a full neural profile of emotional dysregulation in adults with ADHD, we hope to provide insights for improved clinical assessments and treatment. Understanding the neural mechanisms and behavioral manifestations of ER could lead to improvements in psychotherapy interventions for adults with ADHD, with the ultimate goal of improving the quality of life for this population.

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Poster

687. Other Psychiatric Disorders

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Topic: G.07. Other Psychiatric Disorders

Support: Fralin Biomedical Research Institute

Title: High rates of temporal discounting among individuals with heightened dissociative symptomatology

Authors: *J. C. BASSO, M. K. SATYAL, A. METPALLY, W. K. BICKEL;
Virginia Tech. Univ., Roanoke, VA

Abstract: Dissociative disorders are characterized by an involuntary escaping of reality, whereby the individual feels detached or disconnected from their thoughts, identity, consciousness, or memory. The prevalence of these dissociative states is quite common (approximately 50% of adults in the United States report at least one or more depersonalization/derealization episode in their lifetime); however, the diagnosable disorder occurs in only 2% of the population. Dissociative states often develop in response to traumatic events, with positive associations occurring between symptom levels and number of adverse childhood experiences, especially emotional abuse and neglect. Delay discounting measures the process by which the value of a reward declines as a function of its delay from the present. A high discounting rate indicates an excessive preference for immediately available rewards, and a disregard for future, potentially negative consequences. Individuals with a high rate of discounting show a propensity for a variety of maladaptive health behaviors including drug and

alcohol use, unhealthy eating, physical inactivity, and irresponsible spending. Limited previous research has examined the relationship between discounting rates and affective states, and no studies to date have tested the hypothesis that steeper discounting is related to higher levels of disassociation. Data was collected via Amazon Mechanical Turk from n=221 adults (ages 18 to 45). A 5-trial adjusting delay discounting task was used to assess discounting rate, and the Cambridge Depersonalization Scale was used to assess level of dissociative symptomatology. As hypothesized, higher rates of discounting were associated with greater levels of depersonalization ($r(221)=0.163$, $p=0.007$). This effect was seen across all subscales including anomalous body experience ($r(221)=0.185$, $p=0.003$), emotional numbing ($r(221)=0.156$, $p=0.010$), anomalous subjective recall ($r(221)=0.120$, $p=0.037$), and alienation from surroundings ($r(221)=0.139$, $p=0.019$). Probability discounting, a negative behavioral control, did not show any such associations with dissociative state ($r(221)=0.055$, $p=0.419$). These results suggest that temporal discounting may be one of the psychological mechanisms through which dissociative states operate.

Disclosures: **J.C. Basso:** None. **M.K. Satyal:** None. **A. Metpally:** None. **W.K. Bickel:** None.

Poster

687. Other Psychiatric Disorders

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Program #/Poster #: 687.13/W39

Topic: G.07. Other Psychiatric Disorders

Support: NIH Grant DP2MH119735
NSF Graduate Research Fellowship
NIMH Grant K08MH111750

Title: Graph theory analysis of multimodal neuroimaging data in high-functioning adults with autism spectrum disorder

Authors: *R. AYUB[1], R. FLORES[2], L. FUNG[2], M. SAGGAR[2];
[1]Bioengineering, [2]Psychiatry and Behavioral Sci., Stanford Univ., Stanford, CA

Abstract: Complex behavioral abnormalities in Autism Spectrum Disorder (ASD) suggest a disruption in the underlying brain networks. An important question that remains open is whether this disruption is caused by changes in structural connectivity, functional connectivity, or a combination of both. Past neuroimaging studies have found alterations in functional and structural connectivity in subjects with ASD, but they have primarily focused on one neuroimaging modality at a time. It is a well-known fact that both structural and functional connections work together to facilitate cognitive processes, therefore more combined neuroimaging studies are needed for an integrated understanding of brain connectivity. Here, we

conducted a multimodal neuroimaging investigation of high-functioning adults with ASD and age-matched typically developing (TD) controls. Functional networks were created from subjects' (n = 16 ASD, n = 15 TD) resting state functional MRI (rs-fMRI) data by thresholding the ROI correlation matrix at various levels of graph density. Structural networks were similarly created from subjects' (n = 28 ASD, n = 28 TD) tractograms derived from diffusion weighted imaging (DWI) data. Communities in the functional and structural connectome were assigned based on known large-scale resting state networks. We found that TD adults exhibited greater modularity in their functional connectomes than adults with ASD across all graph density thresholds. Interestingly, the structural connectomes showed no statistically significant difference in this same metric. There were no statistically significant differences in the clustering coefficient, global efficiency, and characteristic path length in either the functional or structural connectomes. Our preliminary results suggest that reduced modularity in the functional connectome may suggest a topological reorganization of functional networks in adults with ASD. Lack of group differences in the structural connectome suggest that functional data may be more indicative of changes in brain connectivity in adults with ASD.

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Poster

688. Mechanisms Underlying Reward Dependence

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 688.01/W40

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant AA016179
NIH Grant AA016828

Title: OPRM1 genotype-dependent opioid-ethanol interactions in male rhesus monkeys

Authors: J. S. OVERTON, T. PAREEK, J. E. COOK, R. ANTONYRAJ, *D. M. PLATT; Univ. of Mississippi Med. Ctr., Jackson, MS

Abstract: Opiate and alcohol addictions separately are widespread public health problems that are associated with individual differences in opioid neurotransmission. A single nucleotide polymorphism, A118G, in the human mu opioid receptor gene (OPRM1) may change the way in which the endogenous opioid system mediates reward via the mesolimbic circuitry. The 118G variant is linked to higher levels of alcohol-induced euphoria and an increased risk of opiate and alcohol addiction when compared to the A118 variant. A similar polymorphism in rhesus monkeys (C77G) mirrors the human mutation and its corresponding physiological and behavioral phenotypes. There is growing evidence that opioids frequently are co-abused with alcohol and that this polydrug abuse can increase lethality of the individual drugs, as well as

decrease the effectiveness of opioid maintenance therapy. However, the extent to which OPRM1 genotype influences the drug interaction remains unknown. In the present study, male rhesus monkeys genotyped for the C77G polymorphism (N's: 4 C/C; 4 G/G) were given limited, daily, concurrent access to 4% w/v ethanol solution and water under a fixed-ratio schedule. Once daily ethanol intake was stable, monkeys received pretreatments of saline, morphine (0.03-0.3 mg/kg) or fentanyl (0.001-0.01 mg/kg) prior to the session. Compared to vehicle (saline), both opioids failed to enhance ethanol drinking in C/C animals and even suppressed intake at their highest doses. In G/G animals, morphine appeared to enhance ethanol drinking, while fentanyl did not alter consumption. The results indicate a clear effect of genotype in that C/C animals were more sensitive to the suppressing effects of opioids compared to G/G animals. To the extent that the decreases reflect non-specific behavioral effects, this result suggests that these drug combinations would have more severe side effects in A118-carrying humans. In the G/G animals, the results indicate a clear effect of drug on modulation of ethanol consumption. Although the reasons underlying the observed differences are not clear, they could reflect differences in drug efficacy, duration of action, or signaling bias.

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Poster

688. Mechanisms Underlying Reward Dependence

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Topic: G.08. Drugs of Abuse and Addiction

Support: Department of Anesthesiology and Critical Care (GAB), James Battaglia Endowed Chair in Pediatric Pain Management (GAB)
National Aeronautics and Space Administration 80NSSC17K0060 (AJE)
CHOP Department of Anesthesiology and Critical Care Development Funds (AJE)

Title: A model of chronic voluntary oral oxycodone self-administration in female and male rats

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Abstract: The opioid abuse epidemic poses major challenges for health and socioeconomic systems. The increased prescription of opioids - such as oxycodone - has fueled diversion of

these medications, increasing the number of people who have access to these highly-addictive drugs. For optimal translational relevance, a preclinical model that recapitulates key aspects of prescription opioid abuse in humans is needed. Here we present a novel oral oxycodone self-administration paradigm in rats that results in voluntary intake, long-term opioid exposure, and measurable levels of dependence and motivation to take drug. Adult male and female Long-Evans rats were given unlimited, home cage access to two bottles: for Control rats, both bottles contained water; for Experimental rats, one bottle contained water with Oxycodone. Virtually all Experimental rats voluntarily drank oxycodone (targeted daily dose: 10 mg/kg/day) and escalated their intake over 22 weeks. Females self-administered twice as much oxycodone as males, leading to greater levels of oxycodone in blood, and engaged in more gnawing behavior. Given the continuous access to oxycodone, it is perhaps not surprising that female and male rats showed no signs of spontaneous withdrawal. However, precipitated withdrawal (naloxone 1 mg/kg) revealed high levels of dependence in both sexes in the total withdrawal score, as well as in individual behaviors, such as burrowing, teeth chattering, high walking, diarrhea, and weight loss (e.g. 4x decrease in females and 2x in males compared to their respective Controls). To assess the motivation to drink oxycodone, citric acid at ascendant concentrations (1, 3, and 5 mM) suppressed the intake of oxycodone (Experimental rats) and the intake of water (Control rats); however Experimental rats returned to pre-citric acid preference levels whereas Controls rats did not. Thus, our model reproduces in female and male rats many of the features of human oxycodone abuse, and provides a paradigm for both understanding mechanisms that mediate long-term voluntary drug use and for exploring potential treatment options.

Disclosures: **G. Zanni:** None. **M.J. DeSalle:** None. **H.M. Detsch:** None. **G. Khabib:** None. **S.J. Simmons:** None. **A.A. Dougher:** None. **G.A. Barr:** A. Employment/Salary (full or part-time):; Department of Psychology, University of Pennsylvania. **A.J. Eisch:** A. Employment/Salary (full or part-time):; Department of Neuroscience, Perelman School of Medicine, University of Pennsylvania.

Poster

688. Mechanisms Underlying Reward Dependence

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 688.03/W42

Topic: G.08. Drugs of Abuse and Addiction

Support: R01DA019958

Title: Balanced opioids provide excellent analgesia and reduced side effects

Authors: *J. L. WHISTLER[1], L. HE[3], S. W. GOODING[2], A. GAUR[1];
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Abstract: There remains an ongoing debate as to whether “biased” or balanced” agonists at the mu opioid receptor (MOR) will produce analgesics with reduced side effects. Endorphins and enkephalins, the endogenous ligands at the MOR are balanced agonists at the MOR, signaling to G-protein and effectively engaging beta-arrestins. On the other hand, morphine and all its derivatives are significantly biased for G protein signaling. Here we demonstrate that a modified MOR that signals in a “balanced” way to both G-protein and arrestin produces excellent analgesia, reduced analgesic tolerance, reduced physical and affective dependence, reduced ability to promote compulsive drug seeking behavior, and reduced effects on cognitive flexibility after long term abstinence in knock in mice expressing this altered receptor. We also demonstrate that MOR engagement with arrestin does not increase opioid-induced respiratory depression. Taken together these data suggest that “balanced” opioid agonists with a lack of signaling bias that mirrors that of the endogenous ligands could provide excellent analgesia, no increase in respiratory effects and reduced abuse liability.

Disclosures: J.L. Whistler: None. **L. He:** None. **S.W. Gooding:** None. **A. Gaur:** None.

Poster

688. Mechanisms Underlying Reward Dependence

Location: Hall A

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Program #/Poster #: 688.04/W43

Topic: G.08. Drugs of Abuse and Addiction

Support: 2017R1D1A1A02018695
WISET-2018-551
2016R1D1A1B02010387

Title: Per2 influences locomotor sensitization and reward effects against morphine through dopamine transporter and opioid receptor activities in mesolimbic pathways

Authors: *M. KIM, C. BOTANAS, R. CUSTODIO, L. SAYSON, A. ABIERO, H. LEE, J. CHEONG, H. KIM;
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Abstract: Complex interactions between endogenous and exogenous factors have been proposed to explain the mechanism underlying drug addiction. The genetics underlying circadian rhythms are representations of endogenous factors that influence addiction. Previously, we found that *Per2*-knockout mice and *Per2*-overexpressed mice showed different response towards the rewarding effects of methamphetamine through dopaminergic system in the striatum. Thus, the goal of this study is to investigate the role of *Per2* in drug addiction. We observed locomotor sensitization responses to morphine administration and rewarding effects through a conditioned place preference (CPP) test in *Per2*- knockout (KO) and overexpressed (OE) mice. In addition,

the withdrawal signs were assessed on the 1st withdrawal day after 7 days repeated treatments of morphine. We also investigated the expression levels of opioid receptors (kappa, mu and delta) and dopamine-related genes (DRD1, DRD2, DAT, and TH) in VTA, striatum (NAc), and PFC using qPCR, western blot, and immunofluorescence. *Per2*- KO mice showed increased locomotor sensitization and rewarding effects of morphine compared to WT mice, whereas *Per2*-OE mice showed the opposite. In addition, the results of withdrawal signs were consistent with the behavioral changes in *Per2* KO, OE and WT mice. Moreover, *Per2*-KO mice showed higher expression levels of mu and delta opioid receptors in VTA and lower DAT level in striatum (NAc) than WT mice, while the opposite results were observed in *Per2*- OE mice. Taken together, *Per2* expression level may influence the addictive effects of morphine through mu and delta opioid receptors in VTA and DAT activities in striatum of mice.

Disclosures: M. Kim: None. **C. Botanas:** None. **R. Custodio:** None. **L. Sayson:** None. **A. Abiero:** None. **H. Lee:** None. **J. Cheong:** None. **H. Kim:** None.

Poster

688. Mechanisms Underlying Reward Dependence

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Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 688.05/W44

Topic: G.08. Drugs of Abuse and Addiction

Support: R21 DA044757-01

Title: Next-gen sequencing of RiboTag mRNA from striatal microglia identifies gene sets associated with morphine escalation and naloxone precipitated withdrawal

Authors: *K. COFFEY, A. J. LESIAK, R. MARX, E. K. VO, J. F. NEUMAIER; Psychiatry and Behavioral Sci., Univ. of Washington, Seattle, WA

Abstract: Many facets of opioid dependence contribute to the clinical and social crisis that we are now facing. In addition to the loss of control over drug use that accompanies extensive exposure to opioids, the severity of withdrawal is a major barrier that stops individuals who would like to discontinue opioids from detoxing. Furthermore, these symptoms can precipitate relapse to drug taking in order to alleviate withdrawal. In this experiment we investigated the contribution of microglia to morphine exposure and naloxone precipitated withdrawal. To accomplish this, we utilized RiboTag, a technique which allows for isolation and analysis of RNA that is actively undergoing translation in a specified set of cells. We used male and female transgenic CX3CR1-Cre/RiboTag mice that express HA-tagged rpl22 exclusively in resident microglia. These mice were administered a rapidly escalating, tolerance inducing, non-contingent morphine schedule (versus saline) followed by naloxone-precipitated withdrawal (versus saline), then at 4 hours after naloxone (or saline) we sacrificed the mice and

immunopurified the ribosome-associated RNA from microglia and then analyzed the RNAs undergoing translation using RNAseq. While there are many individual genes that are differentially expressed during morphine exposure and withdrawal, this report focuses on gene set level changes. Gene set enrichment analysis (GSEA) revealed decreases in genes related to neuronal projection guidance, and increases in genes related to aberrant protein folding after escalated morphine exposure. These results suggest escalated morphine exposure forces microglia to reduce some of their healthy-state roles, like aiding neuronal projections, and increase their role dealing with aberrantly folded proteins. During naloxone precipitated withdrawal, microglia massively increase expression of phosphodiesterases. These changes to the translatome of microglia only represent a very narrow window in time, so a second wave of animals will be run to be sacrificed at varying time points after withdrawal. Animals will be sacrificed at 0, 2, 8, and 24 hours after naloxone precipitated withdrawal, and changes to genes of interest will be quantified using RT-qPCR and in-situ hybridization. Careful analysis of these genes should provide new mechanistic understanding of how microglia respond to opioid withdrawal and could lead to the identification of novel target genes or gene sets for promoting adaptive microglial responses and inhibiting detrimental microglia responses.

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Poster

688. Mechanisms Underlying Reward Dependence

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Program #/Poster #: 688.06/X1

Topic: G.08. Drugs of Abuse and Addiction

Support: U01DA04439902 (G.P; T.J.G)

Title: Genetic differences in nicotine withdrawal-induced learning deficits and nicotine metabolism across inbred mouse strains

Authors: *S. M. MOONEY-LEBER[1], L. R. SEEMILLER[1], L. R. GOLDBERG[1], P. SMITH[2], Y. TIAN[3], A. PATTERSON[3], G. PELTZ[4], T. J. GOULD[1];
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Abstract: Nicotine withdrawal produces cognitive deficits and changes in affect, which are associated with an inability to quit. Human studies have shown that these deficits are highly heritable, yet the underlying genetic variants have not been identified. Our lab has previously demonstrated that nicotine withdrawal in mice produces cognitive deficits in fear conditioning.

Here we utilized a comprehensive mouse inbred strain panel to assess the genetic variation associated with nicotine-evoked cognitive deficits. Male mice from 21 inbred strains (C57BL/6J, BALB/cJ, CBA/J, FVB/NJ, NOD/ShiLtJ, A/J, C3H/HeJ, DBA/2J, AKR/J, DBA/1J, 129S1/SvlmJ, SJL/J, SWR/J, LP/J, BTBR T+ ltpr3tf/J, NZB/BINJ, SM/J, MA/MyJ, 129S4/SvJaeJ, 129S8/SvEvNimrJ,129-Elite) received either chronic saline or nicotine (12.6 or 18 mg/kg per day for 12 days) via osmotic minipump, and then were tested for learning deficits using hippocampal-dependent contextual fear conditioning. We identified a significant effect of strain ($F_{17, 465}$ = 73.678, p = 0.0001), and a strain by treatment interaction ($F_{34, 465}$= 1.544, p = 0.028). Moreover, we found deficits in fear conditioning after chronic nicotine in NZB/BINJ (at 12.6 mg/kg/day) and C57BL/6J (at 18 mg/kg/day). Interestingly, we found enhancement of fear conditioning in AKR/J and SJL/J at after chronic treatment with 12.6 and 18 mg/kg/day, both of which could be maladaptive responses. In addition, due to the known role of nicotine metabolism in mediating withdrawal severity, we assessed nicotine metabolism in male C57BL/6J and NOD/ShiLtJ mice by collecting urine and serum after acute nicotine treatment (1 mg/kg). Nicotine metabolites were quantified using liquid chromatography-mass spectrometry (LC-MS), and metabolism-related genes were identified using sequences from Sanger Institute Mouse Genomes Project. C57BL/6J and NOD/ShiLtJ strains had notable differences in nicotine metabolite levels, and non-synonymous mutations were found in *Cyp2f2*, *Aox1*, and *Cyp3a44*. These data demonstrate markedly different responses to nicotine in commonly used inbred mouse strains and provide a foundation for future study of genetic variants underlying cognitive deficits during nicotine withdrawal.

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Poster

688. Mechanisms Underlying Reward Dependence

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 688.07/X2

Topic: G.08. Drugs of Abuse and Addiction

Support: CAPES Foundation
CNPq

Title: Behavioral response in cocaine-sensitized female rats is related to lower GABA levels in the medial prefrontal cortex

Authors: *L. FREESE[1], M. FRAGA DE SOUZA[1], G. CALETTI[4], M. S. NIN[1,4,6], G. K. CURY[2], V. F. PERES[1], R. GOMEZ[4,5], H. M. T. BARROS[1,3];
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Abstract: Cocaine sensitization is greater in female than in male rats and we found that estradiol enhances this behavioral response (Souza et al, 2014). Here, we investigated the *in vivo* changes in extracellular GABA, glutamate and taurine levels after cocaine sensitization in the medial prefrontal cortex (mPFC) of gonadal intact (SHAM) or ovariectomized (OVX) female rats. Adult (±90 post-natal day (PND)) female Wistar rats were bilaterally ovariectomized or sham-operated and randomly assigned to control (CTR), acute (ACT) or repeated (RPT) cocaine administration (15 mg/kg, i.p.) groups, following the classical model of sensitization. After a 10-day wash-out period and 7 days from stereotaxic surgery to implant a guide-canulae in the mPFC, the ACT and RPT groups received a challenge dose of cocaine (15 mg/kg, i.p.). Locomotion was monitored and microdialysis was conducted over 2.5 h to determine extracellular GABA, glutamate and taurine levels. The major finding is that SHAM-RPT group demonstrated behavioral sensitization, and correspondingly did not show a peak of GABA efflux at 30 min At the same time, OVX-RPT rats did not show sensitization and showed a peak of GABA efflux at 30 min. The sham group did show a delayed and permanent increase in GABA efflux and this effect was not mechanistically related to the behavioral response. Acute and repeated cocaine administration increased taurine at 60 min in SHAM and OVX, respectively. In addition, changes in glutamate were measured, and the delayed increase levels only in the ACT-OVX group were observed. The current data do not support a role for a cocaine-mediated stimulation of excitatory transmission within the mPFC via glutamate in the development of behavior sensitization in female rats. Thus, this aspect still needs to be better elucidated. The decrease in GABA levels in the mPFC of SHAM rats was related to a suppression of cocaine sensitization behavior and this effect seems to be dependent of estrogen. The taurine response in the OVX-RPT showed a later and shorter direction of changes, similar to the GABA. The gender difference of the neurobiological basis for the cocaine sensitization is still poorly characterized and these data are the first to typify the levels of some important neurotransmitters in sensitized-female rats.

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Poster

688. Mechanisms Underlying Reward Dependence

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 688.08/X3

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant P50DA037844

Title: Effects of environmental enrichment on behavioral measures of sensation/novelty seeking in inbred Fischer 344 and Lewis rats

Authors: *K. ISHIWARI[1], O. POLESSKAYA[2], A. A. PALMER[2], J. B. RICHARDS[1];
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Abstract: Sensation/novelty seeking (SNS) is a heritable trait and a vulnerability factor for drug abuse. Inbred Fischer 344 (F344) and Lewis (LEW) rats have been used as a model of genetic vulnerability to drug abuse, based on their innate differences in sensitivity to the reinforcing effects of drugs of abuse and responsiveness to stress. We previously observed robust differences between the two strains for two behavioral measures of SNS, locomotor response to novelty and light reinforcement tests [1]. Environmental enrichment produces a variety of beneficial neurobehavioral effects in animal models of neuropsychiatric disorders including drug abuse. The present study examined the effects of environmental enrichment during adolescence on the two behavioral measures of SNS in adult male F344 and LEW rats. Starting on about postnatal day 30, male F344 and LEW rats were housed either in pairs in standard plastic laboratory cages or in groups of 16 in a complex environment consisting of a large multi-level cage filled with pet toys. After six weeks of differential housing, the four groups (2 strains × 2 housing conditions, n=16 each) were compared for their performance on locomotor response to novelty and light reinforcement tests. In the former, rats were tested for locomotor activity for 36 min in dark plastic chambers equipped with an infrared motion-sensor system. Unlike our previous finding, we found no significant strain differences in standard-housed rats in the total distance traveled or rearing, while locomotor activity was significantly reduced in both F344 and Lewis rats reared in the complex environment compared to their standard-housed counterparts. In the light reinforcement test, following six daily habituation sessions in dark chambers, rats were tested for snout poke responding for light onset in six 18-min daily sessions. In accordance with our previous finding, standard-housed F344 rats responded for light significantly more than standard-housed LEW rats, while both F344 and LEW rats reared in the complex environment responded for light significantly less than their standard-housed counterparts, with no difference between enriched F344 and enriched LEW rats. Thus, our results indicated that environmental enrichment attenuated SNS phenotypes and obliterated differences between the two inbred strains observed in standard-housed animals, suggesting that complex rearing environments can buffer against the genetic risk for drug abuse.
1. Richards JB, Lloyd DR, Kuehlewind B, Militello L, Paredez M, Solberg Woods L, Palmer AA (2013). Strong genetic influences on measures of behavioral-regulation among inbred rat strains. Genes Brain Behav. 12: 490-502.

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Poster

688. Mechanisms Underlying Reward Dependence

Location: Hall A

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Program #/Poster #: 688.09/X4

Topic: G.08. Drugs of Abuse and Addiction

Support: CAPES
CNPq (HMTB-1B Researcher Grant)

Title: Behavioral effects of repeated intermittent ethanol access and withdrawal on male and female rats selectively bred for high immobility in the forced swim test

Authors: *F. B. ALMEIDA[1,2], L. M. B. DA COSTA[2], N. HEIDRICH[1,2], A. R. FONSECA[2], P. R. FERNANDES[1,2], F. F. S. DA SILVA[1,2], L. FREESE[1,2], M. S. NIN[4,5,2], H. M. T. BARROS[1,3]; [1]PPG Ciências da Saúde: Farmacologia e Toxicologia, [2]Lab. Neuropsicofarmacologia, [3]Depto. Farmacociências, UFCSPA, Porto Alegre, Brazil; [4]Ctr. Universitário Metodista do IPA, Porto Alegre, Brazil; [5]PPG Ciências Biológicas: Farmacologia e Terapêutica, UFRGS, Porto Alegre, Brazil

Abstract: Alcohol abuse is associated with psychiatric disorders such as depression, though the mechanisms by which these conditions are linked remain incompletely elucidated. One hypothesis is that individuals with a higher individual susceptibility (i.e. genetic construct) to develop depression would be at higher risk of alcohol abuse. The acute ethanol (EtOH) withdrawal produces behavioral manifestations that can be modeled in animals. The main objective of this study was to evaluate behavioral changes during acute periods of abstinence at low doses of EtOH in male and female rats selectively bred to present high depressive-like behaviors, with an EtOH forced diet model. Forty-two adult (PND 40) Wistar rats (males and females) from a high immobility line previously developed in our laboratory (Almeida *et al*., 2018) were submitted to EtOH self-administration from a forced diet (Sustagen® meal) for 21 continuous days (induction phase), where half the rats received an EtOH-containing solution (8% v/v) and the other half received an isocaloric control solution. After this period, the EtOH animals were submitted to intermittent 24 h cycles switching between withdrawal (control solution was offered) and EtOH availability [repeated intermittent EtOH access (RIEA) phase] (Costa *et al*., 2015) for 14 days. In the last day of withdrawal, the forced swim test (FST) was performed after 6 hours without access to EtOH. We observed that that EtOH-exposed rats of both sexes initially consumed more solution than control rats, but this was normalized towards the end of the induction phase. During the RIEA phase, males and females consumed more solution in EtOH re-exposure days in comparison to EtOH withdrawal days and control rats. Partial data analysis of FST behaviors using a Two-Way ANOVA showed a suggestive result regarding EtOH exposure ($P = 0.067$) where EtOH-receiving rats showed a lower immobility

duration than controls. We obtained very similar results in male and female rats regarding EtOH intake and behaviors in the FST, indicating that gender differences are not relevant in this particular model. There seemed to be a line effect due to the very robust increase in EtOH-containing solution intake during re-exposure days, a parameter that was only modestly increased in previously studied *wild-type* rats. The reduction in FST immobility was probably caused by an acute effect of EtOH and likely not related to antidepressant action. Our results support the hypothesis that there are overlapping internal factors that contribute to the development of disorders such as alcohol abuse and depression, resulting in similar outcomes in both sexes.

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Poster

688. Mechanisms Underlying Reward Dependence

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 688.10/X5

Topic: G.08. Drugs of Abuse and Addiction

Support: CNPq (HMTB 1B researcher)
CAPES

Title: Effects of Ibogaine, synthetic indole molecules and environmental enrichment on cocaine-conditioned place preference

Authors: *N. HEIDRICH[1], T. F. BIF[2], C. FEDDERN[2], I. A. DA SILVA[2], S. GOLBSPAN[4], A. R. FONSECA[2], F. B. ALMEIDA[1], P. R. FERNANDES[1], M. N. G. BIAJOLI[3], L. FREESE[1], H. M. T. BARROS[1,3];
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Abstract: We recently found that, besides having a protective role in animal models of addiction, the environmental enrichment (EE) has a neuroprotective effect to cocaine exposure (Freese et al, 2018). Pharmacologically, indole molecules have been growing in interest as treatment for drug addiction. Here, we aim to verify whether the protective effects of EE and treatment with indole molecules, naturally occurring (ibogaine) and synthetic (SS7 and SS12), affect preference for cocaine in male and female rats in the conditioned preference place protocol (CPP). Wistar albino male (n=56) and female (n=51) rats on postnatal day (PND) 21 were

allocated in: standard housing (SH) or enriched housing (EH, n=10/cage), made of polycarbonate transparent cages (80x40x50) with 2 floors and diversified objects rearranged 3x/week). At PND 50, a classical CPP was initiated. Treatments were administered on day PND 62 at morning, around 5 hours before testing: vehicle (VEH: DMSO 80% + saline 20%); ibogaine (IBO): 40 mg/kg; indole molecules SS7 and SS12: 10 mg/kg. Vaginal smear cytology was done daily to verify the female estral cycle. Experiments followed the guidelines of the International Laboratory Animal Science Council and were approved by UFCSPA's Ethics Committee for Research (#233/18). The results are presented as mean±SEM. The estrous cycle distribution of female rats in the CPP day test was: diestrus=46%, metestrus=18%, proestrus=16% and estrus=20%. In the VEH, we found that the EH seem to be able to decrease the time spent (seconds) in the cocaine chamber in males (VEH/SH = 478±55 - VEH/EH=441±73) and females (VEH/SH = 394±57 - VEH/EH=312±52) compared to the vehicle. In male rats, without considering the ambient factor, we found that IBO and SS12 decreased the cocaine chamber time spent in 12% and 30%, respectively. In the female rats, both IBO and SS12 treatment reduced the time in relation to the vehicle by 6%. In the other hand, SS7 treatment had no effect in the male and increased the cocaine chamber time spent in 12% in the female rats. This partial results show promising results for treatment with the SS12 syntetic molecule, in contrast to what happens with the SS7 molecule, that shows an increase in the cocaine chamber time spent. Treatment with the IBO appears to be stable, as expected. These data are innovative because they test the effect of new molecules developed here. We expect to show more robust analysis as we complete our set of experiments.

Disclosures: **N. Heidrich:** None. **T.F. Bif:** None. **C. Feddern:** None. **I.A. da Silva:** None. **A.R. Fonseca:** None. **F.B. Almeida:** None. **P.R. Fernandes:** None. **M.N.G. Biajoli:** None. **L. Freese:** None. **H.M.T. Barros:** None.

Poster

688. Mechanisms Underlying Reward Dependence

Location: Hall A

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Program #/Poster #: 688.11/X6

Topic: G.08. Drugs of Abuse and Addiction

Support: Produtividade 1C CNPQ

Title: The effects of caffeine on alcohol oral self-administration behavior and pre-frontal cortex DANA damage in rats

Authors: P. R. FERNANDES[1], C. FEDDERN[1], A. STEIMETZ[2], M. M. VIEIRA DA CUNHA[1], D. J. DE MOURA[1], J. SAFFI[2], L. FREESE[1], ***H. M. BARROS**[1];
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Abstract: Caffeine and alcohol are some of the most widespread self-administered psychoactive substances, and are known to be extensively co-administered. However, little is known about to which the degree they may mutually change each other's consumption and effects. We aimed to investigate the alcohol, caffeine and alcohol+ caffeine oral self-administration behavior and the DNA damage index (DI) in the prefrontal cortex (PFC). Thirty-two Wistar male rats (± 200 g, 55-65 days old were randomly allocated to sucrose 2% (S), caffeine (0.25 mg/ml) (C), alcohol (10% v/v) (A) or alcohol+ caffeine (10% v/v + 0.25 mg/ml)(A+C). All drugs were prepared in sucrose at 2%. During 7 days, the rats were trained to self-administer sucrose 2% using a FR1 schedule . On day 8, the self-administration of S, C, A, A+C began, lasting for 21 days (FR1, 1 hour/day). The Forced Swim Test (FST) was performed 1 day before the self-administration training and 24 hours after the last self-administration session. Experiments followed international guidelines and were approved by UFCSPA's Ethics Committee for Research (#214/17). The results are presented as mean±sem liquid consumption (ml/kg) . There was no significant difference between the S (54.53 ±0.73 ml/kg) and C (52.62 ±0.44 ml/kg). Consumption of A (31.33 ±0.65 ml/kg) was lower than the S and the C. Consumption of the A+C (28.34 ±0.56 ml/kg) was lower than S, C, A . In the FST test, C presented significantly increased immobility in comparison with all other groups. The A+C group presented significantly less immobility than the other groups. The DI for double-strand breaks was significantly higher in the A group compared with the C and A+C. The major findings of this study are that there is decreased alcohol consumption and less DNA damage when alcohol is co-administered with caffeine. There is great variability in studies results on the effects of caffeine upon alcohol consumption, probably the other studies use the forced administration, which can produce significant behavioral changes. The self-administration model used here has a greater translational validity than other studies and showed that a low dose of caffeine might be protective towards alcohol self-administration and DNA damage in prefrontal cortex cells.

Disclosures: P.R. Fernandes: None. **C. Feddern:** None. **A. Steimetz:** A. Employment/Salary (full or part-time):; CAPES. **M.M. Vieira da Cunha:** A. Employment/Salary (full or part-time):; CNPQ. **D.J. de Moura:** None. **J. Saffi:** A. Employment/Salary (full or part-time):; CNPQ. **L. Freese:** A. Employment/Salary (full or part-time):; CAPES. **H.M. Barros:** None.

Poster

688. Mechanisms Underlying Reward Dependence

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Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 688.12/X7

Topic: G.08. Drugs of Abuse and Addiction

Support: CNPq
Capes
Propesq-UFRGS

Title: Correlations between subunits of GABAA and NMDA receptors in chronic alcohol treated or withdrawal and the effect of taurine in the hippocampus of rats

Authors: *R. GOMEZ[1], A. W. HANSEN[1], F. B. ALMEIDA[2], L. F. PAULA[1], N. A. NIETIEDT[1], R. R. PULCINELLI[1], S. BANDIERA[1], L. D. IZOLAN[1], M. S. NIN[3], H. M. T. BARROS[2];
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Abstract: Chronic use of alcohol and its withdrawal impair the balance between GABAergic and glutamatergic systems. A better comprehension of the different roles of $GABA_AR$ and NMDAR subunits could be helpful to define new strategies to counteract the deleterious effects observed during alcohol withdrawal. Taurine, a sulfonated amino acid, has been proposed to attenuate alcohol withdrawal symptoms due to its neuromodulatory properties. In this study, we evaluated the correlations between $GABA_AR$ and NMDAR subunits expression in the hippocampus of rats chronically treated with alcohol or in alcohol withdrawal, and the effects of taurine treatment on these parameters. Rats received alcohol (2 g/kg) or water by oral gavage (control), twice a day, for 28 days. From day 29 to 33, withdrawal rats received water instead of alcohol and all groups were reallocated to receive 100 mg/kg taurine or saline intraperitoneally, once a day. On day 34, rats were euthanized and the hippocampus was dissected for the measurement of $GABA_A$ (α1, α4, δ, and γ2) and NMDA (GluN2A and GluN2B) receptor subunits mRNA expression by RT qPCR. Though inter-group, absolute levels of $GABA_A$ and NMDA receptor subunits expression did not change in the hippocampus of rats, we found a positive intra-group correlation among the δ $GABA_A$ and the GluN2A and GluN2B NMDA receptor subunits in control rats. These correlations were not present in chronic alcohol-treated rats and withdrawal restored only the correlation between δ and GluN2A. Taurine treatment induced the co-expression of α1 and γ2 $GABA_AR$ subunits in both control and alcohol-treated rats. In alcohol-treated rats, taurine also induced the co-expression of α1 $GABA_A$ and GluN2A NMDA receptor subunits. Taurine did not restore any correlations in alcohol withdrawal rats and extinguished the one between GluN2A and δ subunits. Thus, taurine or alcohol withdrawal did not restore the co-expression between $GABA_A$ and NMDA receptor subunits showed in control rats, but taurine increased the α1 and γ2 $GABA_AR$ co-expression, likely making $GABA_ARs$ more sensitive to GABA neurotransmission.

Disclosures: **R. Gomez:** None. **A.W. Hansen:** None. **F.B. Almeida:** None. **L.F. Paula:** None. **N.A. Nietiedt:** None. **R.R. Pulcinelli:** None. **S. Bandiera:** None. **L.D. Izolan:** None. **M.S. Nin:** None. **H.M.T. Barros:** None.

Poster

688. Mechanisms Underlying Reward Dependence

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 688.13/X8

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH grant AA025038 to V.S.
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Burroughs Wellcome Fund through the Transformative and Translational Program in Addiction Sciences to S.G.Q.

Title: Characterization of a post-dependent phenotype of alcohol use disorder

Authors: *S. G. QUADIR[1], C. D. ROHL[2], A. ZEABI[1], P. COTTONE[2], V. SABINO[3]; [1]Pharmacol. & Exptl. Therapeut., [2]Dept. of Pharmacol. & Exptl. Therapeut., [3]Pharmacol. and Exptl. Therapeut., Boston Univ. Sch. of Med., Boston, MA

Abstract: Alcohol Use Disorder (AUD) is a chronic relapsing condition characterized by compulsive, uncontrolled consumption of alcohol. AUD is also characterized by impairments in decision making, driven by dysregulation of prefronto-cortical regions, including the anterior cingulate cortex (ACC) and the medial prefrontal cortex (mPFC). The overall goal of this research was to characterize the post-dependent phenotype resulting from the exposure to chronic intermittent ethanol (CIE) vapor in rats. In particular, we assessed the effects of chronic alcohol exposure on cognitive tasks and pain sensitivity during both acute and protracted withdrawal. We found that rats in protracted withdrawal exhibit increased impulsive action compared to their air-exposed counterparts. On the other hand, post-dependent rats showed no differences in cognitive set shifting. Furthermore, we found a robust effect of CIE on mechanical sensitivity during acute withdrawal, as measured through the von Frey test. This effect persisted into two weeks withdrawal. Alongside, we found CIE rats exhibit increased sensitivity to thermal stimuli, as measured through the Hargreaves test. Current studies are underway to elucidate the neurobiological mechanisms underlying this aberrant phenotype, with a particular focus on sigma-1 receptor (Sig-1R) and N-methyl-D-Aspartate (NMDA) activity, whose expression we found to be significantly elevated in the ACC during withdrawal from CIE. Additional studies will examine how Sig-1Rs in the ACC are involved in behaviors amplified during the post-dependent state.

Disclosures: S.G. Quadir: None. **C.D. Rohl:** None. **A. Zeabi:** None. **P. Cottone:** None. **V. Sabino:** None.

Poster

688. Mechanisms Underlying Reward Dependence

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 688.14/X9

Topic: G.08. Drugs of Abuse and Addiction

Title: Modulation of emotional and neurogenic deficits elicited in three models of sucrose dependence

Authors: *K. BEECHER, A. JACQUES, S. ALI, N. CHAAYA, A. BELMER, S. BARTLETT; Queensland Univ. of Technol., Brisbane, Australia

Abstract: Obesity has become a major public health concern around the globe, costing Australia an excess of $56.6 billion dollars per year. Recent research suggests that the overconsumption of sugar changes the molecular signalling pathways and brain circuitry similar to other drugs of abuse, which may ultimately contribute to the development of obesity. Many studies suggest sugar-withdrawn rats exhibit both anxious and depressive-like symptoms. However, there is limited research into the emotional affect and neurogenic deficits of sugar-withdrawn mice. Consequently, a model of sugar overconsumption in mice needs to be established. Three mouse models were examined: chronic restricted access to low sucrose concentration (Drinking-in-the-Dark, 5% sucrose solution), chronic restricted access to high sucrose concentration (Drinking-in-the-Dark, 25% sucrose solution) and chronic unlimited access to high sucrose concentration (*ad libitum* access, 25% sucrose solution). To test whether sucrose elicits withdrawal-induced emotional deficits in these 3 different models, the following anxiety/depression paradigms were utilised: marble burying, elevated-plus-maze, open-field, forced swimming test, and novelty supressed feeding test. To investigate the role of sucrose-induced neurogenic deficits, we systemically administered three injections of EdU (50 mg/kg) over 2 weeks (days 0, 7, 14). Each stage of neurogenesis in the dentate gyrus of the hippocampus was quantified in Neurolucida 360 (stage 1: EdU/GFAP+/Nestin+; stage 2: EdU/Nestin+/GFAP-; stage 3: EdU/PSA-NCAM+/DCX+; stage 4: EdU/calretinin+/NeuN+ and stage 4: EdU/calbindin+/NeuN+). Distribution of the different markers within EdU-immunoreactive cell populations were compared between the models of sugar overconsumption. Our results show that the concentration of, and accessibility to, sugar solution produce differential effects on locomotor activity, anxiety, impulsivity, aggressiveness, neurogenesis and weight gain, suggesting that sugar dependence involves particular neural circuits in a complex mechanism.

Disclosures: **K. Beecher:** None. **A. Jacques:** None. **S. Ali:** None. **N. Chaaya:** None. **A. Belmer:** None. **S. Bartlett:** None.

Poster

688. Mechanisms Underlying Reward Dependence

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 688.15/X10

Topic: G.08. Drugs of Abuse and Addiction

Title: Sugar and expression of neuronal nicotinic receptors in the nucleus accumbens

Authors: *S. ALI, K. BEECHER, A. JACQUES, N. CHAAYA, A. BELMER, S. E. BARTLETT;
Queensland Univ. of Technol., Brisbane, Australia

Abstract: It has been estimated that obesity can cause $87.7 billion in additional costs on the healthcare system. Health Survey 2011-2012 showed that children and adolescents (2-18 years) attain 40% of their daily energy intake consumed from high sugar/fat containing foods and beverages. There is evidence to show that high sugar/fat containing food and beverage intake leads to a higher risk for metabolic diseases and neurological disorders. Recent research suggests sugar changes the molecular signaling pathways and brain circuitry in a similar manner to alcohol and nicotine. Nicotinic receptors are an essential target for driving addictive behaviors; however, it has never been proven due to a lack of effective compounds. We expect to classify the role of neuronal nicotinic acetylcholine receptors (nAChRs) located in the nucleus accumbens (NAc) in the overconsumption of sucrose (5% w/v), glucose (5% w/v) and fructose (5% w/v). We have modeled long-term (12-week) voluntary binge-like sugar consumption in mice using the drinking-in-the-dark paradigm. Long-term sugar consuming mice were systemically injected with nAChRs subtype specific antagonists and agonists using Latin square design. Similarly, nAChRs subtypes agonists were microinfused specifically into the NAc. Preliminary data indicates nAChRs subtypes antagonists and agonists differentially modulates sugar consumption. We expect to identify the specific nAChR subunits and brain subregions (NAc core or shell) involved in sugar overconsumption to enable the development of more specific and novel therapeutics for the prevention, management and treatment of obesity resulting from the overconsumption of sugar.

Disclosures: S. Ali: None. **K. Beecher:** None. **A. Jacques:** None. **N. Chaaya:** None. **A. Belmer:** None. **S.E. Bartlett:** None.

Poster

689. Neurobehavioral Effects of Cannabinoids

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 689.01/X11

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant R01 DA020269-01

Title: Increased sensation seeking behavior is associated with caudate volumes in male adolescent marijuana users

Authors: *P. SUBRAMANIAM, E. MCGLADE, D. A. YURGELUN-TODD;
Univ. of Utah, Salt Lake City, UT

Abstract: Marijuana (MJ) is one of the most commonly used drugs among adolescents with an estimated 1.6 million adolescents between the ages of 12 to 17 reporting past month MJ use. Chronic MJ use has been associated with altered neurodevelopmental and behavioral processes that can persist into adulthood. Increased sensation seeking behavior has been suggested as a risk factor for the initiation and use of alcohol and illicit substances including MJ. Studies examining the neural correlates of sensation seeking behavior have shown alterations in regions associated with reward processing including striatal regions. While these regions have been shown to be altered in MJ users, few studies have examined the relationship between adolescent MJ use, sensation seeking behavior and the underlying neurobiology involved. Therefore, we hypothesized that increased sensation seeking behavior would be observed in adolescent MJ users which would be associated with striatal brain regions involved in reward processing. 19 MJ users and 16 non-using controls (HC) were included in the analysis. All participants were male and completed a high-resolution magnetic resonance imaging (MRI) scan on a 3 Tesla Siemens Trio scanner. Participants also completed a structured diagnostic interview (SCID) and clinical assessments including the sensation seeking scale (SSS), a 40-item questionnaire that assesses four different components - Thrill and Adventure Seeking (TA), Disinhibition (DIS), Experience Seeking (ES) and Boredom Susceptibility (BS). Volumetric segmentation of structural MRI brain images was performed using FreeSurfer and data for striatal regions were extracted for statistical analysis. MJ-using adolescents reported significantly higher scores on the DIS ($p<0.001$), ES ($p<0.001$), and BS ($p=0.024$) subscales of the SSS as well as on total SSS ($p<0.001$). Findings showed a significant inverse correlation between the right caudate volume ($R= -0.460$, $p = 0.050$) and total caudate volume ($R = -0.462$; $p = 0.046$) with the BS subscale in the MJ group. No significant between group differences were demonstrated for caudate volumes and no significant correlations were observed between the SSS and caudate volumes in the HC group. Our results showing increased sensation seeking behavior and the negative relationship observed between caudate volumes and BS subscale suggest altered reward processing in

adolescent MJ users. Additional studies evaluating the relationship between subcortical brain regions, sensation seeking behavior and MJ use especially in adolescents are critical to differentiate potential risk factors and/or neurotoxic effects associated with MJ use.

Disclosures: P. Subramaniam: None. **E. McGlade:** None. **D.A. Yurgelun-Todd:** None.

Poster

689. Neurobehavioral Effects of Cannabinoids

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 689.02/X12

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant R01 DA030344

Title: Sex-related differences in subjective, but not neural, cue-elicited craving response in heavy cannabis users

Authors: *S. PRASHAD, R. P. HAMMONDS, A. L. WIESE, A. L. MILLIGAN, F. M. FILBEY;
Ctr. for BrainHealth, Univ. of Texas at Dallas, Richardson, TX

Abstract: Previous research has found sex-related differences in factors that affect efficacy of treatments, including continued use, development of cannabis use disorder (CUD), and relapse. As such, studies indicate that female cannabis users progress more quickly than male users through the milestones of CUD, likely due to an increased craving response in female users. While studies have reported sex-related differences in subjective craving, differences in neural response and the relative contributions of neural and behavioral response remain unclear. We examined sex-related differences in neural and behavioral response to cannabis cues and other cannabis use measures in 112 heavy cannabis users (54 females). We used principal component (PC) analysis to determine the relative contributions of neural and behavioral response and cannabis use measures. We also conducted an exploratory analysis to examine whether menstrual cycle phases underlie any sex-related differences. We found that PC1, which accounts for the most variance in the dataset, was correlated with neural response to cannabis cues and there were no differences between males and females ($p = 0.091$). PC2, which accounts for the second-most variance, was correlated with subjective craving such that females exhibited increased subjective craving relative to males ($p = 0.005$). The exploratory analysis indicated that females in the follicular phase contributed to the sex-related difference in subjective craving, suggesting an important role of menstrual cycle phase. We also found that CUD symptoms correlated with both PC1 and PC2, corroborating the relationship between craving and CUD severity. These results suggest a nuanced relationship between neural and subjective craving

response and CUD that differ between sexes. Accounting for these differences will increase efficacy of treatments and interventions through personalized approaches.

Disclosures: S. Prashad: None. **R.P. Hammonds:** None. **A.L. Wiese:** None. **A.L. Milligan:** None. **F.M. Filbey:** None.

Poster

689. Neurobehavioral Effects of Cannabinoids

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 689.03/X13

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH DA 020129

Title: Sex differences in endocannabinoid system adaptations to noradrenergic depletion in the murine locus coeruleus

Authors: *E. J. VAN BOCKSTAELE[1], J. A. ROSS[2], M. URQUHART[2], S. A. THOMAS[3], K. MACKIE[4], B. A. REYES[5];
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Abstract: The locus coeruleus (LC)-norepinephrine (NE) system is highly responsive to stress-related stimuli, and the dysregulation of the coeruleo-cortical pathway has been implicated in several stress-related psychiatric disorders. The LC is a nucleus on which the endogenous cannabinoid (eCB) and NE systems converge. The eCB system plays a significant role in modulating the stress response, in part by modulating the LC. The eCB synthetic enzyme, diacylglycerol lipase-α (DGL-α), is a key enzyme in the biosynthesis of 2-arachidonoylglycerol (2-AG), the primary eCB that is degraded by monoacylglycerol lipase (MGL). Anandamide (AEA) is a second eCB that is degraded by fatty acid amide hydrolase (FAAH). Here, we investigated expression levels of DGL-α, MGL and FAAH in the LC of a mouse model that is NE deficient due to knock out (KO) of the enzyme Dopamine-β-Hydroxylase (DβH-KO). DGL-α expression was significantly increased in the LC of both male and female DβH-KO mice ($P < 0.05$) when compared to WT, while MGL and FAAH were not altered in male or female DβH KO groups compared to WT controls. This suggests overall increased eCB tone in DβH KO mice in both sexes. A pharmacological lesion by intraperitoneal injection of N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine hydrochloride (DSP-4) was used as a second approach to induce NE depletion in male and female rats. Results showed that in the LC, DGL-α expression was significantly increased in male DSP-4-treated rats ($P < 0.05$) when compared to saline-treated

controls, and a similar trend was observed in DSP-4 treated female rats. While there were no observed differences between groups for MGL expression, FAAH was found to be significantly decreased in DSP-4 treated males and significantly increased in DSP-4 treated females. Additionally, immunoelectron microscopy revealed the presence of FAAH in tyrosine hydroxylase (TH)-immunoreactive (ir) somatodendritic processes of the LC in naïve male rats. Preliminary semi-quantitative analysis shows that approximately 51% (307/592) of TH-ir LC somatodendritic processes are also FAAH-ir. Of the TH- and FAAH-ir somatodendritic profiles, 24% (146/307) formed, potentially inhibitory, symmetric synaptic contacts. Excitatory synapses, identified morphologically by an asymmetric cleft, occurred 11% (67/307), while undefined synapses accounted for 30% (178/307) of the total FAAH and TH-ir profiles. Taken together, the findings indicate that the eCB and NE systems have important reciprocal roles in regulating each other, and further, infer that therapeutics aimed at the eCB system for the treatment of various stress-related neurological disorders may have a direct effect on LC neurons.

Disclosures: E.J. Van Bockstaele: None. **J.A. Ross:** None. **M. Urquhart:** None. **S.A. Thomas:** None. **K. Mackie:** None. **B.A. Reyes:** None.

Poster

689. Neurobehavioral Effects of Cannabinoids

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 689.04/X14

Topic: G.08. Drugs of Abuse and Addiction

Title: Sex differences on the developmental effects of chronic inhaled marijuana: A multimodal MRI study

Authors: *J. R. COLEMAN, Jr[1], A. KNUDSEN[1], I. ALKISLAR[1], M. ATHANASSIOU[3], X. CAI[1], D. MADULARU[4], A. MAKRIYANNIS[2], P. P. KULKARNI[1], C. F. FERRIS[1];
[1]Ctr. for Translational NeuroImaging, [2]Ctr. Drug Discovery, Northeastern Univ., Boston, MA; [3]McGill Univ., Montreal, QC, Canada; [4]Psychiatry, McGill Univ., Verdun, QC, Canada

Abstract: As it is the case worldwide, marijuana (cannabis) use in the United States and Canada is highly prevalent and societal views of its use are changing rapidly, as are the policies that govern the legality of its recreational and medical use. With the recent wave of legalization efforts in both the US and Canada, it is critical that more clinically translatable research is conducted so that we may better understand this drug's long-term effects on the central nervous system. The aim of this study was to assess any sex-based effects of chronic inhalation (PND 23 - PND 51) of vaporized cannabis on brain structure and function in male and female mice using non-invasive multimodal magnetic resonance imaging (MRI) and behavioral assays. Dried, pulverized cannabis plant matter (9.7% THC) or placebo (0.0% THC) was vaporized and inhaled by mice during 30-minute full-immersion exposure sessions, for 28 consecutive days.

Approximately 48 hours after the last exposure, subjects (N=32) were scanned for functional coupling across integrated neural circuits using resting state BOLD functional connectivity, alterations in gray matter microarchitecture using diffusion-weighted imaging with quantitative anisotropy and brain structure using voxel-based morphometry. MRI scans were performed again approximately 3 months post-exposure. All images for each modality were registered to a 3D MRI Mouse Atlas with 140 segmented and annotated brain areas used to generate an unbiased computational analysis of all data. Novel-object recognition (NOR) was conducted to assess recognition memory function. MRI data shows differences in the changes to male and female brain structure and function in areas associated with reward, addiction, and sensory perception, while behavior data shows deficits in recognition memory in males, but not in females. Data are being analyzed to see if these effects last for months in mice (decades in humans). Results from this study demonstrate that sex-based differences in both quantitative MRI measures and qualitative behavioral data exist between males and females following chronic cannabis exposure.

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Poster

689. Neurobehavioral Effects of Cannabinoids

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 689.05/X15

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH/5TL4GM118974

Title: Does chronic exposure to marijuana alter brain structure and function: A magnetic resonance imaging study in adult female mice

Authors: A. TAYLOR[1], A. NWEKE[1], V. VINCENT[2], M. OKE[2,3], *C. F. HOHMANN[1], J. COLEMAN[3], P. KULKARNI[3], C. F. FERRIS[3];
[1]Biol., [2]Psychology, Morgan State Univ., Baltimore, MD; [3]Psychology and Pharmaceut. Sci., Northeastern Univ., Boston, MA

Abstract: As it is the case worldwide, marijuana (cannabis) use in the United States and Canada is highly prevalent and societal views of its use are changing rapidly, as are the policies that

govern the legality of its recreational and medical use. With the recent wave of legalization efforts in both the US and Canada, it is critical that more clinically translatable research is conducted so that we may better understand this drug's long-term effects on the central nervous system. The aim of this study was to assess any effects of chronic inhalation of vaporized cannabis on brain structure and function in adult female mice using non-invasive multimodal magnetic resonance imaging (MRI). Dried, pulverized cannabis plant matter containing 9% THC (n = 10) was vaporized and inhaled by the mice during exposure sessions lasting 30 minutes, for 21 consecutive days. Marijuana plant with less than 0.1% THC (n = 10) was used for placebo. Approximately 48 hours after the last exposure, mice underwent imaging sessions during which resting-state functional MRI, diffusion-weighted, and voxel-based morphometry scans were collected. All images for each modality were registered to a 3D MRI Mouse Atlas with 140 segmented and annotated brain areas used to generate an unbiased computational analysis of all data. The neuroradiological data show changes in several integrated neural circuits including the accumbens/ventral striatum. (Supported by NIH/5TL4GM118974).

Disclosures: **A. Taylor:** None. **A. Nweke:** None. **V. Vincent:** None. **M. Oke:** None. **C.F. Hohmann:** A. Employment/Salary (full or part-time):; Morgan State University. **J. Coleman:** A. Employment/Salary (full or part-time):; Northeastern University. **P. Kulkarni:** A. Employment/Salary (full or part-time):; Northeastern University. **C.F. Ferris:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Animal Imaging Research.

Poster

689. Neurobehavioral Effects of Cannabinoids

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 689.06/X16

Topic: G.08. Drugs of Abuse and Addiction

Support: P50DA044118-01A1

Title: Cannabinoid (THC) exposure during adolescence has enduring effects on hippocampal plasticity and learning in females

Authors: *B. M. COX[1], J. QUINTIANILLA[1], A. A. LE[1], M. AMANI[1], S. V. MAHLER[2], C. M. GALL[1], G. LYNCH[1];
[1]Anat. and Neurobio., [2]Neurobio. and Behavior, Univ. of California Irvine, Irvine, CA

Abstract: Marijuana is the most common illicit drug abused during adolescence, a critical period in brain development. Correlational studies in humans have shown adolescent cannabis use to be associated with cognitive deficits, including deficits in episodic memory, a fundamental component of human cognition. Episodic memory is a complex form of information processing

which involves the acquisition of information into a narrative about what happened, where particular features occurred, and the order in which they appeared ('what', 'where', and 'when'). We have shown that each of these basic elements of an episode involve distinct regions of the hippocampal system. Using behavioral paradigms designed to assess the different components of episodic memory, as well as hippocampal field CA1 dependent object location memory we examined the effects of THC administered daily for 2 weeks during adolescence to both male and female rats and then tested behavior in adulthood. The results point to sex-specific effects of adolescent THC exposure on episodic memory, specifically with females, but not males, exhibiting decreased cognitive abilities on tasks that dependent on hippocampus. Future studies will examine synaptic plasticity in subregions of the hippocampus to help elucidate whether the THC treatments influence hippocampal circuitry in different ways in males and females.

Disclosures: B.M. Cox: None. **J. Quintianilla:** None. **A.A. Le:** None. **M. Amani:** None. **S.V. Mahler:** None. **C.M. Gall:** None. **G. Lynch:** None.

Poster

689. Neurobehavioral Effects of Cannabinoids

Location: Hall A

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Program #/Poster #: 689.07/X17

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA045175

Title: Effects of oral delta-9-tetrahydrocannibinol (THC) consumption on motor activity and anxiety-like behavior in adolescent and adult Sprague-Dawley rats of both sexes

Authors: A. R. BANKS[1], A. P. CHAMBERS[1], E. R. CARLSON[1], K. A. HAMBLEN[1], L. N. CARNEVALE[2], A. DAS[2,3], N.-C. LIANG[1,3], *J. M. GULLEY[1,3];
[1]Psychology, [2]Comparative Biosci., [3]Neurosci., Univ. of Illinois, Urbana-Champaign, Champaign, IL

Abstract: Exposure to cannabis and its primary psychoactive component delta-9-tetrahydrocannabinol (THC) may induce changes in neural circuitry that in turn lead to adverse consequences on behavior. Previous studies in rodents have shown that intraperitoneal or subcutaneous administration of THC has the potential to produce an anxiogenic effect and reduce locomotor activity, but it is unclear if this also occurs following volitional THC exposure. Moreover, most of the studies to date have not investigated the impact of age and sex on the psychoactive effects of THC. In the current study, we allowed male and female rats (n=12/group) to voluntarily consume THC (3.0, 5.0, and 10.0 mg/kg; p.o.) by providing them access to THC-impregnated crackers starting on either P36 for adolescent-onset groups or P80 for adult-onset groups. Locomotor activity in an open-field arena (OFA) was assessed 90 min after rats in these

groups ingested these doses or in control rats given crackers impregnated with sesame oil vehicle. Behavior in an elevated plus maze (EPM) was assessed in a fourth test performed 90 min after rats were given a vehicle or 10 mg/kg THC cracker. Immediately after the conclusion of the EPM test, rats were sacrificed and trunk blood and brains were collected for subsequent analysis of THC and its metabolites using LC-MS/MS. Preliminary results suggest THC induced a dose- dependent decrease in locomotor activity in the OFA, with males exhibiting a relatively greater effect than females. In the EPM, exposure to THC induced a decrease in exploration of open arms with males showing a heightened sensitivity to these effects compared to females. These preliminary findings suggest that rats will voluntarily consume THC via the oral route of administration and at doses that lead to significant effects on locomotor activity and anxiety-like behavior. Moreover, these effects appear to be dependent on sex as males exhibited a relatively greater sensitivity to the effects of THC compared to females.

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Poster

689. Neurobehavioral Effects of Cannabinoids

Location: Hall A

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Program #/Poster #: 689.08/X18

Topic: G.08. Drugs of Abuse and Addiction

Support: NIAAA DICBR

Title: Sleep disturbances in mice during chronic THC administration and abstinence

Authors: *A. KESNER, K. P. ABRAHAO, M. J. PAVA, D. M. LOVINGER;
NIAAA, Rockville, MD

Abstract: The diagnosis of cannabis withdrawal is contentious because reliable, objective measures of withdrawal from delta-9-tetrahydrocannabinol (THC), the major psychoactive ingredient in cannabis derivatives, have been difficult to observe. Typically, in laboratory animal studies withdrawal symptoms are elicited by treatment with a cannabinoid type 1 receptor antagonist, which does not mimic the normal course of withdrawal in human cannabis users. A known consequence of chronic cannabis usage in humans is altered sleep, particularly disputed non-rapid eye movement (NREM) sleep. We sought to determine if cannabis withdrawal-induced changes in sleep can be modeled in rodents using electrocorticogram and electromyogram recordings from chronically implanted mice combined with our fully automated sleep analysis system to score sleep before, during and after chronic injection of either THC or vehicle control. The first THC injection augmented total time spent in non-rapid eye movement (NREM) sleep, but this effect was significantly attenuated following the last injection in the

chronic treatment regimen. Measurements obtained over six days following cessation of THC treatment revealed that time spent in NREM sleep was reduced largely because of a decrease in NREM bout duration. Additionally, rapid eye movement (REM) sleep was reduced on the first day of acute THC administration and was enhanced 6 days following treatment. The augmentation in REM during the abstinence phase of the experiment could be due to an increase in the number of REM bouts, and this effect persisted throughout the 6 days of abstinence. None of these changes were observed in controls. Paradoxically, the power of delta oscillations (0-4 Hz) was no different between THC and controls during the first day of abstinence, but THC mice displayed markedly less delta power by the last day of abstinence. This suggests that impairment of processes contributing to slow oscillations in the cortex gradually begins to manifest over recovery from chronic THC exposure. To assess the effects of extended abstinence from chronic THC treatment, 48 hr recordings were obtained from these mice after 77 days of abstinence. We observed an augmentation of NREM sleep time following extended abstinence from chronic THC, and a reduction in delta power during NREM. These findings indicate a chronic THC regimen can produce overt withdrawal symptoms, and in addition, extended abstinence from chronic THC may reveal allostatic processes that emerge during the recovery from acute withdrawal. We also studied whether our observed sleep effects contribute to behavioral abnormalities. This work was supported by NIAAA DICBR.

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Poster

689. Neurobehavioral Effects of Cannabinoids

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 689.09/X19

Topic: G.08. Drugs of Abuse and Addiction

Support: Nipissing University, Internal Grant

Title: Stress and delta-9-tetrahydrocannibinol exposure in adulthood leads to disinhibited behavior on anxiety related and social tasks

Authors: E. KATAQUAPIT, B. REIMER, G. CAMPBELL, R. SIRISKA, T. FOWLER, A. BROUILLETTE, A. STILLAR, *A. C. W. WEEKS;
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Abstract: Cannabis research continues to be important due to increasing legalization worldwide and uncertainties around potential benefits and/or dangers of consumption. There are also questions around the differences between acute and chronic effects of cannabis and its constituents at various stages of development in both humans and animal models. This study

considered the interaction of chronic stress and repeated delta-9-tetrahydrocannibinol (THC) administration on the subsequent learning and behavior of adult rats. Specifically, forty male Wistar rats were equally and randomly allocated to one of four treatment groups: Stress-THC, No Stress-THC, Stress-Vehicle, and No-Stress-Vehicle. Initially, half of the adult rats (post-natal day (PND) 70) were exposed to a chronic mild stress (CMS) paradigm for 14 days. The CMS paradigm consisted of cage tilts, random light/dark changes, and social isolation. Locomotor activity and anxiety levels were assessed in an open field on PND 84 after the CMS housing was concluded. On PND 85, rats began daily intraperitoneal injections of vehicle or THC for ten consecutive days. The THC doses were incremental at 2.5, 5.0 and then 10.0 mg/kg for 4, 3 and 3 days respectively. Following a six-day drug-free period, anxiety related and exploratory behaviours were measured using an elevated zero maze. The next day, social behaviors were assessed using an interaction task where novel pairs of rats were observed together. Finally, a water maze task was completed over four days to assess spatial learning and memory. Results from the open field test confirmed that the CMS procedures produced the expected changes in anxiety related behavior. There was also a main effect of stress in the social interaction task where rats that received CMS showed a significant increase in social interaction with novel conspecifics. In the elevated zero maze, CMS and THC interacted to produce significant differences. Specifically, the stress/drug group spent more time in the open areas of the maze compared to the stress/no drug group. No changes were observed for the water maze task. When compared to an earlier study that considered adolescent aged animals, the current experiment found that while adult rats present a unique pattern of changes, they have roughly the same amount of behavioral disruption. These results suggest that exposure to CMS and THC, while not impairing spatial memory, interact to produce disinhibited behavior and/or reduced anxiety.

Disclosures: A.C.W. Weeks: None. **E. Kataquapit:** None. **B. Reimer:** None. **G. Campbell:** None. **R. Siriska:** None. **T. Fowler:** None. **A. Brouillette:** None. **A. Stillar:** None.

Poster

689. Neurobehavioral Effects of Cannabinoids

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 689.10/X20

Topic: G.08. Drugs of Abuse and Addiction

Support: Ahmadu Bello University research support

Title: Preservation of analgesic activity of cannabis sativa after dopamine receptor antagonist in Wistar rats

Authors: *A. ALHASSAN[1], A. S. ISA[2], A. MUHAMMAD[2], M. I. A. SALEH[2];
[2]Human Physiol., [1]Ahmadu Bello Univ. Zaria, Zaria, Nigeria

Abstract: Background
Cannabis sativa is a drug of abuse for centuries. However, evidence indicate that *Cannabis sativa* possesses therapeutic potentials, some of which includes, analgesic, antiemetic, anti-spastic, neuroprotective, and anti-inflammatory actions, and it is has also been reported to be effective in certain psychiatric diseases. Nevertheless, the medicinal use of cannabis have been limited mainly by their undesirable psychotropic effects especially addiction. Addiction has been associated with activation of the dopamine pathway, thus blocking the dopamine pathway may mitigate the psychotropic effect of cannabis but the question is, if the beneficial effect will be retained after this blockade.
Aim and Objectives : This study investigated the analgesic potential of cannabis in rats given a dopamine antagonist (haloperidol).
Materials and Methods: Twenty Wistar albino rats were randomly divided into four groups. Group 1 (control) received 1 ml/kg normal saline, group 2 received haloperidol only (1mg/kg), group 3 and 4 received 100 mg/kg cannabis sativa and cannabis sativa (100 mg/kg) + haloperidol (1 mg/kg) respectively. Assessment of mechanical pain threshold was done using the Randall-Selitto analgesiometer.
Results and Conclusion: The results obtained from this study showed that pain threshold for the cannabis sativa was significantly higher ($p < 0.05$) when compared to the control and haloperidol group. Similar result was also recorded for the group that received cannabis sativa and haloperidol. These confirmed the analgesic potential of cannabis sativa. It also indicated that cannabis sativa retained its analgesic activity after administration of haloperidol.
In conclusion, it may suggested that if the psychotropic effect of cannabis sativa is inhibited the analgesic activity remains intact.
Key words**:** Pain, dopamine, haloperidol

Disclosures: **A. Alhassan:** 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.; Ahmadu Bello University. **A.S. Isa:** None. **A. Muhammad:** None. **M.I.A. Saleh:** None.

Poster

689. Neurobehavioral Effects of Cannabinoids

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 689.11/X21

Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA Intramural Research Program (Z1A DA000620-02).

Title: Optogenetic dissection of dopamine-related neural mechanisms underlying cannabis reward versus aversion

Authors: *C. J. JORDAN[1], B. A. HUMBURG[1], Y. HE[1], X. HAN[1], G.-H. BI[1], E. L. GARDNER[1], X.-Q. XIE[2], Z.-X. XI[1];
[1]Natl. Inst. on Drug Abuse, Baltimore, MD; [2]2.Department of Pharmaceut. Sci. and Computat. Chem. Genomics Screening Ctr., Sch. of Pharmacy, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Cannabinoids can exert both hedonic and aversive effects. While some human users report euphoria following cannabis use, others report anxiety, and animal studies suggest cannabis is minimally reinforcing or dysphoric. However, the neural mechanisms underlying cannabinoids' paradoxical effects are poorly understood. In the past, cannabis reward has been attributed to agonist activity at brain CB_1 receptors (CB_1R) on GABA inputs in the ventral tegmental area (VTA), which disinhibits VTA dopamine (DA) neurons. In contrast, we recently reported that Δ^9-THC produces aversive effects by activation of CB_1R on VTA glutamate neurons. In addition to acting on CB_1R, many cannabinoids also exert activity at brain CB_2R on VTA DA neurons. Therefore, we hypothesized that the net rewarding vs. aversive effects of cannabinoids depend upon the balance of cannabinoid activity at multiple cell type-specific receptor mechanisms. To test this hypothesis, we used optogenetic and transgenic approaches to express light-sensitive channelrhodopsin (ChR2) in VTA DA neurons using DAT-cre mice. Optical stimulation of VTA DA neurons induced robust optical intracranial self-stimulation (oICSS) behavior in a frequency-dependent manner, indicating that increased DA is rewarding. Strikingly, responding for oICSS was significantly enhanced by systemic administration of XLR-11, a new synthetic cannabinoid, suggesting that XLR-11 is rewarding by itself likely through activation of CB_1R, and therefore pretreatment produced additive or synergistic effects with optical brain-stimulation reward. In contrast, pretreatment with other mixed CB_1R/CB_2R agonists (Δ^9-THC, WIN55,212-2) or selective CB_2R agonists (Xie2-64 and 2-49) inhibited oICSS maintained by optical stimulation of VTA DA neurons. Taken together, these findings support our hypothesis that the relative activity of cannabinoids at CB_1R vs. CB_2R may account for rewarding vs. aversive effects of cannabis. Cannabinoids that are selective for CB_1R may exert primarily rewarding effects, whereas cannabinoids selective for CB_2R may exert primarily dysphoric effects. Mixed CB_1R/CB_2R agonists may exert either rewarding or aversive effects, depending upon their receptor binding affinities and cellular distributions of CB_1R/CB_2R in different subjects.

Disclosures: C.J. Jordan: None. **B.A. Humburg:** None. **Y. He:** None. **X. Han:** None. **G. Bi:** None. **E.L. Gardner:** None. **X. Xie:** None. **Z. Xi:** None.

Poster

689. Neurobehavioral Effects of Cannabinoids

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 689.12/X22

Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA Intramural Research Program

Title: Pathway-specific modulation of lateral habenula GABAergic inputs by acute and chronic cannabinoids

Authors: *E.-K. HWANG, C. R. LUPICA;
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Abstract: The lateral habenula (LHb) is a brain region implicated in coordinating behavioral responses to punishment, omission of reward, and other negative environmental stimuli. Moreover, LHb neurons increase their activity during behavioral avoidance and in depression-like states. LHb output is largely glutamatergic and the activity of these neurons is strongly controlled by several inhibitory GABAergic afferents. However, how these individual GABAergic inputs are organized to control LHb activity is poorly understood. Here we examine characteristics of two external sources of LHb inhibition arising from the ventral tegmental area (VTA) and nucleus accumbens shell (NAcs), brain areas mediating motivation and reward. Using selective optogenetic activation in rat brain slices, we find that the NAcs and VTA both send monosynaptic GABAergic inputs to the medial LHb, and this inhibits these cells. However, in vitro whole-cell recordings also revealed notable differences in these projections regarding the strength of the inhibition, probability of GABA release, the expression of synaptic plasticity, and sensitivity to modulation by cannabinoids. Thus, only NAcs the inputs to LHb were inhibited by CB1 receptor agonists, and these inhibitory inputs were significantly weakened after chronic exposure to Δ^9-THC (5 mg/kg, 2 weeks), a psychoactive constituent of cannabis and agonist of CB1 and CB2 receptors. Moreover, the inhibition of NAcs GABAergic inhibitory inputs to the LHb by the cannabinoid agonist WIN55,212-2 was significantly reduced following Δ^9-THC exposure, indicating cross-tolerance to Δ^9-THC at these NAcs-LHb GABAergic synapses. These results demonstrate pathway-specific differences in GABAergic control of LHb output, and that cannabinoids differentially controls this inhibition. We hypothesize that the selective modulation NAcs input to the LHb by Δ^9-THC may relate to the amotivational and aversive effects of Δ^9-THC noted in humans and animals in models of reward and addiction.

Disclosures: E. Hwang: None. **C.R. Lupica:** None.

Poster

689. Neurobehavioral Effects of Cannabinoids

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

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Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant P20GM104932

Title: Differential effects of cannabidiol and a novel cannabidiol analog on oxycodone place preference and analgesia in mice; an opioid abuse deterrent with analgesic properties

Authors: *H. M. HARRIS[1], W. GUL[2], M. ELSOHLY[2,3], K. J. SUFKA[4,5,2];
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Abstract: This study sought to compare cannabidiol to a cannabidiol analog, CBD-VHS, and its ability to attenuate oxycodone reward without affecting its analgesic effects. In Experiment 1) Mice were enrolled in the conditioned place preference paradigm and received either saline or oxycodone in combination with one of four doses of cannabidiol or CBD-VHS using 3 sets of drug-/no drug-conditioning trials. Experiment 2) sought to determine whether a dose of cannabidiol or CBD-VHS that blocked opioid reward administered alone or in combination with a sub-analgesic or analgesic doses of oxycodone would affect nociceptive processes on the hotplate and abdominal writhing assays. Results from this study demonstrated CBD-VHS can attenuate the rewarding effects of oxycodone place preference at 8.0 mg/kg and is void of rewarding or aversive properties. Cannabidiol however, did not attenuate oxycodone reward at any dose and produced condition place aversion at 10.0 mg/kg. CBD-VHS alone, but not cannabidiol, produced antinociceptive effects in both nociceptive assays and was most effective when compared to oxycodone against thermal nociception. Interestingly, there was a differential interaction of cannabidiol and CBD-VHS in combination with oxycodone across the two nociceptive assays. CBD-VHS+oxycodone produced subadditive responses on the hotplate assay. Enhanced nociception was observed in the abdominal writhing assay with the administration of cannabidiol or CBD-VHS in combination with sub-analgesic and analgesic doses of oxycodone. These data demonstrate CBD-VHS is superior to cannabidiol in blocking opioid reward, producing analgesia in inflammatory assays, and enhances opioid analgesia in a model of inflammation. These findings suggest CBD-VHS could prove useful in pain management and addiction treatment settings.

Disclosures: **H.M. Harris:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Emerald Biosciences. **W. Gul:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Emerald Biosciences. **M. ElSohly:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Emerald Biosciences. **K.J. Sufka:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Emerald Biosciences.

Poster

689. Neurobehavioral Effects of Cannabinoids

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 689.14/X24

Topic: G.08. Drugs of Abuse and Addiction

Support: Pilot grant from the University of Pennsylvania Research Foundation (URF) to MDB and EH.

Title: Development of a mouse model to study the effects of adolescent vaping of Δ-9-tetrahydrocannabinol (THC)

Authors: *T. M. PATTEN[1], A. DREIER[2], E. A. HELLER[1], M. DE BIASI[2];
[1]Dept. of Systems Pharmacol. and Translational Therapeut., [2]Dept. of Psychiatry, Univ. of Pennsylvania, Philadelphia, PA

Abstract: Cannabis is the most frequently used illicit drug in the world with highest consumption occurring in economically developed countries like the United States, especially among adolescents and young adults. Increased legality of cannabis, and therefore availability, has occurred alongside a widespread popularization of electronic cigarettes (e-cigs) among youth. E-cigs often contain nicotine, but cannabis and other substances can be used in conjunction with these devices. Recent data from the National Youth Tobacco Survey (NYTS) show that nearly 1 in 11 students had used cannabis in e-cigarettes in 2016. Thus, it is increasingly important to establish preclinical models to study cannabis "vaping" in adolescence and to understand its potential effects on the developing brain. The present study utilized an e-cig machine to deliver vaporized e-liquid containing Δ-9-tetrahydrocannabinol (THC) to adolescent C57/BL6J mice of both sexes. Subcutaneous body temperature was measured before and after an acute exposure to either THC vapor or to vehicle control vapor using implantable programmable temperature transponders. The same animals were also tested in the open field arena for locomotor activity 30 minutes after acute e-cig vapor exposure. 24-h after acute exposure to THC or vehicle vapor, tissue was collected from brain regions relevant to reward processing for analysis of post translational histone modifications. A subset of mice was sacrificed immediately after vapor exposure and serum THC concentrations were measured using enzyme-linked immunosorbent assay (ELISA). Adolescent C57/BL6J mice of both sexes exposed to THC via e-cigarette vapor showed dose-dependent changes in physiological endpoints (e.g. subcutaneous body temperature and locomotor activity) compared to controls. Molecular analyses determined the histone expression pattern in THC-exposed compared to vehicle-exposed animals. By using commercially-available products, this study establishes a highly translational method to study THC vaping in adolescents, which is a rising epidemiological concern. In addition, this research could increase our understanding of the effect of THC exposures on the adolescent epigenome.

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Poster

689. Neurobehavioral Effects of Cannabinoids

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

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Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant F32DA047029
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Title: Intravenous self-administration of Δ^9-tetrahydrocannabinol by adolescent rats alters reinstatement and working memory behaviors in adulthood

Authors: *S. J. STRINGFIELD[1,2,3], M. M. TORREGROSSA[1,2,3];
[1]Psychiatry, [2]Translational Neurosci. Program, [3]Ctr. for the Neural Basis of Cognition, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Adolescence is a period of brain development that often coincides with initiation of drug use, including Δ^9-tetrahydrocannabinol (THC), the primary psychoactive component of marijuana. This exposure can alter development on a neuronal and molecular level, leading to deficits in learning and memory and enhancements in addiction-associated behaviors. Using a novel intravenous THC self-administration model, we hypothesized that chronic exposure to THC at voluntarily self-administered doses would result in enhanced drug-seeking behaviors and altered performance on a cognitively taxing working memory task. Adolescent male and female Sprague-Dawley rats operantly self-administered escalating doses of THC, reaching a final dose of 30μg/kg/infusion (moderate dose) or 100μg/kg/infusion (high dose) over 20 days (PND 32-51). Next, lever pressing was extinguished during 9 days of lever extinction training (PND 52-60). Rats were tested for cue reinstatement and incubation of THC-seeking after 10 (PND 61) and 30 (PND 81) days of abstinence. Concurrently during abstinence, rats were trained on the delayed-match-to-sample working memory task. During this task, rats learned to nose poke into one of 5 illuminated sample ports to receive a sucrose pellet reward. After responding into a specific sample port, a variable delay period (0-24s) elapsed before the originally sampled port and 2 adjacent ports were illuminated. If the originally sampled port was correctly chosen, the rat received a sucrose pellet reward. We found that male and female adolescent rats self-administered both moderate and high doses of THC. All animals showed reinstatement and incubation of THC-seeking during abstinence, but female rats demonstrated increased incubation compared to males. Additionally, sex differences arose in the effect of high dose THC exposure on working memory task performance, with females showing reduced performance and males

showing enhanced performance. Thus, intravenous THC self-administration produced measurable, dose-dependent effects on cognitive tasks and addiction-associated behaviors. Ongoing studies continue to investigate putative sex- or brain region-specific differences in neuronal activity and protein expression that may mediate these effects.

Disclosures: S.J. Stringfield: None. **M.M. Torregrossa:** None.

Poster

689. Neurobehavioral Effects of Cannabinoids

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 689.16/X26

Topic: G.08. Drugs of Abuse and Addiction

Support: Fapesp 17/12412-2

Title: Toxicity of cannabidiol in neuroblastoma and neuroprogenitor stem cells

Authors: *M. L. QUINTELLA[1], S. A. ROMARIZ[3], B. M. LONGO[2];
[1]Neurophysiol., [2]Univ. Federal de São Paulo, São Paulo, Brazil; [3]Univ. Federal De São Paulo, São Paulo, Brazil

Abstract: Cannabidiol (CBD) is the second most common phytocannabinoid in the Cannabis Sativa, and recent evidence suggests great therapeutic potential, specially in the field of epilepsy. CBD has been shown to reduce neuronal lesion in central nervous system diseases. Our objective was, therefore, to observe any change in the viability of precursor and differentiated cells exposed to CBD. In order to do so, we quantified the cell viability of undifferentiated and differentiated neuroblastoma (N2a) and differentiated neuroprogenitor stem cells (NPC) with MTT assay. We also observed the capacity of undifferentiated NPCs to form collonies. N2a Cells were deprived of fetal bovine serum and exposed to retinoic acid to differentiate, and after 48 hours of exposure to CBD, fixated with paraformaldehyde. NPCs were fixated after 24 hours of differentiation. Neurosphere growth was used to asses viability of undifferentiated cells. Cell viability tests have shown a dose-specific neurotoxicity in N2a and in NPC. The use of CBD in concentrations equal to or higher than 50 µM inhibit growth of undifferentiated N2a cells ($p<0.001$), equal or higher than 1 µM are toxic to differentiated N2a cells; and doses as low as 5µM are toxic to both differentiated ($p<0.0001$)and undifferentiated NPCs. We conclude that despite the evidence of therapeutical properties of CBD, it is important to emphasize the need to analyse the safety and optimal dose of CBD.

Disclosures: M.L. Quintella: None. **S.A. Romariz:** None. **B.M. Longo:** None.

Poster

690. Working Memory: Prefrontal Cortex II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 690.01/X27

Topic: H.01. Animal Cognition and Behavior

Support: Ministry of Education Tier 2 Academic Research Fund
NUS-NUSH Memory Networks Program

Title: Independent subspaces for working memory and motor preparation in the lateral prefrontal cortex

Authors: *C. TANG[1], R. HERIKSTAD[2], C. LIBEDINSKY[1,2,3], S.-C. YEN[2,4];
[1]Inst. of Mol. and Cell Biol., Singapore, Singapore; [2]Singapore Inst. for Neurotechnology, Natl. Univ. of Singapore, Singapore, Singapore; [3]Dept. of Psychology, Natl. Univ. of Singapore, Singapore, Singapore; [4]Dept. of Electrical and Computer Engineering, Natl. Univ. of Singapore, Singapore, Singapore

Abstract: The lateral prefrontal cortex (LPFC) encodes and integrates multiple types of information, resulting in mixed selectivity in LPFC cells and a high-dimensional representational space. It is not clear what mechanisms are used by downstream regions to read out information from mixed-selective responses in the LPFC. One possibility is to have low-dimensional information subspaces, which allow independent readout of different types of information with minimal interference with information in other subspaces. Here we demonstrate the existence of two independent information subspaces in the LPFC network: one that encoded spatial working memory information, and another that encoded movement preparation information. We identified the two subspaces by decomposing the population firing pattern into two sub-patterns with the lowest possible mutual information (0.076 bits). The two sub-patterns defined two subspaces: one subspace was consistent with working memory, since it maintained working memory information throughout the trial in a relatively stable manner; another subspace was consistent with a motor preparation, since information in this subspace emerged after distractor presentation, and the activity correlated highly with pre-saccadic movement execution signals (more than 50% of the cells showed significant correlation). The contribution of individual cells to the two subspaces were highly correlated ($r=0.69$, $p<0.01$), corroborating the multiplexing roles of mixed-selective cells. The two subspaces efficiently reduced the dimensionality of information from 226 to only 7 dimensions without significant loss of decodable information (85.9±5.6% and 87.4±0.8% for memory in Delay 1 in full space and subspace, 76.7±7.8% and 77.7±1.9% for preparation in Delay 2 in full space and subspace). Error trial responses projected into the two subspaces deviated significantly from those in correct trials (decoding performance dropped from 87.4±0.8% to 36.1±2.9% for memory in Delay 1; from 77.7±1.9% to 43.5±1.9%

for preparation in Delay 2), which indicated that the subspaces were behaviourally relevant. We also found low interference between the two subspaces - the superimposition of the response from one subspace weakly affected the decoding performance in the other subspace (memory decoding dropped from 70.2±1.7% to 51.9±1.6% when preparation activity was added in Delay 2; preparation decoding dropped from 77.7±1.9% to 62.1±1.4% when memory activity was added in Delay 2). Our results suggest that the LPFC may be able to use subspace representations to encode different forms of information within the same neuronal population.

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Poster

690. Working Memory: Prefrontal Cortex II

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Topic: H.01. Animal Cognition and Behavior

Support: Ministry of Education Tier 2 Academic Research Fund (MOE2016-T2-2-117)

Title: Functional specialization of primate lateral prefrontal subregions for spatial working memory

Authors: *P. K. TAN[1], S.-C. YEN[1,2], C. LIBEDINSKY[1,3,4];
[1]Singapore Inst. for Neurotechnology, [2]Dept. of Electrical and Computer Engin., [3]Dept. of Psychology, Natl. Univ. of Singapore, Singapore, Singapore; [4]Inst. of Mol. and Cell Biol., Agency for Science, Technol. and Res., Singapore, Singapore

Abstract: The lateral prefrontal cortex (LPFC) plays a role in the maintenance of working memory. Recent work has suggested that dorsal regions are spatially selective during working memory tasks and that such selectivity decreases in an anterior-posterior gradient. However, it is unclear if such predictions hold in the context of a spatial working memory task with an intervening distractor. Here we characterize functional specialization of the LPFC by quantifying the distribution of classical and mixed selective neurons, selectivity strength, percentage explained variance and cross-temporal decoding performance of subregions of the LPFC. We recorded the activity of single neurons in the LPFC of two monkeys. The microelectrode arrays covered the dorsal and ventral area 8 (frontal eye field), dorsal and ventral area 9/46 (posterior LPFC), dorsal and ventral area 46 (anterior LPFC), area 8B (dorsal to the posterior LPFC) and area 6DR (anterior premotor cortex). The monkeys performed a visually guided delayed saccade task with an interfering distractor. Using cross-temporal decoding, we show that the majority of target location information was found in the ventral posterior LPFC, and this information displayed a marked code morphing (Parthasarathy et al., 2017). Furthermore, we found that the large majority of neurons with nonlinear mixed selectivity reside in the ventral posterior LPFC.

In contrast, the dorsal anterior LPFC displayed almost no memory information, no code morphing, and no neurons with nonlinear mixed selectivity. Our results suggest that an anterior-posterior and dorsal-ventral gradient of spatial selectivity does exist. However, unlike previous reports, we found stronger spatial representations in the ventral compared to the dorsal LPFC.

Disclosures: P.K. Tan: None. **S. Yen:** None. **C. Libedinsky:** None.

Poster

690. Working Memory: Prefrontal Cortex II

Location: Hall A

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Topic: H.01. Animal Cognition and Behavior

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Title: Dopamine neurons of ventral tegmental area modulate working memory performance and the associated neuronal activity in medial prefrontal cortex

Authors: *C. GE[1,2], Z. CHEN[1], H. FAN[1], C. LI[1];
[1]Inst. of Neuroscience,Sibs, CAS, Shanghai, China; [2]Univ. of Chinese Acad. of Sci., Beijing, China

Abstract: The dopamine neurons in ventral tegmental area is important in modulating many brain functions, including working memory, the ability of active maintenance and manipulation of information during a delay period of seconds. However, the mechanism underling behavioral modulation of WM by dopamine neurons is unclear, especially during learning phase. To tackle this problem, we trained mice to perform an olfactory WM task while performing optogenetic and electrophysiological recording experiments. Activation of VTA dopamine neurons and the

dopamine terminals in mPFC during delay period of learning phase improved behavioral performance, whereas suppression dopamine neurons during delay period impaired performance. Consistent with behavioral modulation, bidirectional optogenetic manipulation of dopamine neurons bidirectionally modulated the signal-to-noise ratio and coding ability of mPFC neurons. Using dopamine sensor, we also observed the dynamic changes of dopamine in mPFC during earlier-delay and decision-making/reward periods. Therefore, changes in neuronal activity in mPFC is associated with modulation in VTA dopamine neurons in WM task.

Disclosures: **C. Ge:** None. **Z. Chen:** None. **H. Fan:** None. **C. Li:** None.

Poster

690. Working Memory: Prefrontal Cortex II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 690.04/X30

Topic: H.01. Animal Cognition and Behavior

Support: Brain and Behavior Research Foundation Grant 26089
NIH T32 GM007367

Title: A sensitive period in the postnatal development of prefrontal cortical function and behavior

Authors: *L. J. BENOIT[1], S. BENICH[3], E. TEBOUL[4], E. HOLT[4], S. E. CANETTA[2], C. KELLENDONK[2];
[1]Dept. of Neurobio. and Behavior, [2]Div. of Mol. Therapeut., Columbia Univ., New York, NY; [3]Barnard Col., New York, NY; [4]New York State Psychiatric Inst., New York, NY

Abstract: Sensitive periods denote time windows during which certain brain regions are more susceptible to transient perturbations, which can result in persistent changes in circuitry. These periods have been well characterized in sensory systems, such as the visual system, which integrates excitatory inputs from the two eyes in a competitive activity-dependent manner during the sensitive period. A similar process may exist in the medial prefrontal cortex (mPFC), a structure implicated in many psychiatric disorders and cognitive functions. However, because the mPFC does not receive direct sensory input, it has been difficult to study the role that incoming excitatory input during development plays in the maturation of mPFC circuitry and subsequent cognitive behaviors.
To address this question, we developed an approach in mice using a combination of viral vectors, genetics, and the inhibitory DREADD, hM4DGi, whereby we can transiently modulate one of the main sources of excitatory input to the mPFC, from the mediodorsal nucleus of the thalamus (MD). By virally expressing hM4DGi in the early postnatal MD, we can transiently decrease excitatory input from this structure during defined time windows by administering the ligand for

hM4DGi, clozapine-N-oxide. We have initially chosen to manipulate MD excitability during adolescence, a period during which mPFC circuitry is continuing to mature and one that is conceived as a vulnerable period in the progression of psychiatric disorders. As a comparison, we also transiently manipulate MD excitability in adulthood. Forty days following the end of the adolescent or adult manipulation, we test for persistent effects on mPFC circuitry and behavior. Our data show that transient perturbation of the MD during adolescence (P20-50) results in persistent deficits in the acquisition of an mPFC-dependent task in adulthood. In parallel, we demonstrate long-term decreases in the frequency of excitatory inputs in the mPFC in adulthood following adolescent manipulation using slice electrophysiology. However, the same manipulation during adulthood (P90-120) did not result in persistent behavioral impairments. These data indicate a temporally restricted "sensitive period" during adolescence when perturbations to incoming excitatory input can have persistent effects on mPFC circuitry and behavior. This study represents an important step in furthering our understanding of the mechanisms governing mPFC maturation and may offer insights into processes involved in developing a psychiatric disorder.

Disclosures: L.J. Benoit: None. **S. Benich:** None. **E. Teboul:** None. **E. Holt:** None. **S.E. Canetta:** None. **C. Kellendonk:** None.

Poster

690. Working Memory: Prefrontal Cortex II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 690.05/X31

Topic: H.01. Animal Cognition and Behavior

Support: COBRE 527132
NIH Grant R01 5270633

Title: Topographic and learning-related patterns of prefrontal neuronal activity during credit assignment

Authors: *E. LEE[1,3], W. F. ASAAD[1,3,4,2];
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Abstract: The ability to link effects with their causes is fundamental to learning. One aspect of this is credit assignment, in which the outcome of a choice must be attributed to some earlier event or experience. We trained two monkeys to perform a credit assignment (CA) task in which they learned to attribute a choice outcome to one of several earlier options. The particular option, a visual cue, that deserved credit varied across different blocks of trials. Performance on this task was compared to a simple delayed-match-to-sample (DMS) task in which no credit assignment

was necessary to perform subsequent trials correctly. We implanted large arrays of independently-moveable electrodes over the lateral prefrontal cortex in each animal (96 electrodes in one, 128 in the other). We observed differences in neuronal population activity between early (initial learning) and late (well-learned) trials in the CA task and these differences varied according to the region of the lateral prefrontal cortex. Furthermore, we observed differences between the CA and DMS tasks, particularly with respect to "ramping" activity at the end of the delay period prior to the choice. This ramping activity also varied topographically across the prefrontal cortex.

Disclosures: E. Lee: None. **W.F. Asaad:** None.

Poster

690. Working Memory: Prefrontal Cortex II

Location: Hall A

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Topic: H.01. Animal Cognition and Behavior

Support: the National Science Foundation for Distinguished Young Scholars of China Grant 31525010
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the Key Project of the Shanghai Science and Technology Commission Grant 15JC1400102, 16JC1400101

Title: Delay-period activity of medial prefrontal cortex is critical for working memory specific in learning of both sensory and motor oriented tasks

Authors: *J. YAO[1,2], R. HOU[1], Z. HAN[1], X. ZHANG[1], C. T. LI[1];
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Abstract: Working memory (WM) that involves a brief period of memory maintenance known as the delay period plays a quite important role in our daily life. The maintained information can be either sensory or motor in nature. Our previous work has demonstrated that the delay-period

activity of medial prefrontal cortex (mPFC) is critical for a sensory-oriented WM task specifically during learning, but not well-trained, phase. It is unclear whether this specific involvement of mPFC in learning depends on the task type. Here we trained mice to perform either a sensory-oriented WM task, a delayed paired association (DPA) task, or a motor-oriented WM task, a delayed response task (DRT). We then optogenetically suppressed activity of mPFC excitatory neurons during the delay period in learning and well-trained phases of the two tasks. Behavioral performance was impaired during the learning phase but not after the mice were well trained for both tasks. To investigate the neural correlates of mPFC in both tasks, we performed extracellular recording during a rule-switching task, in which mice need to switch between DPA and DRT task in a block design. In this task, the sensory stimuli to be maintained were the same, but the rule was switched between blocks. We found that the coding ability of mPFC population neurons was increased along learning process of both tasks. We did not observe learning-related modulation in coding ability of WM information for the DPA and DRT tasks. Thus, delay-period activity of mPFC is critical for information maintenance specifically during learning of both sensory- and motor-oriented WM tasks.

Disclosures: **J. Yao:** None. **R. Hou:** None. **Z. Han:** None. **X. Zhang:** None. **C.T. Li:** None.

Poster

690. Working Memory: Prefrontal Cortex II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 690.07/X33

Topic: H.01. Animal Cognition and Behavior

Support: NIH grant NS103155
Yerkes National Primate Research Center Base Grant (OD P51OD011132)

Title: Loss of glutamate signaling from the centromedian-parafascicular thalamus to dorsal striatum impairs working memory and cognition in non-human primates

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Abstract: The circuit involving projections from the centromedian-parafascicular (CM/PF) thalamus to the dorsal striatum plays an essential role in the acquisition and execution of discrimination learning in rodents (Bradfield et al., 2013, Front. Syst. Neurosci. 7:51). CM/PF neurons profoundly degenerate early in the course of neurodegenerative diseases such as Parkinson's disease (PD), raising the possibility that degeneration of the CM/PF-striatal system contributes to early cognitive deficits in PD patients (Smith et al., 2014, Front. Systems Neurosci 8:5). However, the exact role of this thalamostriatal pathway in learning and other cognitive

processes is not well established in primates. To address this question, a highly efficient retrograde gene transfer vector encoding the recombinant immunotoxin (IT) receptor was injected into the dorsolateral striatum (putamen/caudate) in one adult female rhesus monkey to express the receptor in neurons innervating the striatum. IT treatment into the CM/PF of the vector-injected animal caused a selective elimination of neurons in the CM/PF-derived thalamostriatal pathway (Kato et al., 2011, J Neurosci. 31:17169). This experimental animal and a control monkey were tested both pre- and post-surgery in a task measuring attentional set shifting and behavioral inhibition (Intradimensional/extradimensional shifting). Our preliminary data indicate that, as compared to the control animal, the CM/PF-lesioned monkey failed to remember the extradimensional shift task it learned prior the lesion, making more errors to re-learn the task and showing a severe impairment in reversal learning. Both animals were then tested in a working memory task (Spatial Delayed Response) and again the CM/PF-lesioned monkey showed a significant deficit as compared to the control monkey. Yet, the elimination of this pathway did not influence spontaneous locomotion and motor skill learning that are mediated by the dorsal striatum. These preliminary data suggest that removing the excitatory input from CM/PF to the dorsal striatum may result in an enduring deficit in learning-related plasticity.

Disclosures: G.J. Masilamoni: None. **R. Richardson:** None. **Y. Smith:** None. **J. Bachevalier:** None.

Poster

690. Working Memory: Prefrontal Cortex II

Location: Hall A

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Program #/Poster #: 690.08/X34

Topic: H.01. Animal Cognition and Behavior

Support: Whitehall Foundation Research Grant
Schneider-Lesser Foundation

Title: Adaptive coding of multiplexed information in primate lateral prefrontal cortex

Authors: *F.-K. CHIANG[1], J. D. WALLIS[2], E. L. RICH[1];
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Abstract: Mixed-selectivity allows prefrontal neurons to represent high-dimensional cognitive information and adapt executive functions flexibly. Such mixed neural codes not only increase representational capacity in cognitive tasks, by encoding the information efficiently, but may also optimize metabolic costs. Therefore, changes in cognitive task demands may influence the degree of mixed-selectivity. We've recently shown that neural activity in lateral prefrontal cortex

(LPFC) encodes the spatial and sequential information required to perform a visuospatial working memory (WM) task, and the strength of spatial tuning is modulated by behavioral strategies. However, little is known about how these neural ensembles multiplex information in different behavioral strategies. To assess this, we re-analyzed data from two monkeys performing a spatial self-ordered search task with six identical visual targets. The subjects were required to saccade to each target, one at a time in any order, returning their eyes to the center after each target. Therefore, they had to use WM to keep track of which targets had been visited and prepare for next target selection. Blocks of 40 trials with the same target configuration enable us to quantify behavioral strategies. Target color within a trial was the same, but it changed to indicate the onset of a new trial. We used linear discriminant analysis (LDA) to categorically decode information about target location or saccade order from ensembles of LPFC neurons. Target locations were more accurately decoded than saccade orders, and the accuracy of the decoder to predict saccade orders increased when subjects performed more stereotyped selection. To determine how each neuron contributed to the ensemble, we iteratively removed one neuron at a time, analogous to a lesion process, in order of contribution to the decoder. We found that the accuracy of decoding sequential information from the most informative half of neuronal ensembles was similar to that of the entire population. To test how size of the optimal ensemble changes with behavioral strategies, we systematically varied the number of neurons to create decoders based on the most informative units or ensembles. We found that the size of optimal neural ensembles for decoding spatial or order information, but not target color, increased with stereotyped strategies, suggestive of a less efficient neural code. Overall, these results indicate that efficient coding of multiplexed information in LPFC is affected by the behavioral strategy selected by the animal, and can be achieved by relatively small neuronal ensembles.

Disclosures: F. Chiang: None. **J.D. Wallis:** None. **E.L. Rich:** None.

Poster

690. Working Memory: Prefrontal Cortex II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 690.09/DP10/X35

ControlExtraData.DynamicPosterDisplay:
Dynamic Poster
Topic: H.01. Animal Cognition and Behavior

Support: CIHR

Title: Cell type specific impairment of naturalistic spatial working memory coding by ketamine in primate lateral prefrontal cortex

Authors: *M. ROUSSY[1], M. KHAKI[1], N. MORTAZAVI[1], A. J. SACHS[2], L. PALANIYAPPAN[1], J. C. MARTINEZ-TRUJILLO[3];

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Abstract: Through its role as a N-methyl-D-aspartate acid receptor (NMDAR) antagonist, ketamine has been shown to induce schizophrenia like symptoms including impairments in spatial working memory (WM). Computational models propose that NMDAR play a fundamental role in maintaining WM encoding in the prefrontal cortex; however, experimental evidence supporting this in primates is scarce (Wang, 2013). Moreover, how NMDAR antagonism affects information coding in individual neurons and neuronal populations that support naturalistic use of WM remains unclear.

To investigate this issue, we trained two rhesus macaques to perform a spatial WM task in a virtual environment. During a trial, a visual cue appears in 1 of 9 possible locations in a virtual arena. Subjects had to remember the cue location during a 2 second delay period. They were then required to navigate to the cued location using a joystick. Neural recordings were performed on both subjects using two 96 channel multi-electrode arrays located in the lateral prefrontal cortex (areas 8Ad/v).

Here we demonstrate that intramuscular administration of ketamine in non-human primates produce short lasting (~1 hour) impairments in performance during a spatial WM task in a virtual environment that mimics naturalistic settings. This corresponds to a transient loss in the tuning of lateral prefrontal cortex neurons that is required to encode remembered locations in the environment. Narrow spiking (putative) parvalbumin interneurons lose their tuning by decreasing their responses to preferred remembered locations. Contrastingly, broad spiking neurons (primarily putative pyramidal neurons) loss their tuning by increasing their responses to all remembered locations. These effects caused a reduction in the ability of prefrontal neuronal populations to encode mnemonic representations of space.

Our results show that low doses of ketamine produce transient WM impairments during a virtual task that mimics realistic use of WM by reducing the ability of prefrontal neuronal populations to produce reliable memory representations. Results may also reflect mechanisms underlying WM deficits in individuals with schizophrenia.

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Poster

690. Working Memory: Prefrontal Cortex II

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Program #/Poster #: 690.10/X36

Topic: H.01. Animal Cognition and Behavior

Support: DFG JA 1999/5-1

Title: Reorganization of working memory coding after distraction by switching of target-selective populations in primate prefrontal cortex

Authors: *X. LIN[1,2], A. NIEDER[3], S. N. JACOB[1];
[1]Dept. of Neurosurg., Tech. Univ. of Munich, Munich, Germany; [2]Grad. Sch. of Systemic Neurosciences, Ludwig-Maximilians Univ. of Munich, Munich, Germany; [3]Animal Physiol. Unit, Univ. Tuebingen, Tuebingen, Germany

Abstract: Retaining behaviorally relevant information in the face of distraction is a distinctive feature of working memory. Previous studies have shown that the prefrontal cortex (PFC) is able to resist distracting inputs, but the implementation at the single neuron and neuronal population level remains unknown. Relevant information could be carried over using the same code, or there might be a reorganization of code after distraction. Here, we use population analyses with retained links to individual neurons to explore the basis of resistance to distraction in working memory. We analyzed acute extracellular recordings of 726 single units acquired in 78 sessions from the lateral PFC of two rhesus monkeys performing a delayed match-to-numerosity task with distractors. Linear discriminant analysis (LDA) classifiers were cross-temporally trained and tested (100 ms steps, 100 ms FWHM) on either the sample (task-relevant) or distracting numerosity to investigate the persistence and transfer of working memory representations. Examination of discriminant subspaces showed that the decision boundary was mostly captured by the first component. We found that sample information could be robustly decoded from the PFC population even after distraction. Notably, however, the code did not transfer from the first to the second memory delay (preceding and following the distractor, respectively). We selected the dominant sample coding neurons (largest projection onto the first component) in both delay periods. The populations did not overlap. The dominant first delay neurons coded sample information early and persistently until the distractor was presented, but did not continue into the second delay. Instead, they switched to encoding the distractor. Conversely, distractor information was low in the dominant second delay population. Neurons in this group started to represent the sample numerosity late in the first delay, just prior to distraction. Robust cross-stimulus decoding (trained on sample, tested on distractor) confirmed that the task-relevant and distracting stimuli partly shared memory codes and thus competed for the same cognitive resources. In contrast to the dominant neurons, the remaining population exhibited less accurate and more dynamic coding of sample information. Interestingly, this population's code readily transferred from the first to the second memory delay. Together, these findings suggest complementary contributions of distinct subgroups of PFC neurons to working memory maintenance and resistance to distractors, warranting further investigations into their cellular identity and connectivity patterns.

Disclosures: X. Lin: None. **A. Nieder:** None. **S.N. Jacob:** None.

Poster

690. Working Memory: Prefrontal Cortex II

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Program #/Poster #: 690.11/X37

Topic: H.01. Animal Cognition and Behavior

Support: CIHR
NSERC

Title: Reference frames for spatial working memory in dorsal and ventral lateral prefrontal cortices of macaques

Authors: *R. LUNA[1,2], M. P. ROUSSY[1,2], A. J. SACHS[4], S. TREUE[5], J. C. MARTINEZ-TRUJILLO[1,2,3];
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Abstract: Single neurons of the Lateral Prefrontal Cortex (LPFC) of macaques can encode spatial working memory (WM) signals. Nevertheless, it is not clear whether this mechanism retains spatial information in different frames of reference. Here we explored this question using an Oculomotor-Delayed Response (ODR) task, which allowed us to dissociate the memorized spatial locations between two frames of reference (i. e., retino-centered or screen-centered). We trained two rhesus monkeys to fixate a dot that appeared at one of sixteen possible positions on the stimulation screen. Then a cue stimulus transiently appeared at a different position during 1000ms. The animals kept looking at the fixation dot for another 1000ms (WM delay) and upon its extinction they made a saccade to the memorized target location. Liquid reward was delivered for correct responses. We recorded the activity of single-unit cells in the LPFC using two multi-electrode arrays (contact area of 16mm2, 10x10 electrodes) implanted in the dorsal (dLPFC) and ventral (vLPFC) gyri surrounding the Principal sulcus and anterior to the Arcuate sulcus (areas 8A and 9/46, respectively). Next, we computed the average firing rate during the WM delay for all units and decoded their spatial selectivity. The systematic variations in the initial fixation position allowed us to decode the remembered, cued locations relative to the fixation point (retino-topic reference frame) as well as relative to the stimulation screen (spatio-topic reference frame). We recorded 83 and 142 units in the dLPFC and vLPFC areas, respectively. We found that 17% of dLPFC units and 15% of vLPFC units encoded the remembered location in the retinotopic reference frame. Notably, 11% of dLPFC units along with 13% of vLPFC units encoded the remembered location in the spatiotopic reference frame. Our results show that LPFC encodes spatial working memory in both retinotopic and spatiotopic frames of reference, with a slight dominance of the former. Interestingly, they also show that dLPFC contains a larger

proportion of neurons tuned for the retinotopic frame, but a lower proportion tuned for the spatiotopic frame, compared to vLPFC.

Disclosures: R. Luna: None. **M.P. Roussy:** None. **S. Treue:** None. **J.C. Martinez-Trujillo:** None. **A.J. Sachs:** None.

Poster

690. Working Memory: Prefrontal Cortex II

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Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 690.12/X38

Topic: H.01. Animal Cognition and Behavior

Support: NSFC 31571098

Title: Blockade of connexin43 hemichannels impairs working memory and excitatory synaptic transmission in the prefrontal cortex of rats

Authors: *X. TAO, Z. LIU, X. ZHANG;
Inst. of Brain Sci., Shanghai, China

Abstract: The gap junction is essential for the communication between astrocytes and neuron by various connexins , which allows the rapidly exchange of biological information between cells, playing a key role in coordinating the synaptic functions. Cx43 hemichannels (Cx43 HCs) is highly expressed in the central nervous system and have been demonsrated to modualate syanptic plasticity and hippocampal spatial memory. However, whether Cx43 HCs of medial prefrontal cortex involves in synaptic transmission and working memory in the medial prefrontal cortex of rats still remains unclear . To this end, we made use of Gap27, a specific hemichannels blocker for Cx43 HCs,is bilaterally infused Gap27 into the prelimbic (PrL) area of the mPFC followed by the test of working memory in a T maze.Furthermore, we examined the effects of Gap27 on synaptic transmission using whole-cell patch-clamp in acute prefrontal cortex slices. Our results demonstratethat prefrontal cortex Cx43 HCsblockade significantly impair the working memory and synaptic transmission, implying that Cx43 HCs in prefrontal cortex play an important role in prefrontal cortex working memory and synaptic transmission.

Disclosures: X. Tao: None. **Z. Liu:** None. **X. zhang:** None.

Poster

690. Working Memory: Prefrontal Cortex II

Location: Hall A

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Program #/Poster #: 690.13/X39

Topic: H.01. Animal Cognition and Behavior

Support: HHMI

Title: High channel count electrophysiological recordings in prefrontal cortex in a novel spatial memory task

Authors: *C. BÖHM[1], A. K. LEE[2];
[1]Janelia Res. Campus, Ashburn, VA; [2]HHMI Janelia Res. Campus, Ashburn, VA

Abstract: Past research on spatial working memory has largely focused on simple tasks with a binary choice, such as the T-maze. In these tasks, the animal can memorize the location of the goal or the route to the goal from the start location. In addition, such tasks tend to result in stereotyped behaviors for each goal that may themselves produce goal-associated neural correlates. Thus, the animal's strategy to solve the task and the interpretation of neural correlates can be ambiguous. We have devised a novel spatial memory task where rats are required to flexibly encode three spatially distinct goals on a trial-by-trial basis. The goals can be reached via multiple routes, one of which is available in each trial. Knowledge of the available route is only gained after a delay period in which the animal has to perform a nose poke in one of three randomly chosen start positions. This design forces the animal to memorize the spatial location of the goal instead of planning a route from start position to goal position. This allows us to dissociate between neural correlates of route planning and goal representation. In such cognitively demanding tasks a large population of neurons in several brain regions, including prefrontal areas, are expected to be required to coordinate their activity and encode task-relevant variables and rules. Sampling a sufficiently large number of neurons at high temporal accuracy poses a challenge to current electrophysiological recording technology. Here we have employed Neuropixels probes, a new type of high channel count silicon probe featuring nearly a thousand recording sites along a single 10 mm shank, of which 384 can be recorded simultaneously. The shank spans multiple task-relevant brain regions including anterior cingulate cortex, prelimbic cortex and infralimbic cortex. This technology has allowed us to record activity from 100-200 frontal cortical neurons simultaneously in freely behaving rats performing a complex spatial working memory task. The high number of neurons also facilitates single trial analysis, which is highly relevant since the working memory content must be updated from trial to trial and be instantly accessible. We have found that current spatial location at the start or goal positions can be clearly and unambiguously decoded by the combined firing rates of multiple neurons over a range of timescales, from hundreds of milliseconds to seconds. The intended goal location while

the rat is performing the nose poke is not linearly separable in this form. Ongoing analysis is focused on other biologically plausible forms of representation, such as sequences of neural activity or coordinated ensemble activity.

Disclosures: C. Böhm: None. **A.K. Lee:** None.

Poster

690. Working Memory: Prefrontal Cortex II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 690.14/X40

Topic: H.01. Animal Cognition and Behavior

Title: Linking selective pharmacological suppression of HCN1 to synaptic integration, prefrontal cortical function and working memory

Authors: *E. HARDE[1], M. WEBER[1], J. WELLBOURNE-WOOD[1], P. SCHOENENBERGER[1], M. PAINA[2], J.-F. ROLLAND[2], M. CHERNYSHEVA[3], B. KOC[1], R. REDONDO[1], J. WAMSTEEKER CUSULIN[1], F. HELMCHEN[3], E. O'CONNOR[1], B. HALL[1];
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Abstract: HCN channels regulate neuronal excitability, dendritic integration of synaptic inputs, and contribute to synaptic plasticity. HCN1 channels are highly expressed in brain regions associated with cognition including medial prefrontal cortex (mPFC) and hippocampus. Genetic suppression of HCN1 improves working memory by increasing signal-to-noise ratio in mPFC circuits, which suggests that pharmacological suppression of HCN1 channels would have beneficial effect on cognition. Pharmacological characterization to gain insight into the role of HCN channels has largely relied upon antagonism using ZD7288. However, this compound is not HCN isoform selective, it affects other channels, and is not suitable for *in vivo* studies. Here, we have further characterized a tool compound (J&J12e) that has 150-fold higher potency than ZD7288. Using automated and manual patch clamp, we demonstrated fast onset of channel block by J&J12e and observed an 8-fold higher potency for HCN1 over HCN2. J&J12e slowed activation kinetics of HCN1-mediated I_h current in HEK293 cells as well as in brain slices, suggesting an allosteric channel blocking mechanism. In brain slices, J&J12e suppressed HCN-mediated sag response and improved synaptic integration through increased summation of evoked or artificial EPSPs. Additionally, J&J12e showed activity on HCN1 when co-expressed with TRIP8b, on tandem HCN1/HCN2 channels, and on both rat and human isoforms. In contrast to ZD7288, J&J12e passes the blood-brain barrier and is therefore suitable for use *in vivo*. We performed EEG recordings in freely moving rats and found that J&J12e increased power in the gamma frequency range. Using miniaturized microscopes to gain single cell resolution *in vivo*, we show that J&J12e modulates activity of a subset of mPFC neurons. Since

mPFC is critical for working memory, we assessed the compound in behavioral tests including TUNL and T-maze alteration task. Our results indicate that selective, pharmacological inhibition of HCN1 has potential to provide cognitive enhancement through its actions of promoting synaptic integration in brain circuits critical to support working memory.

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Poster

690. Working Memory: Prefrontal Cortex II

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Program #/Poster #: 690.15/X41

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant AG028271
NIH Grant AG058109

Title: High fat diet evokes exaggerated neuroinflammation in prefrontal cortex and impairments in working spatial memory in aged rats

Authors: B. M. GONZALEZ OLMO[1], J. M. JOHNSON[1], ***R. M. BARRIENTOS**[1,2,3,4];
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Abstract: World-wide consumption of saturated fats and refined sugars has dramatically increased across all age groups, including older adults. Not surprisingly, these statistics are highly correlated with the escalating obesity rates in this population. This is concerning because of the well-known associations between obesity and cognitive declines, and aging and vulnerable cognitive function. Because obesity is a complex disease with many comorbidities (making the study of underlying mechanisms difficult and confounded), we employ a short-term diet manipulation protocol. We have previously demonstrated that short-term consumption of a high-fat diet (HFD) among aged rats evokes an exaggerated neuroinflammatory response in the hippocampus and amygdala, causing precipitous memory consolidation impairments of contextual, cued-fear, and reference spatial memory. Here, we explore the effects of HFD in aging on prefrontal cortex function and neuroimmune phenotype. Young adult (3 months old) and aged (24 months old) F344xBNF1 rats were assigned to either chow or HFD for one week. Proinflammatory cytokine levels in the prefrontal cortex were significantly elevated in HFD-fed aged rats compared to HFD-fed young adult rats. In a separate cohort of rats, working spatial memory was assessed using the Morris water maze. In accordance with the neuroimmune data,

HFD-fed aged rats exhibited significantly longer latencies to reach the platform than controls, indicating impaired working memory function. These findings suggest that short-term HFD consumption in the aged rat is sufficient to evoke widespread memory impairments that may be a result of robust neuroinflammatory responses in key memory-mediating brain regions.

Disclosures: B.M. Gonzalez Olmo: None. **J.M. Johnson:** None. **R.M. Barrientos:** None.

Poster

690. Working Memory: Prefrontal Cortex II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 690.16/X42

Topic: H.01. Animal Cognition and Behavior

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Title: Distributed dynamic coding for spatial working memory in hippocampal-prefrontal networks

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Abstract: Spatial working memory (SWM) is a central cognitive process during which the hippocampus and prefrontal cortex (PFC) encode and maintain spatial information for subsequent decision making. This occurs during ongoing computations relating to spatial position, recall of long-term memory, attention, etc. We recorded single units, in both hippocampus and PFC, to define how neural dynamics associated with intermittently presented task parameters relate to continuing oscillatory activity in control rats and those with a brain malformation. Neurons that encode task parameters are those that are well-modulated in time and incorporated into a functional network between regions. Our results implicate a model in which ongoing oscillatory coordination among neurons in the hippocampal-PFC network defines a functional network that is poised to receive sensory inputs that are integrated and multiplexed as working memory. These dynamics are systematically altered in disease and may provide potential targets for stimulation-based therapies.

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Poster

690. Working Memory: Prefrontal Cortex II

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American Federation for Aging Research (D.B.D)

Title: Maternal skewing of the active X chromosome via Xist deletion induces cognitive deficits in young and aging female mice

Authors: *S. ABDULAI-SAIKU[1], D. WANG[1], B. PANNING[2], D. B. DUBAL[1];
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Abstract: The X chromosome is enriched for cognition-related genes. Female mammals have two X chromosomes per cell, one of maternal and one of paternal origin. In development, one X is randomly inactivated by *Xist*, a long noncoding RNA. Thus, females are mosaics; they express the maternal X in roughly half of their cells and the paternal X in the other half. Mosaicism of the active X confers epigenetic diversity since the parent-of-origin governs differences in X gene expression. Interestingly, due largely to the randomness of X inactivation, the ratio of maternal to paternal X expression is skewed in many females. We wondered whether diversity of the active X chromosome's parent-of-origin contributes to cognition. To test this, we generated transgenic mice with a skewed X chromosome inactivation pattern by deleting *Xist* from the maternal X chromosome (XIST mice). This genetic manipulation renders only the maternal X active. In XIST mice and their non-transgenic (NTG) litter-mate controls, we assessed learning, memory and behavior using the Morris Water Maze, interactive place avoidance test, open field and elevated plus maze. We found that female XIST mice were cognitively impaired in the spatial memory tasks measured in the water maze, place avoidance, and the open field, compared to NTG controls. Importantly, pain perception, locomotion and anxiety were equivalent between NTG and XIST females. Select impairments extended to and increased in aging female XIST mice. Thus, maternal skewing of the active X chromosome via *Xist* deletion in female mice impaired cognition – and this worsened with some measures in aging. Since mice were inbred, all X's were genetically identical. Therefore, differences between XIST and NTG mice can be attributed to epigenetic X effects resulting from maternal X origin and/ or *Xist* deletion. Further understanding of how X chromosome skewing influences epigenetics, gene expression, and cognition may offer new insights into new therapeutic targets for cognitive impairment across the lifespan and in aging.

Disclosures: **S. Abdulai-Saiku:** None. **D. Wang:** None. **B. Panning:** None. **D.B. Dubal:** None.

Poster

690. Working Memory: Prefrontal Cortex II

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Title: Longevity factor klotho attenuates cognitive and synaptic deficits related to Parkinson's disease

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Abstract: Cognitive impairment from Parkinson's disease (PD) is a major challenge with no effective medical treatments. Klotho is a pleiotropic protein that, with transgenic elevation, extends lifespan, enhances cognition, increases synaptic plasticity, and counters cognitive deficits related to Alzheimer's disease (AD). In humans, a genetic variant of *KLOTHO,* in the form of KL-VS heterozygosity, increases klotho levels and associates with better healthspan, enhanced executive cognition, and attenuated emergence of certain AD biomarkers. Here, we investigated whether transgenic klotho elevation in mice attenuates deficits related to PD – and whether genetic variation of *KLOTHO* in humans associates with measures of resilience in PD. In our mouse studies, we crossed transgenic mice expressing the wildtype human alpha-synuclein (hSYN) with transgenic mice overexpressing klotho. We measured mortality, spatial and working memory, motor functions, synaptic plasticity, and pathogenic protein levels in littermates using multiple cohorts of mice. In our human studies, we measured baseline cognition and CSF biomarkers in healthy controls (HC) and PD subjects, based on KL-VS status, in the Parkinson's Progression Markers Initiative (PPMI) study. We found that klotho overexpression decreased hSYN-induced mortality in mice. Further, hSYN impaired working and spatial memory and motor functions – and klotho attenuated these cognitive, but not motor, deficits. Klotho overexpression also decreased hSYN-induced synaptic impairments, measured by long-

term potentiation, an effect mediated by a subunit of the NMDA receptor, GluN2B. Biochemical studies showed that klotho decreased total hippocampal levels of the human alpha-synuclein protein, but not other pathogenic proteins. In human PD, KL-VS heterozygotes exhibited better baseline semantic and phonemic fluency across several cognitive tests. While PD subjects as a group showed decreased CSF alpha-synuclein levels, KL-VS heterozygotes showed no changes between HC and PD. Together, these data provide evidence that klotho can counteract cognitive deficits related to PD, possibly by decreasing alpha-synuclein levels – and these findings may be relevant to human PD. Further study of klotho and alpha-synuclein may open new therapeutic pathways to combat cognitive dysfunction in PD and other neurodegenerative diseases.

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Poster

690. Working Memory: Prefrontal Cortex II

Location: Hall A

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Bakar Family Foundations (D.B.D)

Title: The X chromosome factor Kdm6a confers sex-based resilience against Alzheimer's disease-related deficits

Authors: *E. J. DAVIS[1], S. ABDULAI-SAIKU[2], A. J. MORENO[2], L. W. BONHAM[3], G. M. WILLIAMS[4], D. WANG[2], A. P. ARNOLD[6], B. PANNING[5], J. S. YOKOYAMA[3], D. B. DUBAL[2];
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Abstract: Biologic sex influences Alzheimer's disease (AD) - with differing vulnerabilities in men and women. More women suffer from AD, largely due to their longevity since they live to advanced ages when AD risk is highest. In contrast, men with the disease die faster in populations worldwide, indicating a male-disadvantage. We have previously shown that a second X chromosome increases resilience to aging and AD-related deficits using genetic manipulations of gonads and sex chromosomes in male and female hAPP mice and in mouse primary neurons. Here, we sought to investigate how a second X chromosome can confer resilience against AD-related deficits using a mouse model of AD, primary neurons, and a human population representing the spectrum of AD. While XY and XX organisms express only one active X due to X chromosome inactivation (XCI), a few factors escape XCI and thus are higher in females compared to males. One of these genes, *Kdm6a*, escapes in both mice and humans and is a histone demethylase linked to cognitive functions. We thus determined whether higher levels of *Kdm6a* - as found in the XX brain - could counter AD-related vulnerability in the XY brain. We first confirmed the presence of a second X chromosome increased levels of *Kdm6a* in mouse hippocampus; it did so in a manner that was independent of gonadal phenotype or the Y chromosome. We then used lentiviral vectors in mice to modulate *Kdm6a* expression *in vivo* and *in vitro.* Overexpression of *Kdm6a* in the hippocampus of XY hAPP mice to higher levels observed in XX hAPP mice attenuated spatial learning and memory deficits in the Morris water maze. Similarly, overexpression of *Kdm6a* in XY primary neurons decreased Aβ toxicity *in vitro*. Furthermore, knockdown of *Kdm6a* in XX neurons to levels observed in XY neurons worsened Aβ toxicity *in vitro*. Finally, we found that in parallel with female mice, *KDM6A* was also elevated in the brains of women - and that *KDM6A* genetic variation causing higher RNA levels in humans was associated with cognitive resilience. Our findings reveal a role for the baseline XCI escapee *Kdm6a* in countering AD-related deficits. Further understanding of how the second X chromosome confers resilience, and specifically of *Kdm6a*'s downstream mechanisms, could lead to novel therapies for treating AD in both men and women.

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Poster

690. Working Memory: Prefrontal Cortex II

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MEXT KAKENHI Grant JP17K13274
AMED Grant JP19dm0207001

Title: Cellular level functional structures in the monkey prefrontal cortex during working memory

Authors: *H. ABE[1,2], W. SONG[1,3,4,5], N. JU[1,3,4,5], N. ICHINOHE[2,6], S. TANG[1,3,4,5];
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Abstract: The brain performs computation in the network of populations of neurons. Organizing principles of such populations are well studied in the sensory and motor cortices. It remains, however, unclear in the association cortex such as the prefrontal cortex (PFC) important for higher-level cognition. Several studies suggested columnar organizations in the PFC neural activity during working memory, which is a cognitive system temporally holding information for processing and a hallmark of PFC functions. However, fine functional structures have never been visualized in the PFC.
Two adult rhesus monkeys were trained to perform the standard oculomotor delayed response (ODR) task where they had to remember a spatial position. Neural activity was measured using a calcium sensor, GCaMP6s, which was expressed in PFC neurons by injecting an adeno-associated virus vector into multiple sites around the principal sulcus of the PFC in the left hemisphere. While performing the task, calcium signals were imaged from neurons in the superficial layers. We found that functional clustering of neurons was absent in examined 8 sites

near the principal sulcus in two monkeys. One exception was a cluster located near the caudolateral end of the principal sulcus. In this cluster, approximately 40% of neurons had sustained activity representing spatial information while the monkey was remembering an instructed spatial location. The activity of nearby neurons represented similar spatial positions. At more rostral 8 sites, only a minority of neurons (~10%) encoded spatial information and those neurons were located sparsely.
Thus, PFC neurons with similar functional properties were clustered at the caudoralteral site, but not at other rostral sites, suggesting that columnar organizations do not exist ubiquitously in the dorsolateral PFC as a processing unit for spatial working memory.

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Poster

691. Memory Consolidation and Reconsolidation: Molecular Mechanisms

Location: Hall A

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Program #/Poster #: 691.01/Y1

Topic: H.01. Animal Cognition and Behavior

Support: Startup funds from College of Agricultural and Life Sciences at Virginia Tech
Startup funds from College of Science at Virginia Tech

Title: A role for double-strand DNA breaks in epigenetic-mediated transcriptional control during memory reconsolidation

Authors: *S. V NAVABPOUR[1], J. ROGERS[2], T. MCFADDEN[3], S. A. ORSI[4], T. J. JAROME[5];
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Abstract: Consolidation is a process that stabilizes acquired memories in cells and requires increased transcription regulation via epigenetic mechanisms. Numerous studies have revealed that following retrieval, a previously consolidated memory is destabilized and requires increased transcriptional regulation in order to be restablized, a process called reconsolidation. Previously, it was reported that global and gene-specific histone H3 lysine-4 trimethylation (H3K4me3), an indicator of active transcription in cells, is increased in the area CA1 of the dorsal hippocampus one hour after the retrieval of a contextual fear memory and was critical for the reconsolidation process (Webb et al. 2017). However, it is currently unknown how this epigenetic mark is regulated following memory retrieval. Recently, it has been shown that neuronal activity triggers double-strand DNA breaks (DSB) in some early-response genes (Madabhushi et al. 2015). However, little is known about the role of DSB *in vivo* and whether DSB occur following the

retrieval of a memory remains equivocal. Here, using chromatin immunoprecipitation (ChIP) analyses, we report a significant overlap between DSB and H3K4me3 in area CA1 during the reconsolidation of a contextual fear memory. We found an increase in phosphorylation of histone H2A.X at serine 139 (H2A.X(p139)), a marker of DSBs, in the *Npas4*, but not *c-Fos*, promoter region 5 minutes after retrieval, which returned to baseline by 15 minutes, indicating a potential role of DSB in the transcription of some, but not all, critical memory permissive genes. While previous reports found an increase of H3K4me3 in the transcription start site (TSS) region of *Npas4* one hour after retrieval, we observed an increase in H3K4me3 levels in the *Npas4* promoter, but not TSS, region 5 minutes after the retrieval, with no change at *c-Fos* promoter or coding regions. This suggests that H3K4me3 may initially start in the *Npas4* promoter region and move into the coding region as the reconsolidation process progresses. Additionally, the significant overlap between H2A.X(pS139) and H3K4me3 at the *Npas4* promoter suggest that DSBs may be critically involved in increased epigenetic-mediated transcriptional regulation necessary for memory reconsolidation. Consistent with this, our preliminary results show that siRNA-mediated knockdown of topoisomerase II β, the enzyme responsible for DSB, in area CA1 prior to retrieval impairs memory, suggesting the indispensable role of DSB in the memory reconsolidation process. Collectively, our data propose a novel mechanism for memory reconsolidation through the increase of gene transcription via DSB early on after memory retrieval.

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Poster

691. Memory Consolidation and Reconsolidation: Molecular Mechanisms

Location: Hall A

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Program #/Poster #: 691.02/Y2

Topic: H.01. Animal Cognition and Behavior

Support: NSERC

Title: Evidence that muscarinic receptor activation destabilizes object memories via a mechanism involving CaMKII and synaptic protein degradation

Authors: *C. E. WIDEMAN[1], S. D. CREIGHTON[1], K. H. JARDINE[1], K. PEDENKO[1], V. THAYALAN[1], K. A. MITCHNICK[1], B. E. KALISCH[2], W. S. MESSER, Jr[3], B. D. WINTERS[1]; [1]Psychology and Collaborative Neurosci. Program, [2]Mol. and Cell. Biol., Univ. of Guelph, Guelph, ON, Canada; [3]Pharmacol. and Exptl. Therapeut. and Medicinal and Biol. Chem., Univ. of Toledo, Toledo, OH

Abstract: The storage of long-term memory is more dynamic than once believed. Reminder cues can trigger consolidated long-term memories to destabilize, rendering them labile and necessitating protein synthesis-dependent reconsolidation. It has been postulated that the content of long-term memories can be updated when in this labile state. However, not all memories destabilize following reactivation. Our previous work has shown that novel contextual information at the time of reactivation can destabilize otherwise resistant object memories and that this process depends on acetylcholine (ACh) activity at M_1 muscarinic receptors in perirhinal cortex (PRh). Accordingly, pharmacological activation of M_1 receptors can also promote object memory destabilization in the absence of novelty. Both novelty- and M_1-induced object memory destabilization require activation of the ubiquitin proteasome system (UPS). The UPS is critical for regulating turnover of synaptic proteins, and this may reflect a mechanism by which memories physically destabilize at the synaptic level. Calcium calmodulin-dependent protein kinase II (CaMKII) is implicated in proteasome activation. Consistent with this, here we show that CaMKII in PRh is required for both novelty- and M_1-induced object memory destabilization, indicating a mechanism through which M_1 receptors likely activate the UPS for destabilization. We also provide molecular evidence for UPS activation following reactivation with novelty. We observed a reduction in Shank 3, a synaptic scaffold protein, in PRh of rats reactivated with novelty, suggesting that synaptic protein degradation may underlie novelty-induced object memory destabilization. The results of the current study therefore build on our previous work implicating the molecular pathway by which ACh can lead to memory destabilization. Together these findings suggest a novel role for ACh in long-term memory maintenance, whereby muscarinic signaling promotes memory destabilization when new information is present during reactivation. This mechanism is likely important for adaptive long-term memory updating over time.
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Poster

691. Memory Consolidation and Reconsolidation: Molecular Mechanisms

Location: Hall A

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Topic: H.01. Animal Cognition and Behavior

Support: CNPq
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FAPESP

Title: Triggering reconsolidation of an ethanol conditioned place preference (CPP) memory: The role of reactivation`s length and dopaminergic receptors

Authors: *F. Z. BOOS[1], C. A. FAVORETTO[1], F. C. CRUZ[2], I. M. QUADROS[1];
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Abstract: Following retrieval, memory can enter into a labile state (destabilization) and be updated through the reconsolidation process. It has been suggested that occurrence of a prediction error during retrieval is important to induce destabilization, which involves dopamine (DA) signaling. In the CPP literature, reactivation sessions successful to induce destabilization are conducted in a drug-free state. Importantly, studies suggest that DA can be either increased by contextual cues related to the drug, or decreased by prediction error in case the drug was absent. In this study, our goal was to investigate the involvement of D1R in the destabilization of a CPP memory. Therefore, we conditioned mice to CPP with ethanol and later reactivated memory by allowing them to freely explore the contexts in a drug-free state for 5 or 10min. Immediately after, animals receive the protein synthesis inhibitor cicloheximide (CHX) to block reconsolidation, or vehicle (VEH). Next, to assess the D1R involvement in memory destabilization, the same protocol we repeated but the D1R antagonist SCH23390, D1R agonist SKF38393, or VEH i.p. was administered 30min pre-reactivation. We found that CHX disrupted reconsolidation when injected after the 10min reactivation session, but not after the 5min one. In the second experiment, SCH and SKF treatments did not affect recall, and the 10min session unexpectedly decreased preference in most of the groups during test, including VEH-VEH, suggesting that extinction took place. These preliminary results indicate that the CPP memory is not destabilized by a 5min reexposure, but reconsolidation is triggered following a longer 10 min session. However, a 10min reactivation may be in between the time window effective to induce reconsolidation and extinction, and additional studies will be required to infer the role of D1R in destabilization.

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Poster

691. Memory Consolidation and Reconsolidation: Molecular Mechanisms

Location: Hall A

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Program #/Poster #: 691.04/Y4

Topic: H.01. Animal Cognition and Behavior

Support: NIMH 1R01MH117964-01
Carver Chair in Neuroscience

Title: cAMP mediates the impact of sleep deprivation on memory and synaptic plasticity

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Abstract: We spend nearly one-third of our life asleep, yet the biological reasons for this state have not been identified. Sleep facilitates memory storage, and sleep loss leads to impairments in memory. Memory for tasks that involve the hippocampus, a brain region that mediates memory for facts and events, is particularly sensitive to sleep loss. Within the hippocampus sleep loss leads to deficits in synaptic plasticity, decreased dendritic spine density, and decreased protein synthesis. Previous work in our lab found that the reduction of cyclic AMP (cAMP) that occurs as a result of sleep deprivation may mediate those memory deficits, and that rescue of cAMP in the hippocampus of sleep-deprived mice is sufficient to prevent them. Our hypothesis is that cAMP not only acts as a mediator for the cognitive outcomes of sleep deprivation, but also for the observed changes in hippocampal plasticity. By expressing the *Drosophila* G-protein coupled octopamine receptor (OAR) in excitatory hippocampal neurons, we are able to selectively increase cAMP levels in those neurons during a five-consecutive hour sleep deprivation period. Immediately following sleep deprivation, hippocampal slices were prepared for electrophysiological recordings. We found that cAMP rescue during the five-hour deprivation period prevents deficits in 4-train long-term potentiation (LTP), a long lasting (late) form of LTP. This finding demonstrates that cAMP mediates not only the hippocampal-memory effects of sleep deprivation, but also some of the changes in hippocampal synaptic plasticity. Future work will focus on the effect of cAMP rescue on other forms of LTP, and on the effects of cAMP rescue on dendritic spine density in the hippocampus.

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Poster

691. Memory Consolidation and Reconsolidation: Molecular Mechanisms

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Topic: H.01. Animal Cognition and Behavior

Support: the National Science Foundation of China (91632301, to Y.Z.)
the National Science Foundation of China (91632301, to Y.Z.)

Title: The involvement of the hippocampal Rac1 activity in protein synthesis-induced transient amnesia

Authors: *L. LV[1], Y. ZHONG[2];
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Abstract: Memory consolidation is the process that depends on de novo protein synthesis for the stabilization of a long-term memory (LTM). During the process, memory is susceptible to disruption, such as protein synthesis inhibition, resulting in persistent retrograde amnesia. However, thecurrent study reveals that the protein synthesis inhibitor-induced impaired contextual fear memory can spontaneously recoverwith time, which correlates with the levels of Rac1 activity in hippocampal excitatory neurons. A single injection of the protein synthesis inhibitor, either anisomycin or cycloheximide, following single-trial contextual fear conditioning caused transient retrograde amnesia as reflected with a spontaneous recovery of the memory at day 7 after training. By virally expressing the inhibitory DREADDs (designer receptors exclusively activated by designer drugs), hM4Di, we first identified the reversibility of protein synthesis induced amnesiawithin hippocampus, but not mPFC. Since Rac1-dependent active forgetting is involved in dynamic memory maintenance, we were interested in studying whether hippocampal Rac1 activity play roles in the reversibility of protein synthesis-induced amnesia**.** Unexpectedly, we found that a single injection of the protein synthesis inhibitors causes an increase of hippocampal Rac1 activity at day 1 after training. And such increased Rac1 activity returned to the basal level at day 7 after training, accompanying with spontaneously recovery of memory under amnesia. Our data suggest that the reversibility of amnesia correlates with hippocampal Rac1 activity.

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Poster

691. Memory Consolidation and Reconsolidation: Molecular Mechanisms

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Topic: H.01. Animal Cognition and Behavior

Support: Australian Research Council Discovery Project DP170103952

Title: A "synaptic tag and capture"-like mechanism (probably) does not underlie the consolidation of second-order fear

Authors: *D. M. LEIDL[1], B. P. LAY[2], R. F. WESTBROOK[1], N. M. HOLMES[1];
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Abstract: The present experiments originated in our recent findings (Lay et al, 2018) that consolidation of a second-order fear memory requires neuronal activity, but not de novo protein synthesis, in the basolateral amygdala complex (BLA). They tested the hypothesis that proteins synthesized in the BLA to consolidate first-order conditioned fear are exploited to consolidate second-order conditioned fear, similar to “synaptic tag and capture” (STC) identified in brain

slice electrophysiology studies. They did so by reducing the interval between S1-shock pairings (1st order) and S2-S1 parings (2nd order) from 48 hours to a few minutes. We reasoned that, if an STC-like mechanism underlies the consolidation of second-order conditioned fear, then blocking protein synthesis in the BLA during or after first-order conditioning should simultaneously disrupt consolidation of both first- and second-order conditioned fear. We found no evidence to support this hypothesis. Instead we consistently disrupted fear to the first-order S1 but left intact fear to the second-order S2. These results confirm that consolidation of first-order conditioned fear requires de novo protein synthesis in the BLA. They additionally show that consolidation of second-order conditioned fear does not involve an STC-like exploitation of proteins in the BLA.

Disclosures: D.M. Leidl: None. **B.P. Lay:** None. **R.F. Westbrook:** None. **N.M. Holmes:** None.

Poster

691. Memory Consolidation and Reconsolidation: Molecular Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 691.07/Y7

Topic: H.01. Animal Cognition and Behavior

Support: PAPIIT 203918

Title: Differential effect of moderate and intense training on expression in phosphorylated CREB protein in dorsal hippocampus

Authors: *A. C. MEDINA, H. I. GUILLERMO, P. C. BELLO-MEDINA, G. L. QUIRARTE, R. A. PRADO-ALCALÁ;
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Abstract: Phosphorylation of cAMP response element-binding (pCREB) is related to memory consolidation as this molecule participates in gen transcriptional activity in many brain neurons, which is important for synaptic plasticity. There is experimental evidence showing that the mechanism involved in the formation of long-term memory change when subjects are given intense training; in this condition amnestic treatments do not impede memory consolidation. Because the hippocampus has an important role in the memory consolidation, the objective of this study was to determine if amount of pCREB positive neurons in the dentate gyrus (DG) and Ammon's Horn CA1 and CA3 differ in moderate training from intense training. Independent groups of rats were trained in a one-trial step-through inhibitory avoidance task using different intensities of foot-shock (0.0, 1.0, and 3.0 mA). We also studied a group of rats that received the higher foot-shock (3.0 mA) without training and a naive group. Their brains were dissected 1 h after training. pCREB detection was made using an immunohistochemical technique. The results

showed that moderate training induced an increase in the amount of positive pCREB neurons in CA1 and DG, as compared with the naïve group. Intense training induced an increase in positive pCREB neurons in all hippocampal regions, and this increase was greater in CA3. We conclude that positive pCREB neurons in CA1 are involved in memory consolidation of moderate training, while positive pCREB neurons in GD, CA3, and CA1 are implicated in memory consolidation of intense emotional experiences. We thank Norma Serafín, Bertha Islas, Nydia Hernández, Martín García, Alejandra Castilla, Omar González, Ramón Martínez, and Javier Valles for technical assistance. Supported by PAPIIT 203918.

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Poster

691. Memory Consolidation and Reconsolidation: Molecular Mechanisms

Location: Hall A

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Program #/Poster #: 691.08/Y8

Topic: H.01. Animal Cognition and Behavior

Support: 5R01AG051807-04
NIA T32

Title: Effects of exercise on memory performance and hippocampal gene expression

Authors: *A. A. KEISER[1], C. W. BUTLER[2], E. A. KRAMÁR[1], D. P. MATHEOS[1], N. C. BERCHTOLD[2], S. CHEN[3], M. SAMAD[3], C. MAGNAN[3], P. BALDI[3], C. W. COTMAN[2], M. A. WOOD[1];
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Abstract: A growing body of evidence suggests that exercise is capable of improving cognitive function and reducing the risk of cognitive decline associated with aging and Alzheimer's disease (AD). Our labs have previously demonstrated that in males, exercise enables hippocampal-dependent learning in conditions that are normally subthreshold for encoding and memory formation, and depends on hippocampal induction of brain-derived neurotrophic factor (BDNF) as a key mechanism. In male mice with prior exercise experience, only a brief exercise period is required to reactivate the increase of BDNF in the hippocampus, suggesting that there exists a 'molecular memory' for the prior exercise experience that facilitates subsequent learning. However, the underlying mechanisms that mediate the molecular memory are currently unknown. We hypothesize that an epigenetic molecular memory of exercise as a previous experience primes specific genes for subsequent activation upon new learning, resulting in facilitated memory formation. In this study, we used RNA-sequencing to begin to define the

molecular and epigenetic signature underlying exercise-enhanced learning in the hippocampus. The behavioral approach involved examining different periods of initial exercise (0-3 weeks), a sedentary delay period (0-2 weeks), and a second short exercise period (2 days), followed by 3 min subthreshold training in an object location memory task. This allowed us to identify exercise parameters that led to the formation of robust long-term memory for object location, even though animals were given a subthreshold training period. Those parameters were then used to examine hippocampal long-term potentiation (LTP), a form of synaptic plasticity thought to underlie memory. We also used the same parameters to examine gene expression using RNA sequencing during memory consolidation period, one hour after training. Our results indicate that 2 weeks of exercise is sufficient to engage robust memory and LTP, even after one week of sedentary delay. We have also begun to examine how these parameters may be similar or different in females, as well as gene expression profiles engaged in the female hippocampus following exercise and subthreshold training in the object-location memory task. We are also beginning to understand how epigenetic mechanisms may be involved in establishing a molecular memory of exercise and facilitating gene expression during learning. Together, these studies begin to elucidate how a previous experience such as exercise is encoded at a molecular level to facilitate memory.

Disclosures: **A.A. Keiser:** None. **C.W. Butler:** None. **E.A. Kramár:** None. **D.P. Matheos:** None. **N.C. Berchtold:** None. **S. Chen:** None. **M. Samad:** None. **C. Magnan:** None. **P. Baldi:** None. **C.W. Cotman:** None. **M.A. Wood:** None.

Poster

691. Memory Consolidation and Reconsolidation: Molecular Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 691.09/Y9

Topic: H.01. Animal Cognition and Behavior

Support: R01 AG051807

Title: Exercise engages a molecular memory for enhanced cognitive improvement from subsequent physical activity

Authors: ***C. W. BUTLER**[1], A. A. KEISER[1], J. L. KWAPIS[2], N. C. BERCHTOLD[1], V. L. WALL[1], M. A. WOOD[1], C. W. COTMAN[1];
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Abstract: The beneficial effects of exercise on cognition are well established; however specific exercise parameters regarding the frequency and duration of physical activity that provide optimal cognitive health have not been well defined. Here, we explore the effects of the duration of exercise and sedentary periods on long-term Object Location Memory (OLM) in mice. We

use a weak object location training paradigm that is sub-threshold for memory formation in sedentary controls, to demonstrate that exercise enables long-term memories to form. We show that 14- and 21-days of running wheel access enables mice to discriminate between familiar and novel object locations after a 24 hour delay, while 2- or 7-days running wheel access provides insufficient exercise for such memory enhancement. Exercise-induced cognitive enhancement then exhibits considerable decay following 3 days of sedentary behavior. However, exercise-induced cognitive enhancement can be reactivated by an additional period of just 2 days exercise, previously shown to be insufficient to induce cognitive enhancement on its own. The reactivating period of exercise is capable of enhancing memory after 3- or 7-days of sedentary behavior, but not 14 days. These data suggest a type of "molecular memory" for the exercise stimulus, in that once exercise duration reaches a certain threshold, it establishes a temporal window during which subsequent low-level exercise can capitalize on the neurobiological adaptations induced by the initial period of exercise, enabling it to maintain the benefits on cognitive function. These findings provide important information regarding the temporal aspects of exercise-induced cognitive enhancement.

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Poster

691. Memory Consolidation and Reconsolidation: Molecular Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 691.10/Y10

Topic: H.01. Animal Cognition and Behavior

Support: NIMH grant R37 MH065635

Title: IGF2 receptor is required for memory consolidation in the hippocampus

Authors: *X.-W. YU, K. PANDEY, C. M. ALBERINI;
Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: Previous work from our laboratory showed that insulin-like growth factor II (IGF2) is crucial for memory formation. Additionally, supplying IGF2 when the animal is learning, immediately after the learning event, or during memory retrieval enhances memory retention and prevents forgetting. These memory-enhancing effects of IGF2 require its high-affinity receptor, the IGF2 receptor (IGF2R). IGF2R is also known as the cation-independent mannose-6-phosphate receptor, and has been largely studied for its role in sorting proteins to the endosomal and lysosomal compartments. However, the role of IGF2R in memory formation is not yet understood. Here, we used injections of a functionally-blocking IGF2R antibody into hippocampus of rats, and neuron-specific IGF2R knockdown in the hippocampus of mice, to

examine the role of IGF2R in memory consolidation. We found that blocking IGF2R impaired memory consolidation in rats during a limited temporal window. However, we observed no impact on memory encoding, expression, or retrieval. There were also no differences in locomotion or anxiety levels. Similar data were found in mice with IGF2R knocked down in hippocampal neurons. Blockade of IGF2R in rats also prevented the training-induced increase in *de novo* protein translation, measured using the surface sensing of translation (SUnSET) technique. We conclude that hippocampal IGF2R is upstream of training-induced translation of proteins, and is required for memory consolidation.

Disclosures: X. Yu: None. **K. Pandey:** None. **C.M. Alberini:** None.

Poster

691. Memory Consolidation and Reconsolidation: Molecular Mechanisms

Location: Hall A

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Program #/Poster #: 691.11/Y11

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant R01MH100822
NIH Grant R37MH065635
The Dana Foundation

Title: Episodic memory formation in infant rat requires hippocampal regeneration of reduced glutathione

Authors: *B. BESSIÈRES, E. CRUZ, C. M. ALBERINI;
Ctr. For Neural Sci., New York, NY

Abstract: The ability to form and remember long-term memories differs across developmental ages. Episodic memories formed in infant rat (post-natal day 17 - PN17) appear to be rapidly forgotten, a phenomenon found in rodents as in humans and believed to be associated to infantile amnesia, the inability of adults to remember early life experiences. By contrast, juvenile PN24 rats are able to form and express long-term memories. The formation of episodic memories requires the hippocampus, a region metabolically activated by episodic learning. The metabolic energy requirements of the brain are higher during post-natal development than in adulthood, suggesting that different metabolic regulatory mechanisms may underlie the formation of memory during development. However, very little is known about how learning regulates the metabolic responses across developmental ages. To begin filling this knowledge gap we determined how the hippocampal metabolome changes over the course of post-natal developmental ages and in response to learning. Untargeted metabolomic profiling of the rat hippocampus were carried out at PN1, PN7, PN17, PN24 and PN80 (young adult) in untrained condition and 1h after a single inhibitory avoidance (IA) training at PN17, PN24 and PN80.

Statistical and pathway analyses indicated that the hippocampus undergoes significant metabolic changes over development in all classes of metabolites, with the highest diversity and quantity of metabolites measured at PN24. Furthermore, most of the changes associated with learning were observed at PN17 with 54 metabolites significantly downregulated by comparison with the age-matched untrained rats. Among the 20 top-ranked metabolites downregulated, a large proportion are involved in the cellular defenses against oxidative stress, including the reduced glutathione (GSH), which is the most abundant antioxidant in the mammalian brain. We demonstrated that IA learning at PN17, but not at PN24, induces a fast and long-lasting increase in the activity of the hippocampal glutathione reductase (GR), an enzyme involved in the regeneration of GSH from its oxidized form. Using selective pharmacological inactivation of the GR upon IA learning, we then showed that the hippocampal GR-dependent regeneration of GSH is necessary for the formation of long-term memory in infant (PN17) but not in juvenile (PN24) rats. Taken together, our results provide new insights on metabolic regulations occurring in the hippocampus over development and after learning, and identify the glutathione-mediated antioxidant defense as a critical metabolic pathway for memory formation during infancy.

Disclosures: **B. Bessières:** None. **E. Cruz:** None. **C.M. Alberini:** None.

Poster

691. Memory Consolidation and Reconsolidation: Molecular Mechanisms

Location: Hall A

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Program #/Poster #: 691.12/Y12

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant MH065635

Title: Translation-dependent macroautophagy is required for long-term memory formation

Authors: *K. PANDEY, X.-W. YU, A. STEINMETZ, C. ALBERINI;
Ctr. for Neural Sci., New York Univ., New York City, NY

Abstract: Long-lasting memories, which store information for days, months and up to a lifetime, require wave/s of *de novo* translation, which has been extensively investigated in many species and different types of memories. Learning-induced *de novo* translation implies that mechanisms that rebalance protein levels, like protein degradation, must occur in order to control protein accumulation and maintain protein homeostasis. Although protein degradation mechanisms have been implicated in learning and memory, its regulation remains unknown. Here we show that episodic learning in rats significantly increases both the levels of proteins involved in autophagy and lysosomal degradation (macroautophagy), including beclin-1, LC3-II, p62 and LAMP1, and the autophagic flux in their dorsal hippocampus. The increases in macroautophagy proteins upon learning is not accompanied by changes in their mRNA levels, but depend on *de novo* translation

and Arc/Arg3.1. Similarly, autophagic flux requires translation and Arc/Arg3.1. In agreement with this translation requirement, learning increases the recruitment of beclin-1, LC3-II, p62 and LAMP1 mRNAs to the actively translating ribosomes. Finally, pharmacological or targeted molecular disruption of the learning-induced macroautophagy proteins impairs long-term memory, while leaving the short-term memory intact. We conclude that learning-induced *de novo* translation and Arc are required for the induction of macroautophagy, which is critical for long-term memory formation.

Disclosures: **K. Pandey:** None. **X. Yu:** None. **A. Steinmetz:** None. **C. Alberini:** None.

Poster

691. Memory Consolidation and Reconsolidation: Molecular Mechanisms

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Topic: H.01. Animal Cognition and Behavior

Support: MH100822 to C.M.A
MH065635 to C.M.A
5T32AG052909-02 to E.C.

Title: Hippocampal PFKFB3 glycolytic activity is required for memory formation during early development

Authors: *E. CRUZ, B. BESSIÈRES, C. M. ALBERINI;
New York Univ. Ctr. for Neural Sci., New York, NY

Abstract: Glucose is the major source of energy production in the brain, and energy consumption in the brain peaks during late childhood. How glucose metabolism is regulated in juvenile compared to adult brains, particularly in response to learning, remains to be determined. Here we compared the juvenile and adult hippocampi following episodic learning in rats to determine neuronal and/or astrocytic regulations of glucose metabolism. We assessed the expression regulation, in untrained conditions and following learning of 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase-3 (PFKFB3), a key glycolytic-promoting enzyme that catalyzes the production of fructose-2,6-bisphosphate (F2,6BP), a positive allosteric effector of 6-phosphofructo-1-kinase (PFK1), the rate-limiting enzyme of glycolysis. We chose to study PFKFB3 during learning because up-regulation of this enzyme in neurons results in the activation of glycolysis, a metabolic pathway that we found to be up-regulated during learning in development but not adults. Furthermore, because PFKFB3 is degraded by the E3 ubiquitin ligase anaphase-promoting complex/cyclosome-cadherin1 (APC/C-Cdh1), we also assessed the levels of this degrading enzyme. We found that, compared to adult, the juvenile hippocampus, at postnatal day 24 (PN24) has significantly higher basal levels of PFKFB3 and lower levels of

APC/C-Cdh1 in both astrocytes and neurons. Furthermore, inhibitory avoidance learning at PN24 significantly up-regulates PFKFB3 and down-regulates APC/C-Cdh1 in both cell types, suggesting high PFKFB3-mediated glycolytic activity induced by learning during early development. Finally, using molecular interference and pharmacological inhibition, we found that PFKFB3 is required for memory consolidation in juveniles, but not adult rats. Collectively, our findings suggest that, compared to adult, the juvenile brain recruits differential mechanisms of glycolysis regulation to support the consolidation of early-life memories.

Disclosures: **E. Cruz:** None. **B. Bessières:** None. **C.M. Alberini:** None.

Poster

691. Memory Consolidation and Reconsolidation: Molecular Mechanisms

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

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Topic: C.11. Spinal Cord Injury and Plasticity

Support: J.L. Rosa for the generous gift of the tbl/tbl mice
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Spanish Junta de Andalucía BIO-122 and DGICYT BFU2015-64536-R

Title: Mutation of the HERC 1 ubiquitin ligase impairs learning and sinaptic plasticity in the lateral amygdala

Authors: *J. NEGRETE-DIAZ[1], E. JUAREZ-CORTES[2], H. AGUILAR-ZAVALA[2], J. ARMENGOL[3], E. PEREZ-VILLEGAS[3], A. RODRÍGUEZ-MORENO[3];
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Abstract: Long-term potentiation (LTP), expressed as an increase in synaptic strength, is considered an excellent approach to explain the cellular and molecular bases of learning and memory. *Tambaleante* mouse (*tbl*/*tbl)* presents a spontaneous mutation in the E3 ubiquitin ligase protein (HERC1), present a loss of Purkinje cells and suffers an ataxic syndrome. Given that the presence of a mutation in HERC1 in humans correlates with cognitive deficits, we investigated here whether *tbl*/*tbl* mice show alterations in learning, short-term synaptic plasticity (STP) and long-term potentiation (LTP). Field excitatory postsynaptic potentials (fEPSP) were obtained from slices from control and *tambaleante* mice containing the amygdala, stimulating the cortical afferents (external capsule) or the thalamic afferents (internal capsule) and recording from the lateral or basolateral amygdala, respectively. After 10 minutes of basal stimulation at 0.2 Hz, a

theta burst stimulation protocol was applied to induce LTP consisting in: 10 trains of 4 stimuli of 100 microseconds duration, at 100 Hz, with an interval inter stimulus of 10 ms and with 200 ms between trains; this protocol was repeated 5 times every 5 seconds, to return immediately to the basal stimulation for 1 hour. We analyzed the slope and amplitude of the maximum peak of the fEPSP, and the magnitude of LTP after 1 hour of recording post protocol stimulation. The tbl/tbl mice perform worse than wild-type animals in the passive avoidance test, and histologically, the tbl/tbl mice have more immature forms of dendritic spines. Also, we observed a decrease in STP and LTP could not be detected in these mutant mice. These results suggest that the cognitive deterioration presented by individuals carrying a mutation in HERC1 might be due in part to a decrease in synaptic strength and it could involve an alteration to the ubiquitin-proteasome pathway.
KEY WORDS: HERC1, tbl/tbl, Amygdala, learning, LTP

Disclosures: **J. Negrete-diaz:** None. **E. Juarez-cortes:** None. **H. Aguilar-zavala:** None. **J. Armengol:** None. **E. Perez-villegas:** None. **A. Rodríguez-moreno:** None.

Poster

692. Oscillations

Location: Hall A

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Program #/Poster #: 692.01/Y15

Topic: H.02. Human Cognition and Behavior

Support: ERC_StG2012_313749
NWO VICI (#453-12-001)

Title: Modulating social-emotional control by synchronizing rhythmic brain circuits

Authors: *B. BRAMSON[1], I. TONI[2], K. ROELOFS[3];
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Abstract: Regulating social-emotional behaviour depends on prefrontal control over downstream areas such as the amygdala, parietal- and motor cortex (Volman et al., 2011), and is implemented through phase-amplitude coupling between prefrontal theta- and sensorimotor gamma-band rhythms (Bramson et al., 2018). This study tests the possibility of altering the regulation of social-emotional behaviour by manipulating phase-amplitude coupling between prefrontal and sensorimotor cortex. We do that using dual-site phase-coupled transcranial alternating current stimulation (tACS). Forty-one human participants performed a social approach-avoidance task while brain activity was measured with fMRI, and both right anterior prefrontal (aPFC) as well as left sensorimotor (SMC) cortex were focally stimulated with tACS. Participants had to approach angry- and avoid happy faces in affect-incongruent task conditions,

requiring control over prepotent social-emotional behaviour (namely avoid-angry and approach-happy in affect-congruent conditions). During task performance, participants were concurrently stimulated over two sets of ring electrodes (100 mm Ø, 1 mA peak-to-peak, in blocks of 60 sec): theta-band (6 Hz) tACS over the aPFC, and gamma-band (75 Hz) tACS over SMC. There were three stimulation conditions. The power envelope of the SMC gamma-band stimulation was tapered by a 6 Hz sine wave locked to either the peaks (in-phase) or the troughs (anti-phase) of the aPFC theta-band stimulation. In the third stimulation condition (sham), the electric current at both rings was reduced to zero after 10 sec. tACS (verum vs sham conditions) increased task-related BOLD-signal in areas proximate to the stimulation and involved in social-emotional regulation. Facilitation of aPFC-SMC connectivity (in-phase vs anti-phase tACS) led to changes in task-related BOLD-signal over aPFC and SMC in stimulation locations that scaled with reduced behavioural costs (faster reaction times) during social-emotional regulation. Disruption of aPFC-SMC connectivity (anti-phase vs in-phase tACS) led to increased task-related BOLD-signal over left aPFC and posterior parietal cortex (PPC), contralateral to the stimulated aPFC region. Left aPFC scaled with reduced behavioural costs (reduction in error rates) during social-emotional regulation, possibly reflecting a compensatory mechanism. Together, these findings provide novel insights into active and potentially compensatory mechanisms coupling regulatory prefrontal signals with fronto-parietal areas implementing social-emotional actions.

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Poster

692. Oscillations

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Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant MH109548
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McKnight Brain Research Foundation

Title: Higher order theta harmonics account for the detection of slow gamma

Authors: ***A. P. MAURER**[1], Y. ZHOU[2], Y. QIN[2], J. P. KENNEDY[1], N. M. DICOLA[1], S. N. BURKE[1], A. SHEREMET[3];
[1]Dept. of Neurosci., [2]Civil & Coastal Eng., [3]Engin. Sch. for Sustainable Infrastructure and Envrn. (ESSIE), Univ. of Florida, Gainesville, FL

Abstract: The debate over the origins and function of oscillations in the hippocampal local field potential has a long history dating back approximately 80 years (Gerard, Marshall, & Saul, 1936;

Jung & Kornmüller, 1938; Renshaw, Forbes, & Morison, 1940). Recently, the application of different decomposition algorithms to local field potential data have further kindled different interpretations regarding whether or not individual frequency bands of the power spectrum independently support distinct cognitive functions. The current study compared the results of different decomposition algorithms as implemented in contemporary literature to a synthetic time-series dataset. A simple of benchmark test was developed in which a synthetic 8-Hz oscillation along with harmonics up to 32 Hz was placed against a pink noise background to construct time-series data with known parameters. This synthetic time series was then run through a Fourier decomposition, Wavelet as described by Colgin et al. (2009), and ensemble empirical mode decomposition (EEMD) as described by Lopes-dos-Santos et al. (2018). A significant discrepancy across these methods was apparent. While Fourier maintains fidelity with the synthetic trace, resolving all of the harmonics, the wavelet decomposition resulted in a convolution of the harmonics erroneously distributing energy across a broad 25-50Hz range. EEMD failed to remove all of the harmonics of theta and also resulted in a convolution giving the impression of multiple low gamma bands. As this simple benchmark assessment challenges a long-standing dogma in the field, “slow gamma” as a dominant oscillation, we encourage others to test this for themselves.
Nevertheless, we present the results in defense of the idea that the identification of slow gamma as a dominant rhythm is an artifact of not carefully selecting the appropriate analytical parameters. We proceed to demonstrate that studies prior to the discovery of slow gamma, sensitive enough to detect the presence of slow gamma, made no such conclusion. While it has been argued that Fourier cannot be used to identify non-stationary signals, we demonstrate that Fourier is readily able to detect gamma (50-120 Hz) and ripple oscillations from CA1 recordings. Multiple suggestions are presented in order to facilitate spectral analyses moving forward.

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Poster

692. Oscillations

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Program #/Poster #: 692.03/Y17

Topic: H.01. Animal Cognition and Behavior

Support: MH109548

Title: Nonlinear interaction of theta and theta harmonics between hippocampus and medial entorhinal cortex

Authors: *Y. Z. ZHOU, Y. QIN, K. JACK, B. SARA, A. SHEREMET, M. ANDREW;
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Abstract: The hippocampal theta rhythm, believed to support various behaviors including navigation through physical and mnemonic space, has been intensively studied for over 80 years. It was acknowledged early on that the theta rhythm exhibits significant deviations from a sinusoid (John D Green & Petsche, 1961; Stumpf, 1965). This nonlinearity is expressed as second and higher order harmonics that appear as a function of velocity (Sheremet et al., 2016). Moreover, the theta rhythm along with harmonics are also detected in medial entorhinal cortex (Zheng et al., 2015). As the medial entorhinal cortex provides strong afferent input into the hippocampus and also receives CA1 inputs, we sought to determine the relationship between theta and its harmonics between the MEC and across lamina of the hippocampus. Therefore, F344-BN F1 rats from Charles River were implanted with two 32-site silicon probes which for simultaneous recording across CA1 lamina and the dorso-ventral axis of the MEC. Rats were trained to perform a spatial delay alternation task. Standard power spectrum analysis was performed, reconfirming the existence of theta harmonics in MEC which extended upwards of 24 Hz. Therefore, coupling within the MEC was investigated via bispectral analysis while MEC versus hippocampal lamina was conducted with cross-bicoherence. A nonlinear phasing coupling index is introduced to estimate and compare the strength of cross frequency coupling within MEC and cross regions (MEC to HPC). Preliminary analysis result indicates the MEC theta harmonics has stronger nonlinear phase coupling with HPC theta compared with the coupling with MEC theta. If this observation is true, then the harmonics observed in MEC might be generated in and propagated from HPC rather than generated locally.

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Poster

692. Oscillations

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Topic: H.01. Animal Cognition and Behavior

Support: R01 MH109548
R01MH109548S

Title: Theta in the visual cortex

Authors: *J. P. KENNEDY[1], Y. ZHOU[2], Y. QIN[2], S. N. BURKE[3], A. SHEREMET[4], A. P. MAURER[5];
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Abstract: It is widely accepted that the coordination of activity between brain regions is critical to the execution of complex behavior. While the precise mechanisms underlying this coordination are not understood, there is significant evidence that it is accomplished via oscillations in the local field potential (LFP). One of the most prominent examples of this is the 4-12Hz theta oscillation. Specifically, the larger reentrant circuits of the brain may provide the anatomical basis for rhythmic entrainment at theta frequency between the hippocampus and cortex (Edelman, 1987). However, the nature of cortical theta is still a matter of debate. Some have proposed that cortical theta is volume conducted from the hippocampus (Winson, 1974; Bland and Whishaw, 1976; Gerbrandt et al., 1978; Sirota et al., 2008; Senzai et al., 2019), generated locally (Zold and Shuler, 2015), or some combination of the two (Holsheimer et al., 1979; Leung and Borst, 1987). While Sirota and colleagues emphasized that theta in the cortex could be due to the superposition of two or more current sources, it was also noted that neocortical neuron firing and the local gamma oscillation can be entrained by hippocampal theta frequency. An instance of cortical gamma bursts at the theta frequency, when spectrally decomposed will be expressed as having both theta and gamma. Therefore, issues surrounding cortical theta may be one of semantics, attempting to divide a pacemaker from a current generator. Furthermore, while theta in the cortex may be volume conducted, it does not necessarily mean that volume conducted theta is without a physiological influence. We sought to revisit cortical LFP entrainment relative to the hippocampal theta rhythm, investigating the nature of cross-regional interactions and current generation. Four f344xBN hybrid rats were implanted with two single-shank 64 channel silicon probes in the dorsal hippocampus and visual cortex. Notably, spectral decomposition revealed theta and harmonics in the visual cortex. Furthermore, there was power-power coupling as well as phase-phase coupling between the theta and gamma (50-120 Hz) within the visual cortex. The results were reconfirmed using mouse data generously provided by the Buzsaki laboratory (Senzai et al., 2019). Therefore, as gamma is considered to be local and yet is modulated at theta frequency, these results offer preliminary support that the cortical circuitry can provide the ion current to bias the LFP to express theta locally.

Disclosures: **J.P. Kennedy:** None. **Y. Zhou:** None. **Y. Qin:** None. **S.N. Burke:** None. **A. Sheremet:** None. **A.P. Maurer:** None.

Poster

692. Oscillations

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 692.05/Y19

Topic: H.01. Animal Cognition and Behavior

Support: R01 MH109548

Title: Bursting activity propagation within homogeneous and isotropic population of neurons

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Abstract: The mammalian brain is characterized by laminar organizations formed by a variety of neuronal types. While the basic physiology behind an action potential is well understood, cognition occurs as a function of activity across a population. Therefore, it is necessary to know how activity may propagate across a lamina of neurons. Working under the assumption of stochastic synaptic connections, we propose a model which uses a time continuous governing equation of population activity. By introducing a state variable, the mean potential energy, to describe the time evolution of populations we can formulate the equations from an energy perspective. Thus the concept of energy conservation and energy flux can be applied to allow the distribution of energy among neurons to be considered. We use this model to resolve continuous energy transfer of population. Importantly, this model could be applied to networks with single or multiple types of neurons, both homogeneous and in-homogeneous, both isotropic or non-isotropic. Elementary analysis on the model reveals different mechanisms to support waves and energy propagation in isotropic networks. During our theoretical work, two types of propagating waves were identified which are a consequence of different mechanisms: refractory waves and interactive waves. Theoretical analysis indicates the existence of different wave regimes, that might have biological implications. Whether these regimes represent realistic conditions depends on the configuration of connections.

Disclosures: Y. Qin: None. **A. Sheremet:** None. **A. Maurer:** None.

Poster

692. Oscillations

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 692.06/Y20

Topic: H.02. Human Cognition and Behavior

Title: The role of frontal midline theta in reasoning accuracy and conflict detection

Authors: *A. WEIL, C. CARABALLO, E. BREWINGTON, C. JAYCOX, M. HASLAM, K. MEHRTENS, J. NGO;
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Abstract: The neuroscience of judgment and reasoning is still in its infancy, and as such little is known about the neural correlates of individual differences in reasoning ability. Reasoning ability is classically defined as being able to inhibit intuitive responses in favor of more logical answers. For example, in a joint-probability problem a participant might read a description of

Damien, who is from Texas, and feels that he truly embodies what it means to be a Texan. Participants are then asked which of the following two events is more likely: (1) Damien is a ballet dance instructor, or (2) Damien knows how to ride a horse and is a ballet dance instructor. Most participants choose option two, despite it being logically impossible for two events to be more likely than one. These errors in judgment have historically been attributed to participants' inability to detect the conflict between an intuitive and logical response. However, recent work suggests that people may be able to implicitly detect this conflict between logic and intuition, providing a new way to characterize individual differences in reasoning ability. In this study we investigated how individual differences in conflict detection and reasoning accuracy relate to frontal midline theta activity. Frontal midline theta is a frequency band (4-7 Hz) of neural oscillatory activity generated by the medial frontal cortex that has been implicated as a general mechanism of cognitive control. As such, we hypothesize that differences in frontal midline theta power may underlie observed individual differences in reasoning accuracy and the ability to detect a conflict between logical and intuitive responses. Participants reasoned through joint-probability and base rate problems in which half of the problems presented a conflict between logical and intuition, and half did not. Neural data were collected using an ANT Neuro 32-channel electroencephalography net, and power spectrum density was extracted using custom Matlab scripts. Replicating previous work, accuracy was lower on conflicting problems compared to non-conflicting problems for both joint-probability and base rate problems. Most participants were conflict detectors, as evidenced by lower confidence and longer reaction times to incorrect conflicting problems compared to correct control problems. Electrophysiological data suggest that more effortful reasoning processes are reflected in greater frontal midline theta power, providing the foundation for future work on the role of frontal midline theta in judgment and reasoning tasks.

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Poster

692. Oscillations

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Title: Altered hippocampal-prefrontal neural dynamics in mouse models of Down syndrome

Authors: P. CHANG[1], D. BUSH[2], S. SCHORGE[3], M. GOOD[4], T. CANONICA[4], N. SHING[1], S. NOY[1], F. WISEMAN[1], N. BURGESS[5], V. TYBULEWICZ[6], M. C. WALKER[7], *E. M. FISHER[8];
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Abstract: Altered neural dynamics in medial prefrontal cortex (mPFC) and hippocampus may contribute to cognitive impairments in the complex chromosomal disorder, Down Syndrome (DS). Here, we demonstrate non-overlapping behavioural differences associated with distinct abnormalities in hippocampal and mPFC electrophysiology during a canonical spatial memory task in three partially trisomic mouse models of DS (Dp1Tyb, Dp10Yey, Dp17Yey) that together cover all regions of homology with human chromosome 21 (Hsa21). Dp1Tyb mice showed slower decision-making (unrelated to the gene dose of *DYRK1A*, which has been implicated in DS cognitive dysfunction) and altered theta dynamics (reduced frequency, increased hippocampal-mPFC coherence, increased modulation of hippocampal high gamma); Dp10Yey mice showed impaired alternation performance and reduced theta modulation of hippocampal low gamma; while Dp17Yey mice were no different from wildtype mice. These results link specific hippocampal and mPFC circuit dysfunctions to cognitive deficits in DS models and, importantly, map them to discrete regions of Hsa21.

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Poster

692. Oscillations

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Support: NSF CAREER CBET-1351692

NSF BRAIN EAGER IOS-1550994
HFSP Young Investigator RGY0088
Ken Kennedy Institute for Information Technology

Title: Selective disruption of hippocampal sharp-wave ripples leads to impaired object-place recognition memory

Authors: *S. DUTTA[1], A. K. FELDMAN[1], C. KEMERE[1,2];
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Abstract: Rodents have an innate curiosity to explore novel contexts and objects resulting in them spending more time with novel objects and locations as opposed to familiar ones. Extensive work through lesion studies has demonstrated this novelty preference to be hippocampally dependent via novel object test (NOT) paradigms. More recent work has correlated hippocampal CA1 signatures, such as fast-gamma oscillations, to be of importance in NOT object-place recognition memories and demonstrated predictable changes in other transient hippocampal events, such as sharp-wave ripples (SWRs). Specifically, SWRs have been shown to increase after encoding of novel objects and general novelty in the test; however, the concomitant spiking activity has not been correlated with object-place pairings leading us to question the role of these events in encoding objects and place. To interrogate the role of SWRs in encoding novelty, we selectively modulate of SWR activity using our previously engineered closed-loop, open-source SWR detection system during various NOT paradigms. Preliminary results indicate that suppression of SWR activity during object encoding and post encoding sleep sessions impair object-place recognition memory of familiar objects in novel locations but not of novel objects in novel locations. We look to further understand the role of SWRs along with its co-occurring neural activity that would lead to such a deficit in recognition memory by selectively interacting with different subsets of high frequency oscillations and further investigating the modulation of concomitant neural firing patterns. Altogether, our preliminary findings suggest SWRs play a role in object-place pairing consolidation as opposed to simply broadcasting the presence of novelty.

Disclosures: S. Dutta: None. **A.K. Feldman:** None. **C. Kemere:** None.

Poster

692. Oscillations

Location: Hall A

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Program #/Poster #: 692.09/Y23

Topic: H.01. Animal Cognition and Behavior

Title: A metabolic function of the hippocampal sharp-wave ripple

Authors: *D. TINGLEY[1], K. MCCLAIN[1], G. BUZSAKI[2];
[1]NYU Neurosci. Inst., New York, NY; [2]New York University, Sch. of Med., New York, NY

Abstract: The hippocampal sharp-wave ripple (SPW-R) is a 40-150 millisecond event that consists of synchronized spiking from approximately 10-20% of hippocampal pyramidal neurons. These events primarily occur during consummatory behaviors and NREM sleep. The physiological role of SPW-Rs is typically discussed in connection with memory consolidation and action planning, requiring SPW-R spiking content to be communicated to the neocortex. However, several subcortical areas are also recipient and respondent to SPW-R-related synchronous hippocampal activity.
We took an iterative anatomical approach to examine where these population bursts may be transmitted. By looking for the densest anatomical efferents of the hippocampus, we find that the lateral septum is a major recipient of hippocampal projections. In turn, we find that the main efferent projection of the lateral septum is to the hypothalamus. Others have reported that hypothalamic nuclei project heavily to brainstem nuclei, including those that give rise to vagal efferents that innervate the pancreas. Thus, there exists a dense multisynaptic pathway from the CA1 neuron population to insulin-producing beta cells of the pancreas.
To examine whether these anatomical connections are utilized for a physiological function, we simultaneously recorded SPW-Rs in hippocampal CA1 while also monitoring interstitial glucose concentrations in freely behaving rats. We find that SPW-R occurrence reliably predicts a small but consistent decrease in systemic glucose concentrations 2-5 minutes into the future. Preliminary analyses suggest this relationship is not state (sleep vs wake) or movement dependent. Additionally, we find that short duration SPW-Rs, and bursts of SPW-Rs are more strongly correlated with future decreases in glucose concentrations.
Finally, we find that this correlation between SPW-Rs and glucose fluctuations is stronger when food is provided ad libitum, or during meal intake, than during fasting. We propose that these data support the hypothesis that the SPW-R, occurring primarily during periods immediately preceding metabolic changes (i.e. food intake), is a multi-modal signal that is capable of directly influencing the metabolic state of the organism.

Disclosures: D. Tingley: None. **K. McClain:** None. **G. Buzsaki:** None.

Poster

692. Oscillations

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Program #/Poster #: 692.10/Y24

Topic: H.01. Animal Cognition and Behavior

Title: Inferring long-term changes in spike transmission while accounting for time-varying network drive

Authors: *R. HUSZAR[1], S. A. MCKENZIE[2], G. BUZSAKI[3];
[1]New York Univ., New York, NY; [2]NYUMC, New York, NY; [3]New York University, Sch. of Med., New York, NY

Abstract: The storage of information in neural circuits depends on long-lasting modifications of synaptic strengths. However, while many techniques exist to simultaneously record from large numbers of neurons, the tools for large-scale monitoring of synaptic dynamics in freely moving animals are still lacking. Recently, it was demonstrated that fine timescale spiking synchrony can be used to infer monosynaptically connected E and I cells in vivo (English et al., 2017). Here, we consider the reliability of pairwise spiking synchrony (referred to as spike transmission probability) as a proxy measure of synaptic strength (Csicsvari et al., 1998). First, we demonstrate that these estimates of synaptic strength are confounded by measures of instantaneous network drive. More specifically, hippocampal theta phase, ripples and multiunit activity all correlate with spike transmission probability. Furthermore, changes in spike transmission correlate with both changes in pre- and postsynaptic firing rates. In order to regress out the time-varying contribution of different network states to postsynaptic spiking, we make use of a generalized linear model that also includes the influence of presynaptic spikes as one of its regressors. With this statistical framework in hand, we decouple slow changes in synaptic coupling while accounting for changes in postsynaptic rate that unfold at a broad range of timescales. We validate the model on simulated data with known ground truth, and use it to explore synaptic dynamics in extracellular CA1 datasets in both rats and mice involving different stimulation protocols (i.e., on-track stimulation, PV-interneuron stimulation triggered on presynaptic events).

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Poster

692. Oscillations

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Title: Sleep dynamics in the dorsal hippocampus and amygdala

Authors: B. KHOUADER[1], I. INEMA[2], G. BUZSAKI[3], *G. GIRARDEAU[1];
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Abstract: Sleep is a physiological state of reduced vigilance and alertness known to be important for brain homeostasis, memory consolidation and emotional regulation. During sleep, the brain cycle trough two main stages: Non-REM sleep (also called slow-wave sleep) and REM sleep. The neuronal dynamics of REM and Non-REM sleep have been extensively studied, notably in the hippocampus and neocortex, in link with homeostasis and plastic processes related to memory consolidation. The amygdala is a critical brain region for the processing of emotions. However, the sleep dynamics of the amygdala are comparatively understudied, despite a hypothesized role for both REM and Non-REM sleep in emotional memory consolidation. Here, using large-scale recording of LFPs and neuronal assemblies in the hippocampus and basolateral amygdala (BLA) of freely moving rats, we extensively describe the dynamics of neuronal firing in the BLA at transitions between states (Wakefulness/REM/Non-REM), and within REM-sleep. In addition, we analyze how local (BLA) and hippocampal theta oscillations during REM-sleep influence activity in the amygdala. Preliminary results indicate increased firing rates of both pyramidal neurons and interneurons in the BLA at Non-REM to REM transitions, leading to a change in the excitatory/inhibitory balance. Moreover, subsets of BLA neurons are modulated by hippocampal theta oscillation during REM-sleep. Unique firing patterns in the BLA during REM and Non-REM sleep might underlie the specific roles of these two sleep stages in emotional regulation and memory.

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Poster

692. Oscillations

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Title: Long-duration spontaneous and optogenetically prolonged hippocampal sharp wave ripples improve memory

Authors: *A. FERNANDEZ-RUIZ[1], A. OLIVA[2,1], E. F. OLIVEIRA[3,1], F. ROCHA-ALMEIDA[4,1], G. BUZSAKI[1];
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Brain Behavior Inst., Columbia Univ., New York, NY; [3]Neurosci., Albert Einstein Col. of Med., Bronx, NY; [4]Div. of Neurosciences, Univ. Pablo De Olavide, Seville, Spain

Abstract: Hippocampal sharp-wave ripples (SPW-Rs) are highly synchronous network activity patterns. They have been hypothesized to serve as a mechanism to replay previous experiences for memory consolidation and planning of future actions. Most works supporting this framework have been correlational. Although several studies have demonstrated that electrical perturbation of SPW-Rs results in memory deficits, the mechanisms by which such perturbation works are unknown. Furthermore, improvement of memory by manipulating ripples could not be achieved to date. The duration of ripples and associated neuronal sequences show a skewed distribution with a minority of long duration events. We found that the incidence of long duration ripples is increased in various situations demanding learning and memory in rats. Furthermore, correct versus error trials in spatial memory tasks could be predicted from the length of the SPW-Rs. Based on these observations, we hypothesized that prolongation of spontaneously occurring ripples by closed-loop optogenetic stimulation would enhance spatial memory performance. We then combined silicon probe recordings with optogenetic activation of hippocampal pyramidal neurons in rats performing a spatial working memory task. Prolongation of spontaneously occurring ripples by closed-loop optogenetic stimulation, but not randomly induced ripples, increased working memory performance. The neuronal content of randomly induced ripples was similar to short duration spontaneous ripples and contained little spatial information. The spike content of the optogenetically prolonged ripples was biased by the ongoing, naturally initiated neuronal sequences. Prolonged ripples recruited new neurons that represented either the left or right arm of the M-shape maze. Thus, neurons are not randomly recruited by light but constrained by the ongoing network activity. We concluded that long-duration hippocampal SPW-Rs with neuronal sequences replaying large parts of planned routes are critical for memory.

Disclosures: A. Fernandez-Ruiz: None. **A. Oliva:** None. **E.F. Oliveira:** None. **F. Rocha-Almeida:** None. **G. Buzsaki:** None.

Poster

692. Oscillations

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Program #/Poster #: 692.13/Y27

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant T90DA04321

Title: Firing rate heterogeneity during spontaneous activity reflects a balanced neuronal “ground state”

Authors: *D. LEVENSTEIN[1], J. GORNET[2], M. VALERO[3], J. M. RINZEL[4], G. BUZSAKI[5]; [1]NYU, New York City, NY; [2]New York Univ., Brooklyn, NY; [3]NYU Neurosci. Inst., New York, NY; [4]Ctr. Neural Sci., New York Univ. Ctr. for Neural Sci., New York, NY; [5]New York University, Sch. of Med., New York, NY

Abstract: Even within a given cell type, neurons show heterogeneous activity patterns. For example, heterogeneous responses to experimenter-imposed stimuli are frequently studied. However, heterogeneity is also seen in activity not obviously related to stimulus tuning, such as the mean firing rate during "spontaneous" activity (sFR). In theory, sFR heterogeneity might come from variability in 1) intrinsic neuronal properties, 2) network properties, or 3) the environmental frequency of tuned stimuli. However, the relative contributions of these effects are not known. To further characterize sFR heterogeneity, we analyzed the statistics of inter-spike intervals (ISIs) from multiple brain regions in freely behaving rats and their relationship to network activity and behavior.

Regardless of region, we found that forebrain excitatory neurons spend the majority of time in a neuronal "ground state": a low rate mode with irregular ~0.5-5s ISIs that was the main determinant of a neuron's sFR. In vivo experiments with synaptic blockers revealed that ground state activity relies on network input, as the absence of synaptic drive resulted in either silence or regular spiking in neocortical neurons. Comparison with the firing statistics of fluctuation-driven integrate and fire units revealed that the ground state ISIs are consistent with a balanced regime in which sFR heterogeneity emerges from variation in the incoming excitatory/inhibitory ratio, which can be replicated in a network in which each neuron self-balances at a unique firing rate with inhibitory STDP.

While the firing frequency of each neuron was bounded from below by a ground state common among regions, each neuron could fire up to ~100 Hz in "activated states": region and state - specific patterns of ISIs <300ms. Spiking during activated states tended to be more regular, reflecting suprathreshold spiking or coupling to oscillations, and could be evoked by tuned behavior/stimuli.

Together, these results reveal a picture of the activity of individual neurons in the mammalian forebrain in which neurons homeostatically tune the ratio of incoming excitatory and inhibitory synaptic weights to maintain a cell-specific low rate of activity. Balanced input from ongoing brain activity results in a ground state of fluctuation-driven spiking. On top of this ground state, region- and state-specific activated states can be evoked by synchronous or unbalanced inputs that emerge during spontaneous activity or the presence of tuned stimuli.

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Poster

692. Oscillations

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Program #/Poster #: 692.14/Y28

Topic: H.01. Animal Cognition and Behavior

Title: Parametric model of hippocampal place cell activity applied to assess speed modulation of firing rates

Authors: *K. MCCLAIN[1], D. J. HEEGER[2], G. BUZSAKI[3];
[1]NYU Neurosci. Inst., New York, NY; [2]Dept Psychol & Ctr. Neural Sci., New York Univ., New York, NY; [3]New York University, Sch. of Med., New York, NY

Abstract: Hippocampal place cells have been studied for their encoding of a rodent's position in the environment. Two features of place cell activity contain spatial information: 1) the firing rate increases dramatically in a roughly Gaussian pattern centered on a particular location and 2) the phase of spiking within the theta oscillation precesses with respect to position. It has been suggested that rate and phase codes are independent: spike phase codes for position and firing rate for speed. We explore the implications of these overlapping codes in a novel parametric model for place field activity. This model has three primary utilities: 1) generating realistic place cell simulation data, 2) parametrically characterizing place fields to compare across cells, time and condition, 3) conceptualizing a framework for principled hypothesis testing to identify additional sources of variability in place cell data. We model the firing rate of a place cell as a multiplication of parameterized tuning curves with respect to position and theta phase. We model spiking as a Poisson process of this time varying firing rate, and fit to data with maximum likelihood optimization. We apply the model to understanding the influence of running speed on place cell firing rates. Using simulation, we identify an implicit role of speed, as firing rate variability increases at high speeds due to interaction between the two spatial codes. We also investigate the explicit role that speed may play. In real place field data recorded from rats running on a linear track, we observe a heterogeneous distribution of speed modulation across place cells, including some that are inhibited at high speeds. To disambiguate explicit speed dependence from statistical anomaly, we compare how well our real data is captured by speed dependent variations of our model vs. the speed-independent null model.

Disclosures: K. McClain: None. **D.J. Heeger:** None. **G. Buzsaki:** None.

Poster

692. Oscillations

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NIH Grant U19NS104590

Title: Physiological and network properties of down state-active neurons in neocortex

Authors: *M. VALERO, G. BUZSÁKI;
NYU Neurosci. Inst., New York, NY

Abstract: During non-rapid eye movement (NREM) sleep, the neocortex alternates between periods of spiking (UP states) and synchronous hyperpolarization (DOWN states), which defined a dominant ‘slow oscillation’ (1-3 Hz) in the local field potential (LFP). This two-state behaviour is believed to arise from a combination of neuron intrinsic and network properties. Nonetheless, UP state transitions are organized both at the cortical column as well as the ensemble level, providing a scale-free subtract for memory management and homeostasis.It is generally assumed that during DOWN states all pyramidal cells and interneurons are silent. How the transition from DOWN to UP state occurs is not well understood. Recently, we described a small population of V1 layer 6 neurons that displayed a strong inverse correlation with the activity of the simultaneously recorded principal cells and interneurons, particularly evident during non-REM sleep. In this project, we aim to asses the cellular identity and physiological function of the “DOWN state-active” neurons. We combined focal optogenetic stimulation with extracellular silicon probe recording across multiple cortical regions in genetically modified mouse lines, including PV-Cre::Ai32, Sst-Cre::Ai32 and Ht3a(BAC)-Cre::Ai32, which together account for the majority of neocortical GABAergic neurons. We found that DOWN state-active neurons define a specific subtype of putative interneurons of the layer 6 (6.25% of all interneurons for the same layer) present in the several neocortical regions investigated. In general, they show a wide regular spiking autocorrelogram (peaking at 40ms), moderate firing rates (2-6 Hz) during NREM and quiet waking and are virtually silent during REM sleep. That activity profile correlates with their pattern of connectivity, strongly inhibited by at least some subpopulation of PV+ and SSt+ interneurons. Futures experiment with specific optogenetic manipulation of the DOWN state-

active neurons aim to disclose their physiological function, as well as their role in controlling UP and DOWN dynamics.

Disclosures: **M. Valero:** None. **G. Buzsáki:** None.

Poster

692. Oscillations

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Topic: H.01. Animal Cognition and Behavior

Support: Danish Council for Independent Research Postdoctoral grant
Lundbeckfonden Post-doctoral grant

Title: Altered cell assembly dynamics in the hippocampus by focal cooling of the medial septum

Authors: *P. C. PETERSEN, G. BUZSAKI;
NYU Neurosci., New York Univ., New York, NY

Abstract: The hippocampal theta rhythm coordinates spike timing of neurons across multiple structures of the limbic regions. Lesions and pharmacological inactivation of medial septum (MS) result in disappearance of theta and impairment of learning and memory. In the presence of theta oscillations, place fields generate a space-time compressed representation of the environment. We have performed local thermal perturbation of the MS to perturb theta oscillations. We implanted silicon probes in CA1 in the hippocampus and a cooling probe (silver rod in MS, connected to device on the head) in rats. The animals were trained to perform a side alternation task on a figure eight maze, with ongoing cooling sessions, allowing for us to study the effects on spatial neuronal activity in the hippocampus and performing behavioral quantification. Cooling of MS decreased the frequency of theta oscillation by ~2Hz and its power during spatial navigation, and we observed a linear relationship between measured temperature and theta frequency. Cooling also degraded memory performance and we sought out to understand the physiological basis of the impairment. The oscillation frequency of place cells also decreased, proportional to the theta LFP change, thereby maintaining spike phase precession relationship. Both interneurons and pyramidal cells decreased their rate, yet the place field sizes did not change. The space-time compression was also altered, as we observed a slower progression of place cell sequences.Our results reveal that delicate timing changes, such as slowing the sequences of gamma-packaged place cell assemblies, affecting the entire hippocampus, and likely related structures, is sufficient to impair memory mechanisms in the hippocampus. We hypothesize that the impairment results from the inability of downstream structures to correctly read out the temporally altered hippocampal messages.

Disclosures: **P.C. Petersen:** None. **G. Buzsaki:** None.

Poster

692. Oscillations

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NIH Grant MH118928

Title: Uncovering representations of spatially distributed rodent hippocampal LFPs

Authors: *L. CAO[1,4], G. BUZSÁKI[1], Z. S. SHEN[1,2,3];
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Abstract: Rodent hippocampal place cells are well known to have the localized spatial tuning property, and population spike activities from place cell assemblies provide a readout of the animal's spatial location. However, direct use of spike information for population decoding appears challenging due to practical issues of spike sorting, unit classification and instability etc. In contrast, hippocampal local field potentials (LFPs) consist of local subthreshold activities reliably represent neuron assembly activity around the recording site, serving as an alternative and robust information carrier for animal's spatial information representation. To date, however, representations of spatial distributed hippocampal LFPs are not well studied. Previously, researchers have succeeded in decoding rodent's position during navigation based on features extracted from spatially distributed hippocampal LFPs (Agarwal et al., 2014).
Here we employed several supervised and unsupervised methods to investigate representations of rodent hippocampal LFPs when the animal is freely foraging in multiple environments (linear, circular and T mazes) and during the offline state (quiet wakefulness and slow wave sleep). Multiple LFP features (e.g., theta phase, gamma amplitude, and ultra-high frequency amplitude or multiunit activity) are thoroughly examined. We found that spatially distributed theta phase features across silicon probe channels provides a robust and reliable readout of the animal's position during running. Furthermore, unclustered, spatially distributed signals at ultra-high frequency (>300 Hz-5 kHz) allowed a readout of replay content during hippocampal sharp-wave ripple (SPW-R) events, as revealed by Bayesian decoding of virtual track positions. We used a leave-one-out method to investigate the representational contribution of each shank during running and SPW-R events, and found that the magnitude of position prediction from theta and SPW-R signals co-varied with electrode position. We also applied several unsupervised learning methods (such as independent component analysis and dictionary learning) to optimize and visualize the spatially localized LFP features.

Our preliminary results reveal the potential representational power of unclustered, spatially distributed hippocampal LFPs. This approach is useful for an efficient decoding strategy for closed-loop brain-machine interface applications. Further studies of such population representations may provide hints for the animal's planned choices.

Disclosures: L. Cao: None. **G. Buzsáki:** None. **Z.S. Shen:** None.

Poster

692. Oscillations

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 692.18/Y32

Topic: H.01. Animal Cognition and Behavior

Title: Monitoring hippocampo-neocortical interactions using widefield calcium imaging and electrophysiology in behaving mice

Authors: *R. A. SWANSON[1], S. MOUSAVI[2], J. BASU[3], G. BUZSAKI[4];
[1]New York Univ., New York, NY; [2]Neurosci., Fordham Univ., New York, NY; [3]Dept. of Neurosci. and Physiol., Neurosci. Institute, New York Univ. Sch., New York, NY; [4]New York University, Sch. of Med., New York, NY

Abstract: Hippocampal sharp-wave ripple (SPW-R) coupled modulation of neural activity is observed throughout the neocortical mantel during periods of quiescence and non-REM sleep (Buzsaki 2015; Logothetis 2012). However, how this dynamic coupling is spontaneously achieved across spatial and temporal scales in the absence of coordinating sensory input is unknown. The anatomy of hippocampal projections suggests a broad yet systematic topographical communication with neocortical areas. Hippocampal connectivity with the forebrain varies along its longitudinal axis. Furthermore, SPW-Rs are high frequency oscillations that travel along this axis and may occur either locally or globally. This suggests a mechanism whereby SPW-Rs that emerge from the dorsal, intermediate, and ventral segments of the CA1 region may broadcast different content to their downstream targets at the same or different times. The extent to which this transfer occurs has been difficult to investigate, however, due to the spatial limitations of extracellular physiology and the temporal limitations of the BOLD signal. In this study, we present the development of widefield imaging of a dorsal cortical hemisphere, combined with high-density silicon probe recordings in the hippocampus and retrosplenial cortex. This preparation allows us to assess the functional relationship between topographic propagation of SPW-Rs in the hippocampus and functional activation of neocortex. Results, to date, indicate a robust topographic response to dorsal hippocampal SPW-Rs, that vary as a function of both duration and amplitude of SPW-R.

Disclosures: R.A. Swanson: None. **S. Mousavi:** None. **J. Basu:** None. **G. Buzsaki:** None.

Poster

692. Oscillations

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 692.19/Y33

Topic: H.01. Animal Cognition and Behavior

Support: U01NS099705

Title: The effect of sustained inhibition on the generation of hippocampal oscillations

Authors: *S. ROGERS, M. VALERO, G. BUZSAKI;
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Abstract: The role of inhibition in the generation and maintenance of physiological oscillations has been the subject of controversy. Inhibitory interneurons are believed to play critical roles in both synchronizing networks and gating activity that comes through a circuit. Therefore, they have been studied in the context of both epileptic and normal physiological conditions. Of particular interest is the role of inhibition in the trisynaptic loop of the hippocampus, largely responsible for the process of generating sharp wave ripples, which are involved in memory consolidation, and in the generation of epileptiform activity. In the present study, we expressed an excitatory designer receptor exclusively activated by designer drug (Gq-DREADD) in the inhibitory interneurons of the CA1 region of the hippocampus. By activating these interneurons with clozapine n-oxide (CNO), we studied the effect of sustained inhibition on cell firing rates and the generation and maintenance of hippocampal oscillations. We have found that with CNO-mediated activation of interneurons, pyramidal cell firing dramatically reduces, while interneuronal firing both increases and reduces in a complex manner. Furthermore, we found that the system is still able to generate oscillations such as ripples (150-200 Hz), gamma (40 -100 Hz), and theta (5-8 Hz), all oscillations involved in encoding and transmitting information. Interestingly, ripple and gamma power are reduced as predicted by previous studies, while theta is largely conserved. Lastly we have found that a cell's spike firing pattern is largely retained, despite the overall change in firing rate. For example, if a pyramidal cell increases its firing rate during a ripple, this preference for firing during ripples is retained even in the presence of increased inhibition. We also found that the phase modulation of spikes to the theta oscillation is also conserved, despite drastic reductions in overall cell firing. This suggests that increasing inhibition chronically reduces firing rate of pyramidal cells but allows them to retain basic characteristic features.

Disclosures: S. Rogers: None. **M. Valero:** None. **G. Buzsaki:** None.

Poster

692. Oscillations

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 692.20/Y34

Topic: H.01. Animal Cognition and Behavior

Support: Southwestern Medical Foundation
Alfred P. Sloan Foundation
National Institute of Neurological Disorders and Stroke

Title: Bimodal representation of information in the hippocampal theta oscillation during reward-associated navigation

Authors: *M. WANG, B. E. PFEIFFER;
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Abstract: Successful navigation requires accurate encoding of the current location as well as prediction of future outcomes based on prior behavior, and hippocampal place cells are believed to play a central role in these processes. During active exploration, place cells display “phase precession” with respect to the ongoing 4-12 Hz theta rhythm, firing at progressively earlier phases of theta as the rat traverses a cell’s place field. Across large populations of place cells, phase precession is hypothesized to produce theta sequences, temporally organized sequences of neural firing which encode short virtual trajectories. Current models suggest that the theta rhythm may temporally discretize theta sequences into retrospective and prospective segments to alternately facilitate encoding and prediction, but little evidence exists to directly support this hypothesis. Here, we show that during navigation in a memory-dependent, but not a memory-independent task, a large percentage (~34%) of hippocampal CA1 cells display a bimodal relationship with the theta oscillation. While unimodal neurons preferentially fire at the trough of theta, bimodal neurons fire prominently at both the trough and peak of theta. In addition, bimodal neurons alternately display both canonical phase precession (at the trough of theta) and, surprisingly, phase procession (at the peak of theta). At a population level, bimodal neurons contribute to two distinct forms of theta sequences which arise consecutively within the same theta oscillation: a prospective sequence encoding a trajectory in the same direction as the animal’s movement, and a retrospective sequence encoding a trajectory in the opposite direction. Firing within the prospective vs. retrospective sequence is independently modulated, indicating that bimodal place cells may be driven by two distinct sources of theta-frequency input that are phase offset by approximately 180°. During REM, around 30% of unimodal and 50% of bimodal cells shift their preferred firing phase from the major to minor peak, suggesting that bimodal neurons may be selectively sensitive to input from layer III entorhinal cortex. Finally, we observe stronger firing in retrospective, but not prospective, sequences as rats approach goal

locations, implicating this novel process in successful memory retrieval and behavioral performance.

Disclosures: M. Wang: None. **B.E. Pfeiffer:** None.

Poster

692. Oscillations

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 692.21/Y35

Topic: H.01. Animal Cognition and Behavior

Support: 5R01MH065252
R38MH087027

Title: Correlates of behavioral flexibility within the frontal cortex of the macaque during categorization

Authors: *R. LOONIS, E. K. MILLER;
Picower Inst. for Memory and Learning, MIT, Cambridge, MA

Abstract: The capacity to organize sensory and abstract information into categories is a hallmark of cognition. However, excessive adherence to any categorization rule also reflects a failure of cognition, and moderating this tendency is a cognitive capacity known as behavioral flexibility. Ever since the days of Phineas Gauge, the frontal cortices are thought to be central in maintaining flexibility and alternating between behaviorally relevant rules. We trained two rhesus macaques on a dot-pattern categorization task (Posner & Keele, 1968), and recorded concurrently from a wide swath of frontal cortex (pre-arcuate, ventrolateral, and dorsolateral prefrontal cortex). During the test phase of this categorization task, monkeys were allowed to freely view exemplars of two categories, and subsequently choose the exemplar that matched the sample category by maintaining fixation on it for 700 ms. We found that the monkeys' behavior improved with the number of views they made investigating the test exemplars. Correlated with this behavioral improvement, we found a decrease in beta band power within the local field potential during the delay preceding the test phase on trials in which the animal proceeded to view both test exemplars before committing to a choice, as opposed to making a decision based on a single view. In other words, maintaining an “open” mind regarding the correct category resulted in improved performance, and decreased beta band modulation corresponded with this improvement. We also found that the pattern of delay period spike rates on multi-electrode arrays (i.e. how the activities of different groups of neurons increased or decreased together) were distinct between those trials in which the animal would investigate both test exemplars rather then just one. Overall, these results suggest that these frontal circuits play an important

role in maintaining flexible representations of the category identity, and that excess beta band modulations could lead to inflexible behavioral states.

Disclosures: R. Loonis: None. **E.K. Miller:** None.

Poster

692. Oscillations

Location: Hall A

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Topic: H.01. Animal Cognition and Behavior

Support: Office of Naval Research MURI N00014-16-1-2832
ONR DURIP N00014-17-1-2304
Army Research Office W911NF-12-R-0012-02

Title: Prefrontal oscillations modulate the propagation of neuronal activity required for working memory

Authors: *J. SHERFEY[1], S. ARDID[2], N. J. KOPELL[3], E. K. MILLER[4], M. E. HASSELMO[1]; [1]Psychological and Brain Sci., [2]Dept. of Mathematics & Statistics, [3]Boston Univ., Boston, MA; [4]Picower Inst. Learning Memory, Massachusetts Inst. Technol., Cambridge, MA

Abstract: Cognition involves using attended information (e.g., stimuli, rules, responses), maintained in working memory (WM), to guide action. During a cognitive task, a correct response requires flexible, selective gating so that only the appropriate information flows at the proper time. Much evidence suggests that WM information is encoded in the firing rates of populations of neurons in prefrontal cortex (PFC). At the same time, many experiments have demonstrated separate, task-related modulation of oscillatory dynamics in PFC networks. In this work, we used biophysically-detailed modeling to explore the hypothesis that network oscillations, leveraging lateral inhibition, can independently gate responses to rate-coded items in working memory. Consistent with recent data, we modeled the superficial layers of PFC as a WM buffer that stores task-relevant information and the deep layers of PFC as an output gate that governs which information in the WM buffer is propagated downstream to guide action. We investigated two models of the WM buffer: a "classic" model where attractor dynamics generate persistent spiking, and another model motivated by recent findings that WM does not involve persistent spiking but instead involves bursts of beta- and gamma-frequency oscillatory dynamics. In the latter, short-term synaptic plasticity allows maintenance of working memory between intermittent bursts of activity. In both cases, we found that whichever WM item induced a response in the output gate with the shortest period between spike volleys would be most reliably propagated through the output gate. Furthermore, the output gate exhibited network resonance capable of selectively relaying items with resonant oscillatory modulation. We found

that network resonance can be flexibly tuned by varying principal cell excitability. In our PFC model, these dynamics reveal how population rate-coded items embedded in superficial beta and gamma oscillations can be alternately relayed by tuning network resonance in the deep layers of PFC depending on task demands. Our ongoing modeling work explores how gating, mediated by resonance and lateral inhibition, interacts with task-related beta and gamma bursts to govern response in delayed match to sample and contextual association tasks.

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Poster

692. Oscillations

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 692.23/Y37

Topic: H.01. Animal Cognition and Behavior

Support: NIMH R37MH087027
ONR MURI N00014-16-1-2832
The MIT Picower Institute Innovation Fund

Title: Are oscillatory correlates of working memory preserved across cortex?

Authors: *M. LUNDQVIST, A. M. BASTOS, E. K. MILLER;
Picower Inst. of Learning and Memory, Massachussetts Inst. of Technol., Cambridge, MA

Abstract: We have recently found that in prefrontal (PFC) bursts of oscillations in beta (15-35 Hz) and gamma (45-100 Hz) have distinct functional correlates. They were anti-correlated over time and across recording sites. Gamma bursts increased at sites and times where and when information was expressed in spiking; beta showed the opposite. This suggested that interactions between gamma and beta could regulate the expression of information by PFC neurons.
We hypothized that these phenomenon are prevalent across cortex. This idea has support from noninvasive recordings from the occipital cortex in humans, albeit at lower frequencies, alpha (8-12 Hz) and lower beta (12-14 Hz). This difference in oscillatory frequency could be due to differences between species, tasks, cortical regions or recording methods. In addition, the lack of direct access to neural activity in human studies makes oscillatory correlates harder to interpetrate.
To bring clarity to these questions we recorded from multiple electrodes in three cortical areas (V4, parietal cortex and PFC) of rhesus macaques during a working memory task. We analyzed local field-potentials and multi-unit activity in tandem. We found a similar functional relationship between alpha/beta and gamma in all cortical areas. Alpha/beta bursting was suppressed during encoding and retention of information, and anti-correlated with spiking

actvitiy and gamma bursting across time and sites. In all areas, suppression of beta and elevation of gamma was greater at sites where spiking carried information.
However, there were several trends as the cortical hierarchy was ascended from sensory to prefrontal cortex: 1. A gradual increase in the peak frequencies within both the alpha/beta and gamma bands. 2. The alpha/beta and gamma bursts gradually decreased in duration. 3. During memory retention, the gamma burst rate was higher (and the beta burst rate lower) in higher cortical areas. Our findings suggest that alpha/beta gamma interactions are preserved across cortex and may play a general role in regulating expression of information by cortical neurons. Further, the briefer but greater number of gamma bursts during memory retention may serve two roles. The shorter gamma events could help higher cortex segregate different sensory inputs (carried by different bursts) while the greater rate of memory-related gamma bursting could better retain thoose inputs across time.

Disclosures: **M. Lundqvist:** None. **A.M. Bastos:** None. **E.K. Miller:** None.

Poster

692. Oscillations

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 692.24/Y38

Topic: H.01. Animal Cognition and Behavior

Support: NIMH R37MH087027
ONR MURI N00014-16-1-2832
The MIT Picower Institute Innovation Fund

Title: Bilateral transfer of working memory traces in prefrontal cortex

Authors: ***S. L. BRINCAT**[1], J. A. DONOGHUE[2], M. LUNDQVIST[1], M. K. MAHNKE[3], E. K. MILLER[4];
[2]Brain and Cognitive Sci., [3]PILM, [1]MIT, Cambridge, MA; [4]Picower Inst. Learning Memory, Massachusetts Inst. Technol., Cambridge, MA

Abstract: There is evidence that visual working memory (WM) storage is independent in the right and left visual hemifields. Yet somehow WM seems seamless when eye movements shift a remembered location between hemifields. We studied how WM is integrated across the visual hemifields by recording neural activity bilaterally from 256 PFC sites in monkeys performing a change detection task. A central sample object was presented while monkeys fixated to the left or right of it. Following a WM delay, a test object was shown. Subjects had to respond to it only if it changed from the sample. In half the trials, subjects made an instructed saccade in the middle of the delay to the opposite side, shifting the retinotopic location of the remembered object to the other visual hemifield. In the other half, they remained fixated through the delay, keeping the

remembered location constant.
As expected, in no-saccade trials the PFC representation was biased toward contralateral retinotopic locations—decoding the item held in WM from delay activity spike rates in each hemisphere was much more accurate following contralateral than ipsilateral samples. Consistent with a role in suppression, LFP beta-band power had the opposite pattern—stronger for ipsilateral samples. When a saccade shifted the remembered location, decoding accuracy in the "receiver" hemisphere, which shifted from ipsilateral to contralateral, increased to nearly the level of a constant contralateral trace. The "sender" hemisphere, which shifted from contralateral to ipsilateral, faded to the level of a constant ipsilateral trace. Beta power showed inverted dynamics—the receiver decreased and sender increased. A simple model consistent with the data is that inter-hemispheric transfer of a WM trace activates the same ensemble that would encode a constant trace at the same location. This predicts that a decoder trained on constant contralateral trials would generalize to explain post-transfer activity in the receiver. This was not the case—post-transfer cross-decoding accuracy was at baseline levels whether the decoder was trained on delay or sample-period activity in no-saccade trials. At the time of WM trace transfer—but not at analogous time points in no-saccade trials—LFPs transiently synchronized between PFC hemispheres at gamma frequencies. These results provide evidence for transfer of a working memory trace across prefrontal hemispheres during midline-crossing saccades, suggest inter-hemispheric gamma oscillations may mediate the transfer, and show that the transferred WM trace activates a distinct neural ensemble from a remembered visual object at the same location.

Disclosures: S.L. Brincat: None. **J.A. Donoghue:** None. **M. Lundqvist:** None. **M.K. Mahnke:** None. **E.K. Miller:** None.

Poster

692. Oscillations

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 692.25/Y39

Topic: H.01. Animal Cognition and Behavior

Support: American Brain Sciences Chair, and the Department of Veterans Affairs (to B.A.)

Title: A recurrent spiking network model operating on the boundary between asynchronous and oscillatory states explains synchronous (0-lag) spiking deficits observed in primate prefrontal cortex following NMDAR synaptic blockade

Authors: D. A. CROWE[1], M. V. CHAFEE[2], ***B. AMIRIKIAN**[3];
[1]Biol., Augsburg Univ., Minneapolis, MN; [2]Dept Neurosci / Brain Sci., Univ. Minnesota, Minneapolis, MN; [3]Brain Sci. Center, Veterans Affairs Med. Ctr. / Dept. of Neuroscience, Univ. of Minnesota, Minneapolis, MN

Abstract: Schizophrenia involves malfunction of prefrontal circuits, but due to our limited ability to study the function of neurons in the living human brain we have limited understanding of how the disease alters the function of neurons to produce symptoms and cognitive deficits. This is critical because learning how the disease alters the function of the brain at the cell level is the best first step toward identifying treatments that could potentially restore neuronal and therefore network function in the disease. Resolving prefrontal circuit malfunction at a cellular level requires animal and computational models. Here we report a convergence between them that could be relevant to the pathogenesis of schizophrenia.
We recently reported (Neuron 102:21-26. 2018) that blocking NMDAR in monkeys (1) reduces the frequency with which neurons in prefrontal circuits tended to fire action potentials at the same time (0-lag synchronous spiking) while (2) also chronically reducing the number of neuron pairs that exhibited significant effective coupling. Here we explore whether key features of the spike timing dynamics of prefrontal circuits can be explained by a recurrent network model accounting for GABA, AMPA and NMDA synaptic currents. Using mean field approximation (e.g., Renart et al., 2003) describing asynchronous network state and conditions for emergence of network oscillations (Brunel & Wang, 2003) we derived synaptic conductance parameters for a network operating on a boundary between asynchronous and oscillatory states. Simulations of network dynamics with these parameters revealed that the degree of network synchrony measured by the population average 0-lag spike correlation in this regime could be effectively controlled by modulation of recurrent NMDAR conductance and external AMPA currents. Particularly, the model exhibits an increase in 0-lag spike synchrony with a small increase in external currents, similar to the increase we observed in the primate PFC in probe relative to delay periods. Moreover, population 0-lag correlation is reduced following reduction of NMDAR synaptic conductance in the model, replicating a key feature of the primate PFC under drug condition. These results suggest that PFC circuits could be operating on the boundary between asynchronous and synchronous regimes that allows them to switch easily between stationary and oscillatory dynamics. This, in turn, provides a potential control mechanism for behavioral regulation of 0-lag spike synchrony in the brain.

Disclosures: **D.A. Crowe:** None. **M.V. Chafee:** None. **B. Amirikian:** None.

Poster

692. Oscillations

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 692.26/Y40

Topic: H.01. Animal Cognition and Behavior

Title: Effect of various anxiolytics in the radial arm maze and corresponding effect on EEG

Authors: *R. ABRAHAM[1], S. DARIPELLI[2], V. BENADE[2], C. THIRUMALASETTY[2], G. BHYRAPUNENI[2], P. JAYARAJAN[1], R. NIROGI[3];
[1]Pharmacol., [2]DMPK, [3]Discovery, Suven Life Sci., Hyderabad, India

Abstract: Anxiolytics are widely prescribed for psychiatric conditions such as generalized anxiety and various disorders associated with fear. It has been reported that some of these anxiolytics have adverse effects on learning and memory. In the current research we investigated the effect of commonly used anxiolytics in the radial arm maze. We also attempted to understand the electrophysiological effects associated with these anxiolytics on cognition. Chlordiazepoxide, gabapentin and buspirone were chosen for evaluating its effects on learning and memory. The doses chosen were such that anxiolytic effects would be observed. Following treatment, rats were subjected to elevated plus maze. Doses which showed anxiolytic effects were further assessed in the radial arm maze. The anxiolytics were dosed following habituation to the radial arm maze and prior to initiation of trial. It was observed that chlordiazepoxide and gabapentin exhibited cognitive dulling properties but not to the same extent, while buspirone had almost no effect on cognition. To further investigate the effect on cognition, the rats were subjected to EEG spectral analysis. It was observed that chlordiazepoxide and gabapentin modulated spectral bands in the range of 4-8 Hz and 25-50 Hz indicating the modulations in theta and gamma bands which are suggestive of changes on learning and memory.

Disclosures: R. Abraham: A. Employment/Salary (full or part-time):; Suven Life Sciences. **S. Daripelli:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **V. Benade:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **C. Thirumalasetty:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **G. Bhyrapuneni:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **P. Jayarajan:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **R. Nirogi:** A. Employment/Salary (full or part-time):; Suven Life Sciences.

Poster

693. Learning and Memory: Aging

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 693.01/Y41

Topic: H.01. Animal Cognition and Behavior

Support: NIH grant 1-ZIA-AG000340

Title: Memory function after rTMS in aged rats depends on cognitive status

Authors: M. WEILER, H. M. STARNES, P. MORENO-CASTILLA, E. L. R. MELENDEZ, K. C. STIEGER, *J. M. LONG, P. R. RAPP;
NIH, Baltimore, MD

Abstract: Repetitive transcranial magnetic stimulation (rTMS) is an FDA-approved procedure for the treatment of depression, and there is increasing interest in its potential application for other neurological conditions. rTMS can cause either a lasting increase or decrease in cortical excitability; however, identical stimulation patterns may not affect all individuals equally since the effects of rTMS also depend on the baseline excitability of the brain. Aging is associated with shifts in neuronal excitatory/inhibitory balance in specific cortical circuits, and the degree of cognitive impairment in aged humans and animal models has been related to disruptions in this balance.

In order to test the possibility that aging and cognitive integrity influence the behavioral response to stimulation, we evaluated rTMS effects on recognition memory in a rat model of cognitive aging where aged Long-Evans rats were classified as Aged-Impaired (AI) or Aged-Unimpaired (AU) according to their performance in the Morris water maze. We applied intermittent Theta Burst Stimulation under isoflurane anesthesia to 8 young (plus 9 young sham), 4 AU (plus 4 AU sham) and 8 AI (plus 6 AI sham) rats. Cognitive effects were evaluated using a spontaneous odor recognition memory task, relying on rats' innate preference for novelty. rTMS was delivered immediately after the sample odor presentation (i.e., during consolidation) and memory was tested 24 hr later.

Behavioral variability was substantial in stimulated rats, and comparisons between rTMS conditions (stimulated vs. sham) were not statistically significant. The pattern of memory performance within conditions, however, differed dramatically as a function of cognitive status. Specifically, Y and AU sham rats displayed highly reliable odor recognition memory, exploring novel odors significantly above chance, whereas sham treated AI rats displayed no retention. Stimulated Y rats also demonstrated significant memory, although scores were more variable than in sham controls. In stark contrast, the AU stimulated group displayed no significant retention, and rTMS treated AI rats exhibited robust retention relative to chance, comparable in magnitude to Y animals. These results support the view that rTMS may be an effective therapeutic in the treatment of cognitive disorders of aging. However, individual differences in neurocognitive status can critically dictate the response to rTMS, and accordingly, protocols with documented efficacy in young adults might have unexpected outcomes in the context of Alzheimer's pathogenesis or other neurodegenerative conditions.

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Poster

693. Learning and Memory: Aging

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 693.02/Y42

Topic: H.01. Animal Cognition and Behavior

Support: This research was supported by the Ministry of Science & Technology ,Israel

Title: Stress vulnerability correlates with shorter lifespan and early cognitive impairments

Authors: *M. BAIRACHNAYA[1], A. SHNAYDER[1], A. SHEININ[2], I. MICHAELEVSKI[1], A. PINHASOV[1];
[1]Integrative Brain Sci. Ctr. - Ariel, Mol. Biol., Ariel Univ., Ariel, Israel; [2]Sagol Sch. of Neurosci., Tel-Aviv University, Tel-Aviv. Israel, Tel-Aviv, Israel

Abstract: Lack of adaptation to social stress may lead to deterioration of physiological functions and contribute to aging augmentation, age-related diseases and cognitive impairments. In the current study, we used a mouse model of social interactions with inherited traits of dominance (Dom) and submissiveness (Sub), exhibiting resilience or sensitivity to stress respectively, to assess their lifespan, physiological parameters and cognitive abilities. We found that the lifespan markedly differed between Sub and Dom both in males (n=30 for Dom, n=29 for Sub), and females (n=10 per strain). Both male and female Sub animals showed marked hypoglycemia, slow weight gain and decreased skin surface temperature from early life stages. Furthermore, aged Sub mice had overt splenomegaly and significant upregulation of proinflammatory interleukins IL-1b and IL-6 in serum. Animals cognitive performance was evaluated in different age groups (3, 6 and 9-month old) simultaneously with electroencephalography (EEG) monitoring during novel object recognition (NOR) test. Sub mice exhibited a marked cognitive decline from an early age, been accompanied with alterations in frequency bands reflected in significantly lower power in delta (1-4 Hz), theta (4-8 Hz) and low gamma (20-40 Hz) in hippocampus during novel object exploration. Taken together our data reveal that inherent sensitivity to stress determines the predisposition to the accelerated aging and early age cognitive decline correlated with power alterations of frequency bands.

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Poster

693. Learning and Memory: Aging

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Program #/Poster #: 693.03/Y43

Topic: H.01. Animal Cognition and Behavior

Support: NIH grant AG 046266

Title: Three year change in cognition, motor function and stress reactivity in aging marmosets (callithrix jacchus)

Authors: E. S. ROTHWELL, K. P. WORKMAN, ***A. LACREUSE**;
Psychological and Brain Sci., Univ. of Massachusetts, Amherst, MA

Abstract: The literature regarding sex differences in healthy aging is mixed, however women are more susceptible to age-related dementia such as Alzheimer's disease. Longitudinal studies in animal models with high translational value are needed to clarify the nature of the difference in susceptibility to age-related decline. Marmosets are an ideal animal model to study sex differences in aging as they have a naturally short lifespan as well as sophisticated cognitive abilities and rich social lives. We studied a cohort of male (n = 13) and female (n= 14) marmosets from middle age (mean age ~5 at study entry) and followed them longitudinally for 3 years. We evaluated sex differences in age-related changes in cognitive performance, motor skills and stress reactivity. Each year, marmosets were tested on a reversal learning task with three pairs of stimuli, a fine motor task requiring them to grasp small rewards from two staircase apparatus and a social separation task to elicit stress responses. Overall, both sexes improved their cognitive performance across the 3 years of testing, but the practice effect was greater in males than in females. Both sexes exhibited slower motor function with increasing age, but females tended to be faster than males. In the social separation task, stress reactivity, as assessed by agitated locomotion, declined across the 3 years of testing in females but remained stable in males. Together, these findings show that sex influences age-related changes in cognition, motor function and stress reactivity. In addition, high variability in aging patterns suggests that some individuals may follow a trajectory characteristic of pathological aging.

Disclosures: E.S. Rothwell: None. **K.P. Workman:** None. **A. Lacreuse:** None.

Poster

693. Learning and Memory: Aging

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 693.04/Y44

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant 5R01AG057434-02

Title: Behavioral comparison of the C57Bl/6 inbred mouse strain and the CB6F1 hybrid line

Authors: *K. CORDER, S. N. AUSTAD;
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Abstract: The majority of basic biomedical research is conducted using genetically defined, inbred mouse strains. The C57Bl/6 mouse strain is the most widely used genetic background in current rodent research. The rationale for using inbred strains is that because all individuals are genetically identical, phenotypic variation will be minimized allowing more statistically

powerful experiments. However, both theoretical and empirical evidence suggest that F_1 hybrids allow for potentially greater resilience in response to the inevitable stresses of laboratory environments. F_1 hybrids between two inbred strains, which are also all genetically identical, are also heterozygous at every locus at which the parental strains differed. Thus F_1 hybrids may actually make for more powerful experimental results. The purpose of this study is to characterize the differences in both the mean and variability in performance in response to induced stresses in C57Bl/6 mice and the CB6F1 hybrid line. The CB6F1 mouse strain (C57BL/6 x BALB/c) is predicted to show better performance with reduced variability in physical performance, cognitive behavior, and resilience following physiological stress challenges. These results address the issue of whether neurological experiments are more powerful when performed with inbred mice or with F_1 hybrids. To access whether sex plays a role in these experimental paradigms, both males and females were evaluated.

Disclosures: K. Corder: None. **S.N. Austad:** None.

Poster

693. Learning and Memory: Aging

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 693.05/Z1

Topic: H.01. Animal Cognition and Behavior

Support: NIMH Grant 1R01MH101130
NIA Grant R01AG061200
NARSAD Young Investigator Award, Brain & Behavior Research Foundation
ASPIRE Award, University of South Carolina
SPARC Graduate Research Grant, University of So
NSF GRFP 2019

Title: The role of PDE11A4 in age-related decline of social memories

Authors: *K. PILARZYK, N. S. PATEL, A. J. SMITH, M. P. KELLY;
Univ. of South Carolina- Sch. of Med., Columbia, SC

Abstract: Associative memories (aMEMs) are more susceptible to age-related cognitive decline than are recognition memories (rMEMs) for reasons that are not well understood. Age-related increases in phosphodiesterase 11A (PDE11A), an enzyme that breaks down cAMP/cGMP and regulates social behaviors, may be a fundamental mechanism underlying age-related cognitive decline of aMEMs. PDE11A4 is almost exclusively expressed in the ventral hippocampal formation, a brain region key to many types of aMEMs. Previous studies have suggested that cAMP and cGMP signaling are decreased in the aging and demented HIPP which is consistent with our recent observations of aging and dementia-related increases in HIPP PDE11A4

expression, more specifically with a selective increase in the membrane compartment of the VHIPP. Additionally, we have seen significantly elevated PDE11A4 in hippocampus of demented vs. non-demented aged humans with a history of TBI. Therefore, we hypothesized that age-related increases in HIPP PDE11A4 occur in a compartmentalized manner and impair social associative long-term memories (aLTMs). To test this hypothesis, we utilized 1) a genetic deletion of PDE11A4 through a KO mouse, 2) a stereotactic approach to mimic-TBI with overexpression of PDE11A4, and 3) a lentiviral construct (targeting the 'GAF-B' binding domain) that preferentially shifts PDE11A4 from the membrane to the cytosol to reduce expression of PDE11A4. We found that PDE11A KO mice are protected against age-related cognitive decline as old KO mice show robust aLTM for STFP on par with that of young PDE11A WT mice, while old PDE11A WT mice are severely impaired. Further, we showed that the protective effect of PDE11A deletion is reversible by acutely overexpressing PDE11A4 in the hippocampus of PDE11A KO mice. Lastly, we expressed the isolated GAF-B domain to the HIPP of old PDE11A WT mice to disrupt PDE11A4 homodimerization and found it is sufficient to reverse age-related decline of social aLTMs. Together, these data suggest that reversal/mimicry of age-related increases in PDE11A4 expression in the adult hippocampus is sufficient to rescue/cause deficits in social aLTMs.

Disclosures: K. Pilarzyk: None. **N.S. Patel:** None. **A.J. Smith:** None. **M.P. Kelly:** None.

Poster

693. Learning and Memory: Aging

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 693.06/Z2

Topic: H.01. Animal Cognition and Behavior

Support: Project 837-B8-123; Vicerrectory of Research, University of Costa Rica.
Economic travel support: Vicerrectory of Research, University of Costa Rica.

Title: Age, experience, and neurobehavioral domain: Effects of environmental enrichment and social isolation on brain and behavior in middle-aged and aged rats

Authors: *M. ROJAS-CARVAJAL[1], K. RAMÍREZ[2], A. SEQUEIRA-CORDERO[3], J. FORNAGUERA[4], J. C. BRENES[5];
[1]Neurosci. Res. Ctr., Univ. of Costa Rica, Montes de Oca, San José, Costa Rica; [2]Fac. of Dent., [3]Inst. for Hlth. Res., [4]Neurosci. Res. Ctr., [5]Univ. of Costa Rica, Montes de Oca, Costa Rica

Abstract: In rats, environmental enrichment (EE) is a form of physical-social stimulation used for modeling the impact of optimal developmental conditions on animal's phenotype. When implemented during early life, EE improves animal's cognitive skills, reduces anxiety-like traits, and promotes different forms of brain plasticity. Conversely, young animals raised on

impoverished conditions like social isolation (SI), developed poor cognitive skills and increased the reactivity to stress. The sensitive windows for neurobehavioral plasticity become narrower as organisms grow up. It is somewhat unclear, however, to which extent positive or negative experiences throughout adulthood are still able to benefit or compromise behavioral, emotional, and cognitive domains and neural plasticity. To this aim, middle-aged (120 PND) and aged (330 PND) Wistar rats (n=8 per age/group) were reared in EE (large cage filled with ethologically relevant stimuli; group housed), SH (standard housing in polycarbonate cage; 4 per cage), and SI (individually housed in stainless-steel cages) during two months. Afterwards, risk-assessment behaviors (i.e., defensiveness) and novelty habituation (i.e., kinetics of locomotion, rearing, and grooming) were measured in two, consecutive open-field tests. We found that EE reduced risk-assessment behaviors and improved habituation in both age groups, but only middle-aged rats showed an increasing in complex forms of grooming. In SH and SI rats, those behaviors were strongly modulated by age rather than by housing conditions. After the OFT, latencies to scape in the Barnes maze test (i.e., spatial memory) were measured. There, EE also improved spatial memory especially in aged rats, whereas SI caused no particular impairments on this parameter. After testing, we analyzed the expression of different genes closely related to functional and structural neural plasticity (BDNF, GluA1, GluA2, NR2B, CFL1, p250GAP, DNMT3A) in the medial prefrontal cortex (mPFC), the nucleus accumbens (NAcc), and the ventral and dorsal hippocampus (HPC). We found that SI changed the gene expression of the glutamate receptors subunits (e.g., NR2B, GluA1, and GluA2) in the dorsal HPC and NAcc. DNMT3A expression increased especially in the ventral HPC of aged SI rats. The main effect of aging on gene expression resembled the pattern observed in SI rats. In general, the effect of EE and SI conditions dissociated between the behavioral and molecular phenotype they induced and between the two age periods, with SI affecting almost all genes in one brain region or another.

Disclosures: **M. Rojas-Carvajal:** None. **K. Ramírez:** None. **A. Sequeira-Cordero:** None. **J. Fornaguera:** None. **J.C. Brenes:** None.

Poster

693. Learning and Memory: Aging

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 693.07/Z3

Topic: H.01. Animal Cognition and Behavior

Support: Freeburg Foundation
Kavli Institute for Brain and Mind
Allen Institute
American Heart Association

Title: The common marmoset (Callithrix jacchus) as a model for age-related cognitive decline

Authors: *C. GLAVIS-BLOOM, Z. W. DAVIS, J. H. REYNOLDS;
Salk Inst. for Biol. Studies, La Jolla, CA

Abstract: The number one risk factor for Alzheimer's disease is aging. However, it is unclear what aspects of aging contribute to disease vulnerability. The common marmoset (*Callithrix jacchus*) is the shortest-lived anthropoid primate, and their short (~10 year) lifespan offers an opportunity to investigate age-related cognitive decline longitudinally. For this purpose, we are evaluating the performance of marmosets on tasks previously demonstrated to reveal age-related cognitive decline in humans. One of these, the Delayed Recognition Span Task (DRST), is a paradigm that evaluates working memory capacity. The DRST is dependent on the function and integrity of the hippocampus and prefrontal cortex in humans and macaque monkeys (Jeneson et al 2010; Bor et al 2006; Beason-Held et al 1999). Performance on the DRST has also been found to decline with age in both humans and macaque monkeys (Mazurek et al 2015; Maylor et al 2006; Moss et al 1997; Herndon et al 1997). The task begins with a single visual stimulus presented on a touch screen. When selected, a juice reward is delivered. Following a delay (blank screen), the first item and a new item appear simultaneously. If the new item is selected, the monkey receives another reward. New items are continually added until the subject incorrectly selects a previously selected item, or correctly selects the 9th new item, concluding the sequence. Each sequence of trials makes up a "span", and the number of items correctly identified as novel is defined as the "span length" for that trial. The distribution of span lengths provides a measure of memory capacity. Our results show that adult marmosets are amenable to touch screen cognitive testing in their home cages and are highly motivated to participate without food or water restriction. They quickly learn to interact with a touch screen for liquid rewards, and progressively improve performance on the DRST, completing more spans of longer lengths with training. The span length distribution can be changed by extending the delay, requiring monkeys to remember items for longer periods of time. We find that monkeys reliably complete sequences lasting upwards of two minutes, despite their skittish nature and freedom to disengage at any time.

Disclosures: C. Glavis-Bloom: None. **Z.W. Davis:** None. **J.H. Reynolds:** None.

Poster

693. Learning and Memory: Aging

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 693.08/Z4

Topic: H.01. Animal Cognition and Behavior

Support: This research was supported entirely by the Intramural Research Program of the NIH, National Institute on Aging.

Title: Illuminating the neurobiological intersection between sleep and cognitive aging

Authors: *C. MYRUM, M. E. STELZNER, J. B. HUNT, J. M. LONG, P. R. RAPP;
Natl. Inst. of Health: NIA, Baltimore, MD

Abstract: Scores of studies in humans indicate that age-related changes in sleep duration and quality are powerful mediators of the neurobiological effects that contribute to increased risk of Alzheimer's disease and cognitive impairment later in life. However, the molecular pathways underlying this relationship are largely unknown. To address this issue, we first examined whether sleep is coupled to age-related cognitive outcome in a rat model of normal cognitive aging. Aged Long-Evans rats were tested in a hippocampus-dependent version of the Morris water maze, where we observed considerable inter-individual variability among aged animals, mimicking the increased variability observed in human aging. To record sleep, rats were implanted with multichannel electrodes and cortical local field potentials were recorded via electroencephalogram (EEG) for 24 hr. A quantitative spectral algorithm was used to quantify the number of transitions (sleep architecture) and the amount of time spent in rapid eye movement (REM) sleep, non-REM sleep, and awake. A notable preliminary finding from EEG data was that, while the amount of REM sleep did not differ between adult and aged animals as a whole ($p=0.20$), aged rats with memory impairment exhibited significantly more REM than aged rats with intact memory ($p=0.008$) and adult rats ($p=0.03$) during the dark (wake) period. Capitalizing on our ability to link age-related cognitive status with age-related changes in sleep, we then examined potential mediators of this relationship. We began by quantifying expression of Arc—a protein that is essential for long-term memory formation, dysregulated in cognitive aging, and upregulated during REM sleep. In adult rats, we found that Arc expression peaked after 3-4 bouts of REM across the hippocampus, most prominently in the CA1 subregion ($p=0.03$). Initial analyses showed that three bouts of REM induced significantly less hippocampal Arc expression among aged rats than in adult rats. However, expression failed to differ across cognitive impaired and unimpaired aged rats. Ongoing experiments aim to examine additional aspects of REM-induced Arc expression in aging, including potential changes in synaptic dynamics and Arc+ neuronal ensemble reactivation during post-behavior sleep.

Disclosures: C. Myrum: None. **M.E. Stelzner:** None. **J.B. Hunt:** None. **J.M. Long:** None. **P.R. Rapp:** None.

Poster

693. Learning and Memory: Aging

Location: Hall A

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Program #/Poster #: 693.09/Z5

Topic: H.01. Animal Cognition and Behavior

Support: FOSSIS-CONACyT 273308
DGAPA-PAPIIT: IN212919

Title: Impact of high-fat diet and aging on cognitive function: Relation with glial fibrillary acidic protein levels

Authors: *L. AYALA-GUERRERO[1,2], F. BERMUDEZ-RATTONI[1], K. GUZMAN-RAMOS[3]; [1]Neurociencias Cognitivas, Inst. De Fisiología Celular, Ciudad de México, Mexico; [2]Posgrado en Ciencias Biológicas, UNAM, Ciudad de México, Mexico; [3]Ciencias de la Salud, Univ. Autónoma Metropolitana, Lerma, Mexico

Abstract: The chronic intake of a high-caloric diet and a sedentary lifestyle are causing two major health problems in the world, obesity and overweight. Along with the peripheric consequences of such states, are the increased risk to suffer cognitive impairment or dementia. Another important factor for the development of cognitive impairment is old age, and even though aging is a natural process that implies a decline of cognitive function, the presence of metabolic diseases such as diabetes, metabolic syndrome, obesity or overweight on elderly population, increased by 1.29-fold the risk to develop mild cognitive impairment or dementia. It is most likely that peripheric metabolic dysfunctions lead to central nervous damage, causing cognitive decline. Both, aging and metabolic disorders are associated with the production of oxidative stress in the brain and neuroinflammation, which is considered the main culprit of the development of such cognitive deterioration. Astrocytes are the most abundant cells in the brain and respond to any type of brain insult through astrogliosis.

One characteristic of astrogliosis is the increase in glial fibrillary acidic protein (GFAP), which is a major cytoskeleton protein of astrocytes, which is essential for the formation, growing and proliferation of astrocytes. It has been reported that astrogliosis increase during aging and after exposure to a high-fat diet in young mice, so it is possible that GFAP would be a good biomarker of central injury and aid us to predict the beginning of cognitive decline.

To test this hypothesis, we first analyzed the cognitive performance and expression of GFAP on the dorsal hippocampus (HIP) and the insular cortex (IC) of male and female C57BL/6 mice of 5 (n=9), 10 (n=15), 15 (n=12), and 19 (n=10) months. Then, we analyzed the same parameters from C57BL/6 mice of 5 (n=7) and 10 (n=12) months exposed for 5 months to a diet composed of 10% fructose and 60% caloric intake of fat. We found a progressive decline of cognitive function in memory dependent of tasks such as object recognition memory and Morris's water maze in normal aging. In addition, we found a progressive increase in the immunoreactivity of GFAP in HIP and IC. Conversely, high-fat/fructose diet in adult mice induces increased weight, central adiposity, glucose intolerance, causes mild cognitive impairment and increases immunoreactivity of GFAP in HIP and IC as the older untreated mouse. These results indicate that GFAP may be a molecular correlate of cognitive performance decline that could be used as a biomarker for brain damage.

Disclosures: L. Ayala-Guerrero: None. **F. Bermudez-Rattoni:** None. **K. Guzman-Ramos:** None.

Poster

693. Learning and Memory: Aging

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 693.10/Z6

Topic: H.01. Animal Cognition and Behavior

Support: NRJ Fondation
ANR MemoryTrack

Title: A new method for discriminating normal versus slow learners in a large population of aged mice

Authors: C. DUFFAU[1], S. HADZIBEGOVIC[1], V. ANDELKOVIC[1], I. LAGROYE[2], B. BONTEMPI[1], ***O. NICOLE**[1];
[1]CNRS, Univ. Bordeaux, UMR-CNRS5293, Bordeaux, France; [2]UMR 5218 Lab. de l'Intégration, du Matériau au Système (IMS), Bordeaux, France

Abstract: Cognitive disabilities that occur with age represent a growing and expensive health problem. Normal aging is associated with a progressive cognitive decline, particularly in memory functions. In rodents, this decline has been shown in different learning and memory paradigms requiring navigation though space. However, consistent with what is observed in the human population, alteration of cognitive functions is extremely variable within cohorts of animals. Building upon the analysis of a comprehensive set of observations derived from a large population (n = 111) of aged (22 month-old) mice submitted to spatial discrimination testing in an 8-arm radial maze, we generated a categorization index that provides a continuous, graded measure, of the severity of age-related impairment in spatial memory and enables to identify mice with the greatest learning difficulties. Mice were required to locate the 3 constantly baited arms of the radial maze. Reference memory training consisted in 8 equivalent blocks of six trials separated by a 1 day interval. Each trial started with all 8 arms opened and terminated when the mouse entered the third baited arm and returned to the central platform of the maze. The number of total errors (i.e., entries into nonbaited arms and repeated visits to baited arms) decreased significantly over the 8 training blocks in aged and young animals, both groups achieving the same level of task mastery after 8 days of training. However, close analysis of the slope of their learning curves revealed that young mice learned the position of the three baited arms faster than aged mice. To capture this differential speed of spatial learning into a reliable and discriminative memory performance index, we first normalized the performance of each mouse with respect to its number of errors committed the first day of training, then calculated when an exponential fit crossed the 50% best performance level achieved by each individual upon completion of training (lower asymptote), and finally created best fit individual psychometric curves. This method of analysis enabled to clearly isolate two populations of aged mice, one with a memory

performance similar to that of young mice (normal learners) and another exhibiting a reduced speed of learning (categorized as slow learners). Thus, the performance index generated may serve as a valuable categorization tool to discriminate normal versus slow learners within cohorts of aged animals. It should be potentially useful in conjunction with other behavioral or neurofunctional measures in correlational studies aimed at investigating individual differences during the course of the aging process.

Disclosures: C. Duffau: None. **S. Hadzibegovic:** None. **V. Andelkovic:** None. **I. Lagroye:** None. **B. Bontempi:** None. **O. Nicole:** None.

Poster

693. Learning and Memory: Aging

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Program #/Poster #: 693.11/Z7

Topic: H.01. Animal Cognition and Behavior

Support: This research was supported by the Intramural research Program of the NIH and Alzheimer's Research Funding, National Institute on Aging.

Title: Successful trajectories in aging: Reserve and resilience in RatS (STARRRS) building a resource of longitudinal data for the study of neurocognitive reserve in aging

Authors: *C. BANUELOS, J. M. LONG, K. FISHBEIN, R. A. MCDEVITT, K. PERDUE, R. SPENCER, P. R. RAPP;
Natl. Inst. on Aging, NIH, Baltimore, MD

Abstract: Normal aging in humans and animals is associated with increased variability in cognitive function, with some individuals, despite exhibiting typical neurobiological consequences of aging, showing preserved cognition and others showing substantial impairment. The underlying mechanisms that mediate these divergent cognitive trajectories remains largely unknown. Accordingly, and in response to the recommendations of the 2017 Cognitive Aging Summit III, the Intramural Research Program of the National Institute on Aging is launching a major resource initiative to support the longitudinal study of neurocognitive reserve and resilience in rats. This resource is intended to generate an open database of longitudinal phenotypic data, neuroimaging scans, tissues, and other samples for distribution, utilizing a validated Long Evans rat model that features reliable individual differences in neurocognitive outcomes with age. A key design goal is to maximize the value of the resource to the research community. Our presentation will outline initial design concepts, infrastructure, and other project support with the aim of defining anticipated capabilities and soliciting further input from the interested scientific community. In brief, male and female rats will be followed from youth to approximately 24 months of age with state-of-the-art technologies to assess brain structure and

function non-invasively and with dynamic phenotypic measurements. Neuroimaging infrastructure will include a Bruker Biospec® 9.4T/20cm MRI with CryoProbe™ technology and spectroscopic capabilities. A variety of behavioral assessments will be available, including home cage activity, digitized gait analysis, water maze, olfactory discrimination, elevated plus maze, operant testing, open field activity and others. Periodic longitudinal sampling of biological materials (blood, feces, vaginal smears) and physiologic measures (body weight, temperature) will be available, in addition to terminal samples for post mortem analysis in relation to cognitive outcomes. Input from an NIH Request for Information (https://grants.nih.gov/grants/guide/notice-files/NOT-AG-19-017.html), and a focused work group at the September 2019 "Workshop on Research Definitions for Reserve and Resilience in Cognitive Aging and Dementia" (https://reserveandresilience.com/) will be presented.

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Poster

693. Learning and Memory: Aging

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Topic: H.01. Animal Cognition and Behavior

Support: Clark Foundation
ATA
Project Emmet

Title: Intranasal insulin enhances spatial memory and intrinsic excitability of aging hippocampal neurons by altering expression of Ca^{2+}-dependent K^+ channels and of calcium-sensors for Ca^{2+}-dependent K^+ channels

Authors: *N. R. TANDON[1], L. T. THOMPSON[2];
[1]Biol. Sci., [2]Behavioral & Brain Sci., Univ. of Texas at Dallas, Richardson, TX

Abstract: The elderly population (age 65 and over) is estimated to double in number by year 2050. This will increase the socioeconomic burden associated with cognitive decline population associated with normal aging, pathological aging caused by Alzheimer's disease (AD) and other dementias, and with diabetes mellitus. While many pharmacological treatments have shown promise in ameliorating age-related cognitive decline, they have unfortunate side effects. Intranasal insulin has proven to improve cognitive deficits in clinical trials with AD and MCI patients, with few reported side effects. Maimaiti et al. (2013) showed cognitive improvement in aging rats treated with intranasal insulin. They also showed insulin-dependent decreases in the amplitude and duration of post burst afterhyperpolarizations (AHPs), which are significantly

increased in aging hippocampus leading to reduced intrinsic excitability. However, the molecular or cellular targets of insulin in hippocampal neurons that leads to insulin-dependent decrease in AHP in aged rats are yet unknown. Our objectives were to study the effects of insulin: 1. on hippocampal-dependent spatial and working memory consolidation and 2. on proteins involved in Ca^{2+}-dependent intrinsic excitability−the SK2 channel proteins underlying the mAHP, and the Ca^{2+}sensors calmodulin and hippocalcin respectively for the mAHP and sAHP.Young (4-6 mo) and old (20-24 mo) FBNs rats were used and handled daily for 7 d before treatment began. Subsets from each cohort were treated either with intranasal saline or with intranasal insulin (2 IU, Humalog) for 21 d. Morris water maze and spontaneous alternation tasks were performed to assess behavior. Hippocampal slices were collected from each group and were either stimulated with aCSF or with insulin-aCSF (24nM) for 10 min, then processed and analyzed using western blotting to assess protein expression. Our results show improved learning and spatial memory consolidation in both aging and young rats treated with intranasal insulin; the effect was larger and more significant in aging rats. Our western blot results show significant decreases in hippocalcin protein expression in aged hippocampal slices stimulated with insulin, while no significant effect of insulin was seen on hippocalcin expression in young tissue. Insulin stimulation altered expression of SK2 and calmodulin in both aging and young hippocampus; but the difference was not significant. Insulin appears to have age-related cognition and excitability enhancing effects that suggest potential future clinical benefits.

Disclosures: N.R. Tandon: None. **L.T. Thompson:** None.

Poster

693. Learning and Memory: Aging

Location: Hall A

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Program #/Poster #: 693.13/Z9

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant AG052934

Title: Linking an increased afterhyperpolarization to cognitive deficits in a mouse model of aging

Authors: *S. J. MOORE[1], V. A. CAZARES[2], G. G. MURPHY[2];
[1]Mol. and Behavioral Neurosci. Inst., [2]MBNI/Physiology, Univ. of Michigan, Ann Arbor, MI

Abstract: Cognitive impairments in the aged population are generally associated with neurodegenerative disorders like Alzheimer's disease, but in fact, they often occur in the absence of overt pathology. As the aged population continues to expand in the coming decades, more and more people will be affected by age-related decreases in cognitive function, which degrade an individual's ability to function independently and adversely impact the quality of life. It can be

difficult to study the “normal” (i.e. non-pathological) aging process in a laboratory setting because of the long time frame required (typically 2-3 years in mice) and the paucity of genetic models of aging. Previous work in rodents has shown that aging is associated with an up-regulation of L-type voltage-gated calcium channel (LVGCCs), which is correlated with age-related memory impairments in hippocampus-dependent learning and memory tasks. Thus, we generated a novel transgenic mouse line which over-expresses the LVGCC, CaV1.3, as a mouse model of normal aging (Krueger et al., BBR, 2017). Our recent work shows that this mouse model recapitulates age-related cognitive deficits, such as a decrease in learning and memory performance assayed by the Morris water maze, as well as age-related changes in neuronal physiology, including an increase in the amplitude of the post-burst afterhyperpolarization (AHP) assayed by whole-cell current-clamp recordings in CA1 pyramidal neurons. Several earlier studies found that an increase in the AHP was accompanied by a decrease in neuronal excitability (i.e. action potential firing); these findings led to the hypothesis that decreased excitability represented the cellular mechanism underlying the observed deficits in learning and memory. Interestingly, in our experiments, firing rate was unchanged, even when the AHP was significantly increased, suggesting that decreased neuronal excitability is not necessary, and may not be sufficient, to account for age-related changes in cognitive function. We are now examining other potential mechanistic links between the AHP and deficits in learning and memory, including AHP-mediated modulation of the phase response curve (PRC), a measure of the timing of action potential firing relative to the timing of input throughout the phasic oscillations of a neuron, which reflects complex interactions between diverse intrinsic conductances that lead to spike generation. Taken together, our studies may further elucidate the cellular mechanisms that contribute to changes in neuronal function that occur with age, and identify potential therapeutic targets aimed at ameliorating age-related cognitive decline.

Disclosures: **S.J. Moore:** None. **V.A. Cazares:** None. **G.G. Murphy:** None.

Poster

693. Learning and Memory: Aging

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Program #/Poster #: 693.14/Z10

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant R01AG059028

Title: Changes to the structure and function of layer 3 pyramidal neurons and the effects of curcumin intervention in the prefrontal cortex of aging monkeys

Authors: *W. W. CHANG[1], M. MEDALLA[1], T. L. MOORE[1], D. L. ROSENE[1], D. PATHAK[1], V. TURNBULL[1], J. GOODLIFFE[1], T. GUILLAMON-VIVANCOS[2], J. I. LUEBKE[1];

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Abstract: A significant proportion of humans and non-human primates exhibit declines in working memory during normal aging. While the neural bases of these age-related changes in cognition are poorly understood, they have been associated with a number of sub-lethal changes to the structural and functional properties of neurons in prefrontal regions that are key mediators of working memory. For example, layer 3 (L3) pyramidal neurons in *in vitro* slices of the dorsolateral prefrontal cortex (dlPFC, area 46) of aged rhesus monkeys exhibit significantly increased input resistance (Rn) and action potential (AP) firing rates compared to neurons in young subjects (Chang et al., 2005). Furthermore, these neurons exhibit a significant decrease in dendritic spine density with age (Coskren et al., 2015). What is not yet understood is the time-course of the development of these neuronal alterations during the aging process and whether they can be ameliorated by the powerful anti-oxidant and anti-inflammatory agent curcumin. To address these questions, we compared the structural and functional properties of L3 pyramidal neurons in slices prepared from the dlPFC of behaviorally characterized rhesus monkeys between the ages of 8 and 29 years of age using *in vitro* whole-cell patch clamp recordings and high-resolution digital neuronal reconstructions. In these animals, performance on the delayed recognition span-spatial task (DRST-spatial)—a measure of spatial working memory—declined linearly with age ($p<0.02$). Interestingly, neurons began to exhibit reduced spine density as well as hyperexcitability in middle-age but to a lesser extent than what we have previously reported in aged subjects. Furthermore, Rn declined linearly with age ($p<0.003$), AP firing rates increased linearly with age ($p<0.005$), and spine density was reduced with age ($p<0.01$). Long-term (~2 years) dietary curcumin treatment led to greater improvements on the DRST-spatial task across repeated testing ($p<0.03$); but did not reverse the age-related alterations to neuronal properties, as excitability and spine density in neurons from subjects that received curcumin (n=8) did not differ from those of the untreated animals (n=5). These results suggest that significant changes to the structure and function of neurons that may contribute to cognitive deficits occur early during the aging process, and that while dietary curcumin mitigates cognitive deficits, it does not reverse or delay age-related changes in neuronal properties.

Disclosures: W.W. Chang: None. **M. Medalla:** None. **T.L. Moore:** None. **D.L. Rosene:** None. **D. Pathak:** None. **V. Turnbull:** None. **J. Goodliffe:** None. **T. Guillamon-Vivancos:** None. **J.I. Luebke:** None.

Poster

693. Learning and Memory: Aging

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 693.15/Z11

Topic: H.01. Animal Cognition and Behavior

Title: Exercise mitigates chemotherapy-induced cognitive impairment

Authors: *K. GILLEY[1], G. SULLENS[1], M. J. SEKERES[2];
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Abstract: Chemotherapy-induced cognitive impairment (CICI) is commonly reported by human breast cancer patients, generally involving disruptions of memory and executive functioning. We use a pre-clinical model to determine if long term exposure to cardiovascular exercise (running) may protect against the development of CICI symptoms in a transgenic breast cancer mouse model. Previous pre-clinical studies have shown that post-treatment exercise reduces memory dysfunction and increases rates of hippocampal neurogenesis in rodents. Voluntary running throughout middle-age provides protective effects on neurogenesis, BDNF expression, and cognition into older age for female mice. In rodents, running after chemotherapy reduces CICI severity. Neural regions typically associated with CICI in memory and executive functioning include, respectively, the hippocampus and frontal lobe. To assess cognition and hippocampal and frontal lobe function in transgenic tumorigenic mice and in wild type controls, mice were given a pre-treatment and post-treatment behavioral test battery including spatial water maze, novel object recognition, context fear conditioning, and conditional associative learning. Behavioral tests indicate that tumorigenic subjects have reduced cognitive functioning with some savings in the fear conditioning and spatial water maze tasks for mice who engaged in pre-treatment running. We additionally observed larger tumor volume for mice who engaged in pre-treatment running, suggesting that long-term exercise may enhance rates of tumor growth in animals genetically predisposed to developing cancer.

Disclosures: K. Gilley: None. **G. Sullens:** None. **M.J. Sekeres:** None.

Poster

693. Learning and Memory: Aging

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 693.16/Z12

Topic: H.01. Animal Cognition and Behavior

Support: Intramural support from National Institute on Aging

Title: Recognition memory is associated with different patterns of regional volumes in young and aged monkeys

Authors: *C. P. COOPER[1], A. T. SHAFER[2], S. L. ROSSI[1], N. ARMSTRONG[2], J. YOUNG[1], C. HEROLD[1], Y. YANG[3], E. A. STEIN[4], S. M. RESNICK[2], P. R. RAPP[1];
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Baltimore, MD; [3]Magnetic Resonance Imaging and Spectroscopy Section, [4]Cognitive Neurosci. and Psychopharmacology Section, NIH, Natl. Inst. on Drug Abuse, Baltimore, MD

Abstract: Cognitive aging varies tremendously across individuals, with some people remaining cognitively intact while others experience substantial decline, even in the absence of disease. Such decline is often accompanied by regionally specific reductions in brain volume. However, the co-occurrence of neurodegenerative disease in humans can obscure changes in brain volume attributable to normal aging, distinct from pathological processes. In order to define regional brain aging associated with individual differences in memory, we used a standardized neuropsychological test, delayed non-matching to sample (DNMS), to asses visual recognition memory in young adult (mean = 10.2 years, n = 6) and aged (25.5 years, n = 10) rhesus monkeys, which do not suffer spontaneous neurodegenerative disease with age. Volumetric T1-weighted MRI scans were acquired from anesthetized animals on a Siemens Trio 3T scanner and analyzed by voxel-based morphometry (SPM12 with DARTEL implemented in MATLAB, oriented and masked to the D99-SL macaque atlas). We demonstrate that brain regional volumes significantly correlated with acquisition and memory performance on DNMS are distinctly different in young adult and aged rhesus monkeys. Faster task acquisition (i.e., fewer trials to criterion) inversely correlated with larger medial temporal lobe (hippocampus, amygdala, entorhinal cortex, perirhinal cortex, inferotemporal area) volume in the young, whereas larger prefrontal regions (orbital, ventrolateral, and dorsolateral prefrontal areas) correlated with fewer trials to reach criterion in aged monkeys. When the memory demands of the procedure were increased by imposing longer retention intervals, average recognition accuracy in young positively correlated with medial temporal lobe, cingulate cortex and cerebellar (lobule IV, lobule V, crus I and crus II) volumes. In contrast, average performance across delays in the aged brain positively correlated with prefrontal, striatum and insula volumes. These results suggest that the pattern of regional volumes coupled with DNMS performance are distinct in young adult and aged monkeys. The data from young monkeys are consistent with lesion and functional MRI findings implicating the medial temporal lobe and prefrontal cortex in visual recognition memory. Interestingly, our results also introduce the cerebellum as potentially important for medial temporal lobe-dependent memory. Overall, these findings support the perspective that the aged primate brain can display substantial structural reorganization, potentially supporting significant compensatory or adaptive functional capacity in the cognitive trajectory of aging.

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Poster

693. Learning and Memory: Aging

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 693.17/Z13

Topic: H.01. Animal Cognition and Behavior

Support: CONACYT, cvu327002

Title: Sex differences in the effect of voluntary exercise on cognitive flexibility in older mice

Authors: *D. ISLAS-PRECIADO[1], M. IBRAHIM[2], N. BLACK[1], C. K. BARHA[3], T. LIU-AMBROSE[3], L. A. GALEA[2];
[1]Djavad Mowafaghian Ctr. from Brain Hlth., [2]Dept. of Psychology, Djavad Mowafaghian Ctr. for Brain Hlth., [3]Dept. of Physical Therapy, Djavad Mowafaghian Ctr. from Brain Hlth., Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Although studies show that aerobic training (AT) promotes memory and executive functions, a large degree of variation still exists in AT efficacy on cognition among older adults. Evidence suggests there may be a sex difference in cognitive response to AT such that women benefit more so than men (Barha et al., 2018). This sex difference may be related to the ability of AT to influence sex and stress hormones, perhaps via adrenal gland production of steroid and stress hormones. Cortisol levels are increased in older age and are linked to poorer cognition and smaller prefrontal cortex (PFC) (Stomby et al., 2016). These effects are more pronounced in women (Otte et al., 2005). Cognitive flexibility (CF) is a higher order PFC-dependent executive function that comprises the ability to control and direct behaviour to cope with novelty and facilitate adaptation (Banich et al.2009). Interestingly, CF is one of the first cognitive spheres affected in aging and dementia. Therefore, identifying potential therapies to improve cognition and the underlying mechanisms is imperative. Here, we explored whether AT could be an effective intervention to ameliorate CF in older males and females by using the 'visual discrimination and reversal' paradigm in Saksida-Bussey touchscreen chambers. C57BL/6J male and female mice aged 12-13 months were randomly assigned to either sedentary control or AT group. AT animals were given free access to running wheels for 2 weeks, and then food-restricted to 90-95% of their free-feeding body weight to increase motivation for task completion. Exposure to running wheels remained over the course of cognitive assessment. Preliminary data show that AT females learned to discriminate the stimulus faster than control females and males. In addition, AT females needed fewer sessions to reach criteria for reversal than males. These findings suggest greater AT efficacy in females despite no differences between sexes in average of total distance ran. Analyses to evaluate neurogenesis, stress, and sex hormones are ongoing. Our data suggest that voluntary running for 80 days in middle-aged mice improves cognitive flexibility more effectively in females than in males.

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Poster

693. Learning and Memory: Aging

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 693.18/Z14

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

Support: NIH Grant R56AG059284
NIH Grant P51OD01133

Title: Detection of age-specific decline in cognitive and motor performance in baboons using CANTAB and object retreival task with barrier detour

Authors: G. CHOUDHURY, ***M. DAADI**;
Texas Biomed, Southwest Natl. Primate Res., San Antonio, TX

Abstract: Aging brain cells is one of the major underlying pathophysiological processes contributing to the progressive decline in motor skills and cognitive functions. The difference in performances observed between young and old test subjects across species highlights the effects of aging on brain functions; however, the specific age in an individual's lifespan whereby a precipitous decline in brain functions begins is unknown. This inflection point in age-related decline is important for the physiological understanding of normal cell longevity and senescence and for timing therapeutic interventions. Nonhuman primates (NHP) are phylogenetically close to humans and share many similarities, including age related decline in neural and immune functions thus complex human-like behavioral endpoints may be measured. In the present study we integrated three clinically relevant outcome measures to investigate the effect of age on cognition, motor function and diurnal activity in older baboons. We used the Object Retrieval Task with Barrier-Detour (ORTBD), Cambridge Neuropsychological Test Automated Battery (CANTAB) and actigraphy to investigate age-related decline in cognition, motor skills, and diurnal / nocturnal activities, respectively. The data show significant age-related decline in movement planning, learning novel tasks, in simple discrimination tasks and in motivation. These results suggest that baboons may offer a model of dementia and early cognitive decline.

Disclosures: G. Choudhury: None. **M. Daadi:** None.

Poster

694. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 694.01/Z15

Topic: H.01. Animal Cognition and Behavior

Title: Bidirectional coupling of grid cell and place cells as a mechanism for robust spatial representation across multiple maps

Authors: *H. AGMON[1], Y. BURAK[2];
[1]ELSC, Hebrew Univ. of Jerusalem, Jerusalem, Israel; [2]Edmond and Lily Safra Ctr. for Brain Sci., Hebrew Univ., Jerusalem, Israel

Abstract: Grid cells and place cells play an important role in spatial encoding. Grid cells in the medial entorhinal cortex have multiple periodically spaced firing fields that form a hexagonal lattice and are largely similar between environments. Hence, they are considered as reasonable candidates to be associated with path integration. Hippocampal place cells, on the other hand, typically display at most a single environment specific receptive field, and are associated with contextual memory since they exhibit 'global remapping', drastically changing their firing field between environments. In the past decade many experimental and theoretical studies examined the influence that grid cells and place cells might have on one another. Studies have demonstrated correlated phenomena between activities of grid cells and place cells under various manipulations, yet the exact mechanism and functional relationship between grid cells and place cells and its significance to encoding of spatial location is still unclear. Some studies have suggested that grid firing patterns are the main determinant of place cell firing while other studies have challenged this view arguing that grid fields are formed as a result of place cell input. Overall, studies so far were primarily concerned with uni-directional manipulations and their implications, namely, they dealt either only with the effects and emergence of grid cells from place cells inputs or vice versa. Instead of treating grid cells and place cells as two separate populations in successive stages of a processing hierarchy, we develop in this work a detailed computational attractor model with mutual interacting connections between grid cells and place cells and demonstrate the functional significance of such coupling. In this framework grid cell and place cell activities serve as complementary and interacting representations that work in combination to support the reliable coding of large-scale space over multiple environments.

Disclosures: H. Agmon: None. **Y. Burak:** None.

Poster

694. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

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Topic: H.01. Animal Cognition and Behavior

Support: PRESTO Career Development Award (JPMJPR1681), Japan Science and Technology Agency
Whitehall Foundation Research Grant, 2017-08-01)
Alzheimer's Association Research Grant (AARG-17-532932)
Fay-Frank Grant (BRFSG-2017-04), Brain Research Foundation

Title: Impaired spatial representation in hippocampal entorhinal circuit of knock in Alzheimer's model

Authors: *H. JUN[1], S. SOMA[1], A. REDDY[1], T. SAITO[2], T. C. SAIDO[2], K. M. IGARASHI[1,3,4]; [1]Anat. and Neurobio., Univ. of California Irvine Sch. of Med., Irvine, CA; [2]RIKEN Ctr. For Brain Sci., Wako, Japan; [3]Ctr. for Neurobio. of Learning and Memory, [4]Inst. for Memory Impairments and Neurolog. Disorders, Univ. of California Irvine, Irvine, CA

Abstract: Alzheimer's disease (AD) is a progressive neurological disorder that debilitates our mind and memory. AD patients show impairments in multiple dimensions of memory including spatial memory and navigation, which causes wandering behavioral symptoms. Despite significant advances made in uncovering molecular and cellular mechanisms behind AD pathology, a limited number of studies have been performed to investigate changes that occur in the brain circuits of AD. By understanding what type of neuronal activities are lost and demonstrating the relationship between the dysfunctional neural network and cognitive deficits, we may be able to develop novel therapies targeted to reactivate these activities in AD patients. We focus on the circuit comprised of the entorhinal cortex (EC) and the hippocampus involved in memory formation and retrieval. Histological and imaging studies in AD patients and animal models have shown that the EC is a primary site of atrophy and activity loss in the early phases of AD. However, it is still unclear what type of activity is lost in the EC of AD patients, or even in AD mouse models. Using a novel amyloid precursor protein (APP) knock-in mouse model (Saito et al., Nat Neurosci 2014), we found that grid cells, a cell type harboring spatial memory-related activity in the medial entorhinal cortex (MEC), are impaired in APP knock-in mice. Place cells, another spatially-tuned neurons in the hippocampus, are also impaired. Our results provide evidence to demonstrate that the entorhinal-hippocampal spatial representation is impaired in the AD mouse model.

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Poster

694. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 694.03/Z17

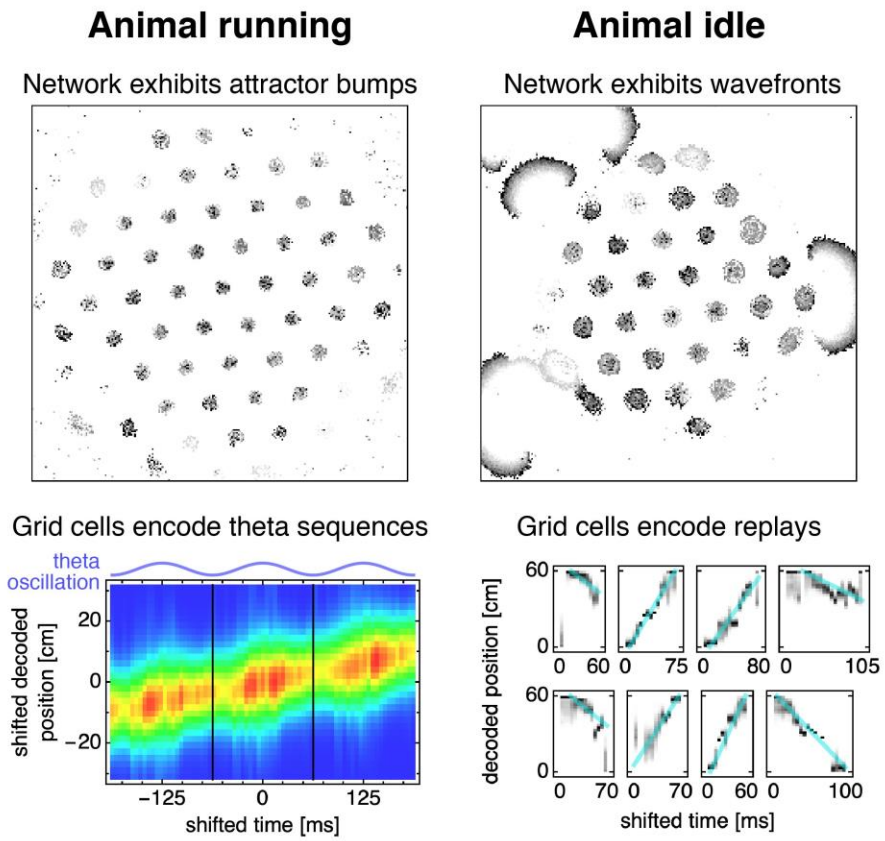
Topic: H.01. Animal Cognition and Behavior

Support: Army Research Office Grant W911NF-13-1-0390
Miller Institute for Basic Research in Science

Title: Replay as wavefronts and theta sequences as bump oscillations in a grid cell attractor network

Authors: *L. KANG, M. R. DEWEESE;
Redwood Ctr. for Theoretical Neurosci., Univ. of California, Berkeley, Berkeley, CA

Abstract: Grid cells and place cells fire in sequences that represent rapid trajectories in space. During locomotion, theta sequences encode sweeps in position starting slightly behind the animal and ending ahead of it. During quiescence and slow wave sleep, bouts of synchronized activity represent long trajectories called replays, which are well-established in place cells and have been recently reported in grid cells. Theta sequences and replay are hypothesized to facilitate many cognitive functions, but their underlying mechanisms are unknown. A leading mechanism proposed for grid cell formation is the continuous attractor network. We demonstrate that it naturally produces theta sequences and replay as distinct consequences of modulating external input. Driving inhibitory interneurons at the theta frequency causes attractor bumps to oscillate in speed and size, which gives rise to theta sequences and phase precession, respectively. Decreasing input drive to all neurons produces traveling wavefronts of activity that are decoded as replays.



Disclosures: **L. Kang:** None. **M.R. DeWeese:** None.

Poster

694. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 694.04/Z18

Topic: H.01. Animal Cognition and Behavior

Support: MEXT KAKENHI 16H06544

Title: Neural activity in the central complex of the crickets during phonotaxis

Authors: ***K. KAI**[1], H. SHIDARA[1], N. ANDO[2,3], H. OGAWA[1];
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Abstract: Animals navigate themselves to a specific location such as feeding place, nest, and mating partners. For orienting to the desired goal, animals integrate multiple information about the goal location from surroundings and proprioceptive signals caused by self-movement in the specific brain region to encode the current heading and to produce proper steering commands. Many studies in insect suggested that the central complex (CX), a medial region in the brain, is the center of goal-directed behavior. A group of neurons in the CX is sensitive to the polarized-light, the essential cue for homing behavior in desert ants and honeybees. Neural activity recorded from the CX of cockroaches are related to walking speed and angular velocity. Furthermore, Calcium imaging in *Drosophila* CX revealed that the population vector of ellipsoid body (EB), the lower unit of CX, encodes the animal's angular velocity as well as its head-direction. However, at least in insect, few researches have investigated the neural mechanisms underlying the ethologically-meaningful orientation. Female crickets approach to the singing male by hearing its calling song, called phonotaxis. It is well-known that the auditory system of the cricket shows directional responses to the calling song and that magnitude of steering toward the sound source depends on the sound location, suggesting that directional information of sensory cue will be processed for making motor command in the brain. Then, using the cricket phonotaxis as a model, we explored neural mechanism encoding the goal direction and relevant steering commands in the cricket brain. We performed intracellular recording from the CX of female cricket during walking under the auditory VR environment. We found that a subset of the tangential neurons in the EB encoded the head direction in darkness. No CX neuron, so far, responded to the calling song. These results imply that the directional information of sound source by-passes the CX and that the CX tracks the internal heading based on self-motion during phonotaxis.

Disclosures: K. Kai: None. **H. Shidara:** None. **N. Ando:** None. **H. Ogawa:** None.

Poster

694. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 694.05/Z19

Topic: H.01. Animal Cognition and Behavior

Support: ANR-18-CE92-0051-01
CNRS
Université Paris Descartes

Title: Presubicular layer 3 neurons receive convergent input from anterior thalamus and retrosplenial cortex

Authors: L. RICHEVAUX[1], L. SCHENBERG[1], M. NASSAR[2], C. MAUTHE[1], I. COHEN[3], M. BERANECK[1], ***D. FRICKER**[1];

[1]Descartes Univ., [2]Collège de France, CNRS, Paris, France; [3]INSERM U1130 / CNRS UMR8246 / UPMC, Paris, France

Abstract: The presubiculum is a key structure for spatial orientation coding, located between the hippocampus and the entorhinal cortex. It is part of the brain wide head direction circuit, and its neurons are sensitive to an animals' head direction. The presubiculum is well positioned to integrate vestibular sensory input and visual landmark information, conveyed via the anterior thalamic nuclei and the retrosplenial cortex, respectively. Here we investigated the functional connectivity between these two afferent regions and the presubiculum, using anatomical tracing, optogenetics and electrophysiological patch clamp recordings in mouse brain slices. Retrograde tracing experiments with retrobeads or AAV2retro showed that neurons in the anterior thalamus and in the retrosplenial cortex provide major inputs to the presubiculum. Using anterograde viral vectors, Channelrhodopsin-2 fused to a fluorescent reporter protein was expressed in the anterior thalamus or the retrosplenial cortex, in order to specifically stimulate with light transfected axons in the presubiculum. As previously reported, we found that thalamic axons innervated the superficial layers of the presubiculum, and mono-synaptically excited principal neurons of layer 3, upon blue LED stimulation (onset latencies, 2.5 ± 1.0 ms). Retrosplenial axons also ramified in the superficial layers of the dorsal presubiculum and thus overlapped with thalamic inputs. Following photostimulation of retrosplenial axons, we recorded excitatory postsynaptic events from principal neurons of presubicular layer 3. These EPSPs had monosynaptic latencies of 3.2 ± 1.2 ms. Both thalamic and retrosplenial light-evoked events persisted in the presence of TTX and 4-AP. The intrinsic properties of postsynaptic presubicular neurons were similar, suggesting that thalamic and retrosplenial inputs target a same population of neurons. To directly investigate the convergence of thalamic and retrosplenial inputs onto single layer 3 neurons, we injected two different viral vectors to express blue and red shifted channelrhodopsins, Chronos and Chrimson, in the thalamus and the retrosplenial cortex, respectively. Calibration experiments indicated that axons originating form either region may be stimulated largely independently, when using brief pulses of 470 nm (0.5 ms) or 627 nm (2 ms) light and within a range of low light intensities (up to 0.5 mW). Combined, double wavelength optical stimulation experiments will help our understanding of multisensory information processing in single neurons in the presubiculum.

Disclosures: D. Fricker: None. **L. Richevaux:** None. **M. Beraneck:** None. **L. Schenberg:** None. **I. Cohen:** None. **C. Mauthe:** None. **M. Nassar:** None.

Poster

694. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 694.06/Z20

Topic: H.01. Animal Cognition and Behavior

Support: Simons Collaboration on the Global Brain, Grant 542949
NIH Grant R01-AT010459
NIDCD R21 DC015602

Title: Multimodal encoding of navigation variables in the anterior limbic system

Authors: *J. LAURENS[1], A. ABREGO[1], H. CHAM[1], Y. YU[1], N. ROTDEM[1], J. AARSE[2], D. DICKMAN[1], D. E. ANGELAKI[2];
[1]Neurosci., Baylor Col. of Med., Houston, TX; [2]Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: The brain's navigation system integrates egocentric sensory information to create a sense of position in allocentric space. Here we used a multimodal model (Hardcastle et al. 2017) to systematically assess how neurons throughout the navigation circuit encode an array of egocentric, allocentric and internal variables. We recorded neuronal activity in the murine anterior thalamic nuclei (ATN; antero-dorsal, antero-ventral and latero-dorsal; 6 animals, n=281 neurons), retrosplenial cortex (RSC; 4 animals, n=180 neurons) and anterior hippocampus (3 animals, n=112 neurons), as well as in the cingulum fiber bundle (5 animals, n=380 neurons) and the white matter regions surrounding the hippocampus (6 animals, n=267 neurons), while animals foraged in a circular arena.
As expected, we identified well-known cell types, such as head direction cells (45% of ATN cells) and hippocampal place and speed cells (19% and 20% of hippocampal cells, respectively). In addition, our approach revealed that 12% of ATN neurons encode the animal's allocentric position, similar to place cells, and that half of ATN neurons respond in phase with LFP in the theta band (4-12Hz). In line with other recent studies, we also found that a large fraction (45%) of RSC neurons, as well as some (9%) hippocampal neurons, encode the egocentric position of the arena's boundary.
We observed that tetrodes could readily record spiking activity in the cingulum fibers bundle and in white matter surrounding the hippocampus. These spikes typically had short durations (<0.33ms trough to peak), typical of axonal spikes. Cingulum units were recorded at the level of the anterior RSC, where the cingulum likely conveys predominantly ATN and RSC connections. We found that the population activity closely resembled a combination of ATN and RSC responses, in equal proportions, suggesting that navigational variables represented in these regions travel through the cingulum to reach other regions. Fibers traveling through the white matter in the vicinity of the hippocampus carried a mixture of navigation variables.
Our results draw a new picture of the information encoded and projected by the anterior thalamus and retrosplenial cortex, and offer new insights on navigational variables represented in the hippocampus and its vicinity. They also stress the importance of using unbiased multimodal models to assess population responses in navigation areas of the brain.

Disclosures: **J. Laurens:** None. **A. Abrego:** None. **H. Cham:** None. **Y. Yu:** None. **J. Aarse:** None. **N. Rotdem:** None. **D.E. Angelaki:** None. **D. Dickman:** None.

Poster

694. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 694.07/Z21

Topic: H.01. Animal Cognition and Behavior

Support: National Defense Science & Engineering Graduate Fellowship

Title: Neural correlates of locomotion, cues, and context in the interactions between hippocampus and lateral septum

Authors: *H. S. WIRTSHAFTER[1], M. A. WILSON[2];
[2]Picower Inst. Learn/Memory, [1]MIT, Cambridge, MA

Abstract: The lateral septum (LS) has been implicated in anxiety and fear modulation, and may regulate interactions between the hippocampus (HPC) and regions that mediate goal directed behavior. In this study, we simultaneously record from cells in the LS and the HPC during navigation and conditioning tasks. We identify a speed and acceleration spiking code in the LS that does not map to states of motivation or anticipation. We also identify an overlapping population of LS cells that change firing to cue and reward during conditioning. These cells display sharp wave ripple and theta modulation, spatial firing fields, and responses similar to the HPC during conditioning. These HPC-associated cells are not disproportionately speed or acceleration modulated, suggesting that these movement correlates are not hippocampally derived. This suggests a role for the LS in evaluating movement-dependent changes in context that can be used to guide task-relevant behavior.

Disclosures: H.S. Wirtshafter: None. **M.A. Wilson:** None.

Poster

694. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation IV

Location: Hall A

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Program #/Poster #: 694.08/Z22

Topic: H.01. Animal Cognition and Behavior

Support: Swiss Natl Found Grant No 166318
Canton de Vaud
Synapsis Foundation

Marie Heim Voegtlin Stiftung
Fond Jean Falk-Vairant

Title: A novel function of the thalamic reticular nucleus in the spatial navigation system

Authors: G. VANTOMME, Z. ROVÓ, G. KATSIOUDI, E. BÉARD, V. PERRENOUD, L. M. J. FERNANDEZ, *A. LUTHI;
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Abstract: The thalamic reticular nucleus (TRN) exerts inhibitory control over thalamo-cortical loops throughout all vigilance states. However, much of its portions, in particular the connectivity of its anterior, non-sensory sectors, are still largely unexplored. Through antero- and retrograde tracing and cellular electrophysiology, we identified the dorsal presubiculum (dPreS) and the anterior thalamic nuclei (ATN) as part of a thalamo-cortical loop involving the non-sensory TRN in mice. The dPreS, which is part of the parahippocampal formation, and the ATN are two key structures for spatial navigation. Presubicular excitatory glutamatergic synapses formed on TRN and ATN are part of a feedforward circuit through which TRN-mediated inhibition generates large burst-mediated inhibitory synaptic currents. Both synaptic pathways showed little depression when activated repeatedly, enabling persistent membrane depolarization and repeated firing of their postsynaptic targets. To explore the role of TRN in the spatial navigation system, we (1) recorded anterodorsal thalamic neurons from freely behaving mice and (2) combined a Morris Watermaze task with specific chemogenetic silencing of the non-sensory TRN. (1) The width of the tuning curve of head-direction neurons in the anterodorsal nucleus was broadened upon chemogenetic silencing of TRN neurons (n=8, p=0.04). Moreover, half of the head-direction neurons (n=4/10) showed action potential discharge patterns consistent with feedforward inhibitory responses upon light activation of the dPreS. These data suggest that feedback projections from the dPreS to the ATN recruit the TRN to sharpen the tuning of thalamic head-direction neurons. (2) Silencing of non-sensory TRN did not show any strong learning impairment in the watermaze task. Careful analysis of probe sessions at the end of the training period revealed that TRN silencing caused mice (n=11) to swim persistently in the area of the target quadrant unlike control mice (n=13), which investigated the rest of the maze after an initial period in the target quadrant (p=0.015). These data suggest that the non-sensory TRN participates in spatial orientation in the watermaze and guides an appropriate behavioral response that is, in this case, enlarging the exploration area.

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Poster

694. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 694.09/Z23

Topic: H.01. Animal Cognition and Behavior

Support: Epitarget

Title: Hippocampus, medial prefrontal cortex and nucleus reuniens neuronal patterns predict behavior during a working memory task

Authors: *A. F. VICENTE[1], W. CLAWSON[2], A. GHESTEM[1], C. BERNARD[3], P. P. QUILICHINI[4];
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Abstract: A dialogue between hippocampus (HPC) and medial prefrontal cortex (mPFC) in spatial working memory has been previously shown. Although HPC sends projections to mPFC, there are no return projections from mPFC to HPC. Nucleus reuniens (NR) is a good candidate to influence the interaction between HPC and mPFC due to its reciprocal projections to both brain areas. Furthermore, recent studies found an alteration in working memory performance following the inactivation of NR. In order to get a better understanding of the role of NR in working memory and its interactions with HPC and mPFC, we recorded simultaneously multi-unit activity and local field potentials in the 3 areas with silicon probes while Long-Evans rats performed a delayed-non-match to position task on a T-maze. We classified trajectories in 4 types of trials: left sample, right sample, left choice and right choice, depending on whether the rat entered in the left or right arm, and whether the trial was a sample (non-working memory dependent) or a choice (working memory dependent). We compared the original spikes trains with surrogate spikes trains created by shuffling left sample and right samples trials, and left choice and right choice trials. This procedure allowed us to identify neurons discharging differentially for right, left, sample and choice trials, and to detect the maze segments where discharge was different. Most neurons in the 3 areas differentiated between left and right, or sample and choice trials before the animal entered in the left or right arm, indicating that neuronal discharge predicts left/right and sample/choice trajectories. Additionally, we will analyze if neuronal discharge also predicts behavior during inter-trial periods. Further analyses will examine if these neurons are phase-locked to the ongoing hippocampal oscillation.

Disclosures: A. F. Vicente: None. **W. Clawson:** None. **A. Ghestem:** None. **C. Bernard:** None. **P.P. Quilichini:** None.

Poster

694. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 694.10/Z24

Topic: H.01. Animal Cognition and Behavior

Support: ISF grant 281/15

Title: Representation of space in the goldfish brain

Authors: *E. VINEPINSKY, L. COHEN, O. BEN-SHAHAR, O. DONCHIN, R. SEGEV; Ben Gurion Univ., Beer Sheva, Israel

Abstract: Navigation is one of the fundamental cognitive capability found in many animals across all of the animal kingdom, and specifically fish. This ability is important for finding food, shelter and mates in order to survive. However, almost nothing is known about the neural representation of space in the brain of animals outside the mammalian class. Goldfish, which is part of the largest vertebrate class, the bony fish, also have the cognitive ability to navigate using allocentric and egocentric cues. Furthermore, the lateral pallium in the goldfish brain is a possible homolog of the mammalian hippocampal formation and associated with allocentric navigation. Using a novel wireless recording system, we measured the activity of single cells in the lateral pallium in a freely swimming fish while it explores essentially two-dimensional environment. We report evidence for representation of space in the form of cells that were active in specific locations in the environment. Those cells resemble cell types which are found in the mammalian hippocampal formation and believed to be the building blocks which drive the navigation system. Our study sheds light on how spatial information is encoded in the fish brain and whether the mechanisms of the neural navigation system are preserved across evolution.

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Poster

694. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 694.11/Z25

Topic: H.01. Animal Cognition and Behavior

Support: NIH DC 2390

Title: The nucleus prepositus of mouse encodes eye-related information during passive and active head movement

Authors: *H. CHANG[1,2], S. ZHU[1], K. E. CULLEN[3];
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Abstract: The vestibular system plays a crucial role in our everyday life as it ensures gaze and postural stabilization and the sense of self-motion by detecting the head motion in space. To maintain a stable representation of spatial orientation, visual and non-visual signals such as vestibular and proprioceptive signals are required. It has been proposed that the nucleus prepositus hypoglossi (NPH) and the supragenual nucleus (SGN) in brainstem relay vestibular information from the vestibular system to head direction (HD) network. The prevailing view based on experiments in rodents is that this pathway produces a 'neural compass' of the head's direction relative to space that is vital for navigation. However, the NPH has also been long-known to comprise the oculomotor integrator which plays an essential role in eye movement control by holding the eye at an eccentric position in orbit after the saccade. Further, a recent study in non-human primates (Dale & Cullen, 2013), established that neurons in the NPH predominantly encode eye-related rather than head-related movement signals during both passively-generated and voluntary head movements. To date, however, it remains unknown whether neurons in the NPH of rodents encode eye-related and/or head-related movement signals. We hypothesized that NPH neurons in mouse, as in primate, preferentially encode eye-related rather than head-related signals during voluntary movement. To test this hypothesis, we performed in vivo recording of NPH neurons in mouse during passive and active head movement while simultaneously measuring eye movements. To measure mouse eye movement during active head movements, we used an AMR magnetic field sensor, which measured the location of a magnet implanted in the eye in orbit. During passive movements, we recorded the activity of NPH neurons during head-retrained behavioral protocols (Medrea & Cullen, 2013) including vestibular-ocular reflex (VOR), visuo-vestibular conflict (VORC), optokinetic reflex (OKR) and changes in static eye position (SEP) to dissociate eye and head movement sensitivities. The recording was also made during voluntary head movements. Notably, the mice were trained to make voluntary head movements to the left and right in response to an auditory tone. Our preliminary single unit recording experiments indicate that indeed consistent in the non-human primate model, neurons in the NPH of mice primarily output eye-related information during both passive and active head movement and function to stabilize gaze.

Disclosures: H. Chang: None. **S. Zhu:** None. **K.E. Cullen:** None.

Poster

694. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation IV

Location: Hall A

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Program #/Poster #: 694.12/Z26

Topic: H.01. Animal Cognition and Behavior

Support: Simons Foundation through the Simons Collaboration on the Global Brain
Howard Hughes Medical Institute through the Faculty Scholars Program

Title: Mechanistic models of place cell statistics in large environments

Authors: *M. Y. YIM[1], T. TAILLEFUMIER[1,2], I. R. FIETE[3];
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Abstract: In large environments, hippocampal place cells individually exhibit multiple stable firing fields, with great diversity in the number of fields expressed across cells. Moreover, the likelihood of a cell expressing a field persists across environments. We seek to understand the factors that could explain the placement of fields and their statistics across place cells. The existence and relative stability of place fields even in parts of the environment that lack detailed external local spatial cues suggests that they are informed by motion integration, presumably derived from entorhinal grid cell inputs. We thus investigated the degree to which grid cells, with their spatially periodic responses, might account for the statistics of place fields within and across cells. First, at the single-cell level, how much flexibility is there in the placement of multiple fields with grid cell input alone? We answer this question by computing the number of possible field arrangements for a place cell, and deriving stringent theoretical bounds for the distance over which arbitrary field arrangements are realizable. We found that only a very small fraction of possible field arrangements are achievable in large spaces, and that the range over which all field arrangements are possible is a miniscule fraction of the unique coding range afforded by grid cells, suggesting that place fields are either primarily driven by non-grid cues that derive from local external spatial cues, or that they fall in highly constrained arrangements when they are driven by grid cell inputs. Second, we studied the influence of grid cell inputs on the statistics of downstream place cells in population models with a variety of learned or random connections, to model the distribution of place cell firing propensities and generate predictions about the signatures of grid cell-driven responses. In all model variants, if the firing threshold (excitability) across place cells is similar, then grid cell inputs but not spatially localized inputs reproduce the distribution of place cell firing propensities. In all model variants, the predicted spatial frequencies associated with grid cell firing are overrepresented in the power spectral density of the place field distribution in both 1D and 2D environments, even after we include a range of spatially localized input and noise levels. Our theoretical study thus provides numerous

testable predictions for information flow from grid cells to place cells in individual hippocampal subregions.

Disclosures: **M.Y. Yim:** None. **T. Taillefumier:** None. **I.R. Fiete:** None.

Poster

694. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 694.13/Z27

Topic: H.01. Animal Cognition and Behavior

Support: Wellcome Trust Investigator Award (200855/Z/16/Z)

Title: Investigation of directional firing by grid cells

Authors: *K. Z. GERLEI[1], J. PASSLACK[1], H. STEVENS[1], M. ALLERHAND[2], I. PAPASTATHOPOULOS[2], M. F. NOLAN[1,3];
[1]Ctr. for Discovery Brain Sci., [2]Ctr. for Statistics, [3]Simons Initiative for the Developing Brain, Univ. of Edinburgh, Edinburgh, United Kingdom

Abstract: Grid cells in the medial entorhinal cortex have spatially periodic firing fields that are important for spatial navigation and may contribute to cognitive processes more generally. Grid cells have been categorized according to whether their firing fields are modulated by heading direction: conjunctive grid cells are active at particular locations when animals move in the cell's preferred direction; in contrast pure grid cells do not fire preferentially in a preferred movement direction. We investigated whether firing of grid cells is nevertheless direction-dependent. We recorded extracellular neuronal activity with tetrodes from the medial entorhinal cortex of mice (n= 16, 8 females and 8 males, mean age = 10.6 weeks SD=1.7 weeks) that explored a 1 meter square empty open field arena with a polarizing cue on one wall. We performed automated spike sorting using MountainSort (Chung et al. 2017, Neuron 95 (6): 1381-1394) and identified spatially selective cells including head-direction cells, pure and conjunctive grid cells. We found that the distribution of directions in which pure grid cells were active differed significantly from the animal's heading direction (n = 29 / 29 pure grid cells) indicating that grid firing is direction-dependent. To test whether the head-direction selective firing is a result of different head-direction preferences in individual grid fields, we analysed directional firing in individual fields. We found that individual firing fields of pure grid cells have head-direction selective firing. We repeated this analysis on data from rats (Sargolini et al. 2006, Science 312 (5774): 758-62) and found similar results. Our results suggest that the firing properties of pure grid cells depend on head-direction. This finding has implications for theorized functions and mechanistic models of the grid system.

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Poster

694. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

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Topic: H.01. Animal Cognition and Behavior

Support: BIF PhD Fellowship (R.V.)
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Title: A cortico-tectal circuit controls orienting to shelter during instinctive escape

Authors: *R. VALE[1,2], D. CAMPAGNER[1,3], P. IORDANIDOU[1], V. STEMPEL[1], S. KESHAVARZI[1], T. W. MARGRIE[1], R. S. PETERSEN[4], T. BRANCO[1];
[1]Sainsbury Wellcome Centre, UCL, London, United Kingdom; [2]MRC Lab. of Mol. Biol., Cambridge, United Kingdom; [3]Gatsby Computat. Neurosci. Unit, London, United Kingdom; [4]Univ. of Manchester, Manchester, United Kingdom

Abstract: The ability to rapidly escape to shelter when confronted with predatory threat is essential for survival. In mice, exposure to imminent threats elicits shelter-directed flight that is preceded by a fast head-orientation movement towards the shelter position. This head movement is extremely accurate, and can be implemented without sight of the shelter, by relying exclusively on memory. While orienting to shelter is done instinctively by the animal, it is a computationally challenging action, as it requires mapping the current position with respect to the memorised shelter location, onto an appropriate egocentric head rotation movement.
In this work we have investigated the neural basis of orienting the head to shelter during escape, using behavioural assays, projection- and cell type- specific chemogenetics, and single unit recordings in freely moving mice. Consistent with the known role of the superior colliculus in the control of egocentric saccades and head-rotation movements, we found that inactivation of the lateral superior colliculus (lSC) impairs orientation to shelter. Using monosynaptic retrograde rabies tracing, we identified the retrosplenial cortex (RSC) as a lSC input projection well-positioned to provide allocentric and head-direction information to the lSC. In agreement, chemogenetic inactivation of this projection introduced large errors in head orientation to shelter, and caused animals to escape in random directions. Furthermore, silicon probe recordings revealed neurons in both RSC and lSC that encode the angular offset between the animal's

current position and the shelter. We are currently combining single unit recordings with chemogenetic inactivation of lSC-projecting RSC neurons, to test the model that the lSC receives shelter-vector angle information from the RSC to generate shelter-orienting movements. Preliminary data suggest that RSC inactivation selectively disrupts the mapping of head-orienting actions onto allocentric space, while leaving sensory-driven egocentric orientation intact. These results advance our understanding of escape behaviour, and may provide general principles for the computation of goal-directed actions.

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Poster

694. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 694.15/Z29

Topic: H.01. Animal Cognition and Behavior

Title: Evidence against the attractor network hypothesis for grid cell activity in entorhinal cortex

Authors: *M. B. STEMMLER;
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Abstract: Grid cells in medial entorhinal cortex (mEC) are organized into distinct modules; within each module, the spatial firing fields of grid cells form a common hexagonal lattice with a fixed spacing between fields, a fixed orientation, and a fixed shear [1,2]. Within one module, the firing fields measured for any particular grid cell reflects a rigid translation of this common lattice. Theoretical models propose that these features result from a single attractor state of network activity [3-5]; as the animal moves through space, the attractor state simultaneously moves through mEC.
Yet the firing fields are far from uniform, as the peak firing rate within each field varies considerably [6,7]. We show that these variations obey a long-range spatial structure: a slowly varying envelope across space modulates the firing rates from firing field to firing field. Interestingly, such behavior is uncommon in attractor networks, which typically exhibit stable hexagonal patterns. Only in a narrow parameter regime can an Eckhaus instability with long-range spatial variation in field amplitudes occur, just before the activity pattern in the network changes from hexagons to stripes [8]. Evidence suggests that the spatial variation in firing fields in grid cells is not of this type, which argues against the theory that grid cells' activity arises through dynamical self-organization in a continuous attractor network.
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grid cells. *Nature* 2015, **518**:207-212.
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Disclosures: M.B. Stemmler: None.

Poster

694. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 694.16/Z30

Topic: H.01. Animal Cognition and Behavior

Support: Wellcome Trust Investigator Award (200855/Z/16/Z)

Title: Distance codes in the medial entorhinal cortex during goal directed navigation

Authors: *S. A. TENNANT[1], H. STEVENS[1], W. YANG[1], K. Z. GERLEI[1], J. HUA[1], H. CLARK[1], E. R. WOOD[1], M. F. NOLAN[1,2];
[1]Ctr. for Discovery Brain Sci., [2]Simons Initiative for the Developing Brain, Univ. of Edinburgh, Edinburgh, United Kingdom

Abstract: Successful navigation relies on accurate estimates of location. This can be achieved using landmarks or by path integration, where location is inferred from the direction and distance travelled relative to a known start point. Within the entorhinal cortex, grid, head direction, speed and border cells encode information that could be used to estimate location. It is not known whether these are the only codes used to represent location, or whether during specific behavioural tasks additional codes emerge to support goal directed navigation. To address this, we recorded with tetrodes from neurons in the medial entorhinal cortex (MEC) whilst wild-type mice engaged in a spatial memory task that can be used to assay path integration and cue-dependent navigation (Tennant et al. 2018, Cell Reports 22, 1313-1324). In this task mice are

trained to locate a reward zone marked with a visual cue within a virtual linear track. Use of path integration strategies can be tested in trials in which the reward zone is unmarked. We found a subset of neurons in the MEC that had distinct and striking patterns of activity whilst animals moved along the track. These neurons linearly increased or decreased their firing rate as a function of distance to or from the reward zone or boundaries of the track. Thus, these neurons provides a read out of position relative to salient track features. In a subset of neurons distance codes were present only on trials where the animal successfully completed the task, suggesting these representations may underlie successful task performance. Together these data support the idea that neurons in the MEC encode distances using a linear code that may support self-localisation in learned behaviours.

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Poster

694. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 694.17/Z31

Topic: H.01. Animal Cognition and Behavior

Support: National Natural Science Foundation of China, NNSFC Grant#31872775
A start-up fund#2017R028 from Army Medical University
A start-up fund#2018A034 from Xinqiao Hospital

Title: A novel somatosensory spatial navigation system outside the hippocampal formation

Authors: X. LONG[1], ***S.-J. ZHANG**[2];
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Abstract: The hippocampal-parahippocampal network has long been regarded as the central hub for the brain's spatial navigation system. Decades of research on the brain's spatial representation for position, orientation, border/boundary, speed and distance have intensively explored the hippocampal formation, revealing many functionally specialized yet different types of spatial cells, including place cells, head-direction cells, border/boundary-vector cells, speed cells, conjunctive cells and grid cells. Nevertheless, studies from patients with large medial temporal lobe lesions suggest that the hippocampal formation is not essential for space memory, indicating that spatial navigation might be computed with another still unknown representation system outside the medial temporal lobe structures. Such an extra-hippocampal navigational system has never been identified, however. To search for another possibly existed spatial navigation system outside the hippocampal formation, we implanted microdrives into the

primary somatosensory cortex of adult Long-Evans male rats and recorded neuronal activity and local field potential of individual somatosensory cells in two-dimensional opening environment. Surprisingly, we found the existence, in the rat somatosensory cortex, of a novel “all-in-one” spatial navigational system, which contained the full spectrum of all distinct spatial cell types including place cell, head-direction cell, boundary-vector/border cell, conjunctive cell, speed cell and grid cell. All recorded somatosensory spatial cells, from freely behaving rats with microelectrodes, showed similar firing characteristics to those detected previously in the canonical hippocampal-parahippocampal structures. Whisker-trimmed rats still remained similar spatial firing properties, eliminating the possibility that our detected different somatosensory spatial cell types were reflected by sensory responses typical to the primary somatosensory cortex. Additionally, a series of control experiments including running on the raised platform without walls, no food chasing and in darkness confirmed both specificity and consistency of similar functionally distinct somatosensory spatial cell types to those previously identified in the classical hippocampal formation. This newly detected somatosensory navigational system extends the classical theory of a cognitive map about space beyond two discrete hippocampal-entorhinal regions into another single highly hierarchical neocortical domain, providing possible alternative and sophisticated computational algorithms for spatial memory and cognitive mapping.

Disclosures: **X. Long:** None. **S. Zhang:** None.

Poster

694. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 694.18/Z32

Topic: H.01. Animal Cognition and Behavior

Title: A model for the processing of temporal relationships in navigation using phase coding

Authors: *E. PARRA BARRERO, S. CHENG;
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Abstract: Mammals are notable for their capacity to display flexible behavior and deal with changing contingencies. In order to do this, they need to be able to learn, represent and operate on the temporal relationships that link different states to the actions that lead from one state to another. A good case of study for this phenomenon is spatial navigation. In particular, we focus on the temporal relationships linking positions and movements, which are thought to be encoded within the grid cell network in the medial entorhinal cortex. We propose a model for the processing of these temporal relationships in which path integration, prediction of future positions, movement planning and inference of past states can all be accomplished by pattern completion in a network capable of representing positions and movements corresponding to the

recent past, present and future. We hypothesize that the temporal dimension is represented in the brain by the phase of firing relative to the theta oscillation. We test our hypotheses in two ways. First, we develop and simulate neural network implementations of our model and apply them to a simple navigation task in order to fully flesh out the model and arrive at new testable predictions. Secondly, we analyze whether experimental findings on phase coding are consistent with our model. To do so, we develop a parametric phenomenological model of phase coding to generate spikes under different coding assumptions. The model's spikes are then analyzed in the same way as experimental data, thus allowing for direct comparisons. Our results expose a contradiction in experimental findings that has gone unnoticed so far. Some studies indicate that activity in different phases of the theta oscillation reflect positions that lie a certain distance ahead of or behind the animal's current position, while other results imply phase coding for positions that were or will be reached a certain time interval in the past or the future, respectively. Overall, our work sheds light onto the nature and functional role of phase coding and suggests a novel paradigm for representing and reasoning about temporal relationships in the mammalian brain.

Disclosures: **E. Parra Barrero:** None. **S. Cheng:** None.

Poster

694. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation IV

Location: Hall A

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Topic: H.01. Animal Cognition and Behavior

Support: National Natural Science Foundation of China, NNSFC Grant#31872775
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Title: Speed cells in the somatosensory cortex

Authors: *X. LONG[1], S.-J. ZHANG[2];
[1]Dept. of Neurosurg., Xinqiao Hosp., Chongqing, China; [2]Dept. of Neurosurgery, Xinqiao Hosp., Army Med. Univ., Chongqing, China

Abstract: Grid cells were proposed to function as path integrators, which continuously update, based on its directional and speed information, the internal representation of the animal’s relative location within the environment. The generation of regularly periodical grid cell firing is currently modeled with either oscillatory interference or continuous attractor network but both models require speed signal. Although speed cells are present not only in the medial entorhinal cortex (Kropff et al., 2015, Hinman et al., 2016, Pérez-Escobar et al., 2016, Ye et al., 2018) but also in the hippocampus (Góis and Tort, 2018), whether speed cells are encoded for path integration computations outside the hippocampal formation remains elusive. We recently

identified a novel “all-in-one” spatial navigational system in the somatosensory cortex (Long and Zhang, bioRxiv, https://doi.org/10.1101/473090, 2018), which contains the full spectrum of all distinct spatial cell types including place cell, head-direction cell, boundary-vector/border cell, conjunctive cell, and grid cells within the single somatosensory area. To search for possibly existed somatosensory speed cells, we implanted microdrives into the primary somatosensory cortex of adult Long-Evans male rats, recorded neuronal activities and local field potentials of individual somatosensory cells and performed a series of computational analyses with different approaches. Accordingly, we found that the instantaneous firing rate of a distinct subpopulation of somatosensory neurons was linearly correlated with running speed, and those somatosensory speed cells also intermingled with other distinct spatial cell types but had little overlapping with other spatially modulated cells in the somatosensory cortex. Specifically, somatosensory speed cells were encoded mainly by fast-spiking GABAergic interneurons as well as by excitatory pyramidal neurons. Moreover, speed score for fast-spiking interneurons was significantly higher than that of excitatory principal cells in the somatosensory cortex, consistent with the similar findings in the medial entorhinal cortex (Kropff et al., 2015, Ye et al., 2018). In the meantime, a subset of somatosensory speed cells showed a negative correlation with running speed. Furthermore, a proportion of somatosensory speed cells also exhibited theta rhythmicity. How somatosensory speed cells contributed to a possible parallel or independent somatosensory spatial navigation system outside the hippocampal formation awaits further investigation.

Disclosures: X. Long: None. **S. Zhang:** None.

Poster

694. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation IV

Location: Hall A

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Program #/Poster #: 694.20/Z34

Topic: H.01. Animal Cognition and Behavior

Support: MH079511

Title: Phase coding of spatial trajectories by lateral septum neurons

Authors: *H. T. BLAIR[1], A. G. HOWE[2], G. BLAIR[3], R. M. DE GUZMAN[4];
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Abstract: The lateral septum (LS) is a major subcortical output target of the dorsal hippocampus. It has recently been reported that LS contains neurons which precess in phase against hippocampal theta rhythm, in such a way that they encode a rat’s position along navigational trajectories (Tingley & Buzsaki, Neuron 98:1229, 2018). To further investigate this phase coding phenomenon, we recorded theta-modulated neurons (n=136) from LS while male Long-Evans rats (n=3) foraged randomly for sucrose pellets in a circular arena. During 41

recording sessions lasting 2-3 hours, rats spent a majority of their time (>70%) foraging along thigmotaxic trajectories near the cylinder walls. We analyzed whether the theta phase offset between pairs of simultaneously recorded neurons encoded the rat's position during clockwise (CW) or counterclockwise (CCW) laps around the arena. 565 unique pairs of theta-modulated cells were identified, with some pairs held across multiple sessions. To analyze phase coding, each neuron's spike train was converted into continuous waveform referred to as the *pseudo LFP*, which tracked the cell's theta rhythmicity in time. The instantaneous phase offset between two theta-modulated neurons was measured as the circular difference between the phases of their pseudo LFPs. We found that 20% (114/565) of the cell pairs precessed in phase against one another during CW or CCW laps around the arena, with a preferred slope of 1 theta cycle/lap. About 2/3 of these pairs precessed against one another only during one foraging direction (e.g., CW), and became phase locked to one another in the opposite direction (e.g., CCW). For the remaining 1/3 of precessing pairs, one cell precessed against the other during laps in either direction, but no cell was ever observed to pre-cess against its partner in one direction, and pro-cess against its partner in the other. 18% (101/565) of cell pairs were rigidly phase locked to one another at all times. Based upon our analyses, we classified LS units into two types: 1) phase locking units (32%; 43/136) that exhibited strong theta rhythimicity and high firing rates, and were rigidly phase locked to one another at uniformly distributed offsets, and 2) phase shifting units (22%; 30/136) that precessed against phase locking units with a preferred slope of 1 cycle/lap.

Disclosures: H.T. Blair: None. **A.G. Howe:** None. **G. Blair:** None. **R.M. De Guzman:** None.

Poster

694. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 694.21/Z35

Topic: H.01. Animal Cognition and Behavior

Support: National Medical Research Council, Singapore (NMRC/OFIRG/0046/2017-00)

Title: Optogenetics-assisted characterization of parvalbumin-expressing interneuron activity in the dentate gyrus of freely behaving mice

Authors: L. F. COBAR ZELAYA, K. LIT, *A. TASHIRO;
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Abstract: Expression of a Ca^{2+} binding protein, parvalbumin, defines a subtype of inhibitory interneurons. These parvalbumin-expressing (PV^{+}) interneurons mostly consist of basket cells, which target the soma of granule, mossy and other basket cells, and axo-axonic cells, which innervate the axon initial segments of granule cells. Thereby these interneurons control the

generation of action potentials in their postsynaptic neurons. The activity of PV interneurons in the dentate gyrus has not been investigated in freely behaving rodents during exploration.
To identify PV^+ interneuron activity in extracellular unit recording, we used an optogenetics-assisted approach. We delivered light into the dentate gyrus of transgenic mice expressing channelrhodopsin-2 in PV^+ interneurons and used light-induced spikes as a marker for PV^+ interneuron activity. With this method, we successfully identified cells which exhibited a statistically significant increase in firing after light stimulation. The majority of these cells fired with short latency after light delivery (2.8-6.5 ms) and high response reliability (>99%), which supports that these light-responsive cells are PV^+ interneurons directly activated by light, as opposed to their postsynaptic neurons activated through synapses. During exploration under physiological conditions (without light stimulation), these cells showed typical features of putative interneurons in classical electrophysiological classification: high firing rate (25-40 Hz), frequent occurrence of short inter-spike intervals (~10 ms) and modulation by theta oscillations. We also identified cells which did not show light-induced spikes. Many of these cells seemed to show reduced firing in ~30-ms period following light stimulation, although reduction was often obscure due to low background firing rate. This inhibitory effect suggests that these cells are postsynaptic neurons inhibited by PV^+ interneurons. During animal's exploration, some of these cells showed features of classical putative interneurons while others were putative principal cells. Some putative interneurons had similar characteristics to light-responsive cells, but others were a distinct type dominated by longer inter-spike intervals (>20 ms). Some of putative principal cells showed stable place cell activity.
Our results indicate that PV^+ interneurons show a subtype of putative interneuron activity classically identified in freely behaving rodents. Their inhibitory control over other PV^+ interneurons and principal cells agrees with known synaptic targets of PV^+ interneurons in the dentate gyrus.

Disclosures: **L.F. Cobar Zelaya:** None. **K. Lit:** None. **A. Tashiro:** None.

Poster

694. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 694.22/Z36

Topic: H.01. Animal Cognition and Behavior

Support: Biotechnology and Biological Sciences Research Council (BB/J009792/1)
Wellcome Trust (WT103896AIA)
Middlesex Hospital Medical School General Charitable Trust grant to JSS

Title: Orienting in a visual world: An intact cortical visual pathway is necessary for landmark anchoring of rat postsubicular head direction cells

Authors: *J. S. STREET, K. J. JEFFERY;
Inst. of Behavioural Neurosci., Univ. Col. London, London, United Kingdom

Abstract: In solving navigational tasks, rats must integrate rich visual scenes into their cognitive map so as to align their representations of space with the world. These spatial representations in the brain include head direction (HD) cells, which encode the azimuth bearing an animal faces in an environment, and provide a likely neural substrate for a 'sense of direction'. Although HD cell activity is maintained using vestibular information, visual information can be used to reorient cell activity through 'landmark anchoring' to prominent cues.
Which features within a visual scene are integrated into the HD signal, and through what pathway does this information enter the HD system? Do the cortical and subcortical visual pathways perform different roles in processing landmarks? We hypothesised that, if the HD system receives information solely from the cortical pathway, anchoring would be impaired if this pathway was disrupted.
We present HD cells recorded from the postsubiculum of rats with lesions of the lateral geniculate nucleus, a key relay nucleus of the cortical visual pathway, but an intact subcortical pathway. Rats foraged in a cylinder with two large visual cues attached to the walls at 180 degrees apart. The symmetry of the cue configuration enabled testing of detection and discrimination of different cue cards: high-contrast, patterned, and control cues. The cylinder was rotated between trials to test for landmark anchoring.
For all cue configurations tested, landmark anchoring was impaired in HD cells recorded from lesioned animals compared with HD cells from animals with sham lesions. This effect was graded, with residual weak cue control observed to high-contrast cues in lesion HD cells, whereas no cue control was observed to patterned cues.
These results indicate that an intact cortical visual pathway is necessary for the accurate integration of landmark information into the HD system, and may also underlie visual information flow into other areas of the spatial navigation network. Future work may target striate and extrastriate visual cortex to test how these areas process cue-relevant information and contribute to its integration into abstract representations of space.

Disclosures: J.S. Street: None. **K.J. Jeffery:** None.

Poster

694. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 694.23/Z37

Topic: H.01. Animal Cognition and Behavior

Support: Alberta Innovates – Health Solutions Polaris award
Alberta Innovates – Health Solutions graduate studentship

Natural Sciences and Engineering Research Council of Canada grant #RGPIN-2017-03857
Research Foundation – Flanders (FWO) grant G0D0516N
KU Leuven Research Council grant C14/16/048
National Science Foundation grant #1631465
Canada Foundation for Innovation grant #33598

Title: Scalable landmark-relative path integration sequences in mouse retrosplenial cortex

Authors: D. MAO[1], V. BONIN[2], ***B. L. MCNAUGHTON**[3];
[1]Baylor Col. of Med., Houston, TX; [2]Imec NERF, Leuven, Belgium; [3]The Univ. of Lethbridge, Lethbridge, AB, Canada

Abstract: Retrosplenial cortex (RSC) neuronal populations exhibit sequential activity that tiles the entire track space relative to reward events. We used cellular calcium imaging in RSC of mice moving in a linear virtual reality-treadmill environment, to study how the integration of locomotion, visual flow, and visual landmarks may give rise to these RSC population sequences. A prominent population showed sparse firing sequences that were anchored to the visual virtual environment whose boundaries were associated with reward delivery. This sequential activity required active movement through the environment. Importantly, the same sequences scaled proportionally with the gain between locomotion and visual motion such that they predominantly tracked reward-relative distance based on locomotion-updated visual flow but not locomotion per se. A separate population also tracked the distance from multiple visual landmarks in a rate-dependent manner. These results suggest that RSC integrates external sensory cues with internal self-motion representations to create a distance code relative to various salient inputs.

Disclosures: D. Mao: None. **V. Bonin:** None. **B.L. McNaughton:** None.

Poster

694. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 694.24/Z38

Topic: H.01. Animal Cognition and Behavior

Title: Testing a two-component model of path integration in *Drosophila*

Authors: *D. TURNER-EVANS[1], S.-Y. TAKEMURA[1], S. ALI[1], K. JENSEN[2], A. SHERIDAN[1], T. PATERSON[1], H. J. HABERKERN[1], T. WOLFF[1], C. CHRISTOFOROU[1], C. MANAGAN[1], R. RAY[1], J. S. LAURITZEN[1], D. BOCK[3], S. PLAZA[1], V. JAYARAMAN[1];
[1]Janelia Res. Campus, HHMI, Ashburn, VA; [2]Cambridge Univ., Cambridge, United Kingdom; [3]Univ. of Vermont, Burlington, VT

Abstract: For over 20 years, a two-component model has been invoked to explain the neural mechanisms of path integration in invertebrates (Hartmann and Wehner, 1995). A circularly connected group of neurons form a ring attractor, with each individual neuron coding for a particular heading, while a second population of neurons integrates distance traveled. Heading and distance are then combined in a homing vector that can be read out downstream to lead the animal back to its nest.
A central region of the insect brain, known as the central complex, has long been implicated in navigation behaviors and, recently, has been suggested to host both a ring attractor (Kim*, Rouault*, et al, 2017) and anatomy that would enable distance estimation for path integration (Stone et al., 2017). We are now using a combination of experimental techniques to test and expand upon the two-component model of path integration in *Drosophila melanogaster*.
In a large, collaborative effort, we reconstructed connections between central complex neurons using two, independent adult fly brains that were imaged using electron microscopy. We also used RNA sequencing and fluorescence *in situ* hybridization to identify the constituent neurotransmitters and receptors. Guided by the connectivity data, we built anatomically accurate firing rate models to explore the potential roles of the neuron types in navigational computations. Predictions about activity correlates of the different neuron classes were then tested with two-photon calcium imaging in behaving animals while functional roles of these classes were probed with opto- and thermogenetic perturbation during behavior.
We found connectivity, anatomical structure, and physiology that were broadly consistent with existing models while also identifying newfound complexity. For example, hyper-local recurrent connections may help to maintain a memory of the animal's heading even in the absence of localizing sensory cues. Additionally, a class of interneurons functions as a hub in the network, passing heading information downstream to be combined with forward velocity, the integration of which may lead to a homing vector. Our preliminary findings suggest that the two-component model provides a suitable framework to test the mechanisms underlying path integration yet doesn't capture all of the functionalities of the actual biological circuit.

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Poster

694. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 694.25/Z39

Topic: H.01. Animal Cognition and Behavior

Support: HFSP (RGY0088),

Dunn Foundation

Title: Hippocampal encoding of space during navigation of an acoustically defined virtual environment

Authors: *S. GAO[1], A. BANTA[2], J. DE GEE[2], Z. MRIDHA[2], W. ZHANG[2], C. KEMERE[1,2], M. J. MCGINLEY[2];
[1]Electrical and Computer Engin., Rice Univ., Houston, TX; [2]Neurosci., Baylor Col. of Med., Houston, TX

Abstract: Remembering and navigating environments is of great importance for humans and animals alike. Spatial navigation in animal models has traditionally been studied using only visual cues, particularly in virtual reality settings. However, auditory cues play an important role in navigation for animals, especially when the visual system cannot detect objects or prey, such as in the dark. It is thus surprising that only few navigation studies have incorporated auditory cues, and none that we are aware of have used exclusively auditory landmarks. Here, we have developed a virtual reality platform for mice aimed to bridge the gap in understanding how the auditory system and the hippocampus interact to use auditory spatial cues for memory-guided navigation. We ask whether the animals can navigate a virtual environment that lacks any visual spatial information, and instead is defined by sparse acoustic landmarks.
The virtual environment is composed of a repeating sequence of three acoustic landmarks, separated by three silent zones. Within one of the silent zones there is a hidden reward location. Head-fixed mice traverse the virtual environment by walking on a cylindrical treadmill. Animals learn the spatial environment, as shown by robust anticipatory licking when approaching the hidden reward location. In ongoing experiments, we are performing high-channel (128) electrophysiology in hippocampal CA1 to examine the mechanisms of hippocampal coding. We use an automated spike sorting algorithm to extract large number of units (e.g. 50) from each recording. We have identified units that exhibit place-cell characteristics: spatial selectivity and place-fields distributed along the virtual track.
Our results suggest that memory-guided navigation is possible with exclusively acoustic landmarks. Our virtual environment paradigm provides the first evidence of a place map derived from purely auditory landmarks and provides a foundation for study of hippocampal-cortical interactions during navigation of acoustically defined virtual spaces.

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Poster

694. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 694.26/Z40

Topic: H.01. Animal Cognition and Behavior

Support: Chinese Scholarship Council (201608000007)
BBSRC (BB/Joo9792/1)
Wellcome Trust Investigator Award (WT103896AIA)

Title: Retrosplenial 'bi-directional' cells become tetra-directional in a fourfold-symmetric environment

Authors: *N. ZHANG, K. JEFFERY;
Univ. Col. London, London, United Kingdom

Abstract: Head direction (HD) cells signal direction, and together represent a global sense of direction. An unusual sub-type termed bi-directional (BD) cells has been discovered in dysgranular retrosplenial cortex (RSC). BD cells fire when a rat faces either of two opposite directions in an environment having 180° rotational symmetry. In this 2-box, two connected visually identical boxes are oriented in opposing directions so that when the rat moves from one box to the other, the visual cues reverse. We asked whether the BD pattern emerges from the environment or is intrinsic to the cells. To test this, we changed the overall rotational symmetry of the environment, to either infinite (circular) or fourfold (90° rotations). If a BD pattern is seen in all environments, it is likely to be an intrinsic property of the cells; otherwise it might be environmentally driven. We first recorded RSC neurons in rats foraging in circular arenas, before and after 2-box trials. All HD cells (n=50), as expected, remained unidirectional regardless of environments. BD cells (n=70) showed mixed responses in circular arenas: 1. Half of the BD cells either became inactive or lost directional anchoring; 2. Some of the other half had a singular pattern; and 3. A small subset maintained a BD firing pattern, possibly due to previous 2-box experiences. The general absence of a BD pattern in the circular arena suggests that the pattern is highly specific to the 2-box and derives from the environment structure. Then in a 4-box (four connected visually-same boxes, each rotated 90° relative to its neighbours), we found tetra-directional (TD) cells (n=16) that were directionally tuned to four directions, producing an overall ‘clover’ pattern. One subset of TD cells, showed a singular tuning pattern in each box and shifted directions by 90° between boxes. A second population, intriguingly maintained a fourfold pattern even within single boxes, possibly receiving feedback from HD cells. We conclude that the properties of these multi-directional cells arise from the environment structure. Extending from bi-directionality, the phenomenon of tetra-directionality provides new insights regarding the underlying computational mechanism of coupling between visual inputs and global heading in RSC.

Disclosures: **N. Zhang:** None. **K. Jeffery:** None.

Poster

694. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 694.27/Z41

Topic: H.01. Animal Cognition and Behavior

Support: European Commission M-GATE Grant 765549

Title: The stabilization of the medial entorhinal cortex representation of a novel environment requires normal NMDA receptor function

Authors: *O. M. CHADNEY, B. R. KANTER, C. LYKKEN, N. Z. BORGESIUS, K. ASUMBISA, C. G. KENTROS;
Kavli Inst. for Systems Neurosci., NTNU, Trondheim, Norway

Abstract: The medial entorhinal cortex (MEC) processes spatial information used to shape a stable representation of self-location in downstream place cells, enabling accurate navigation. Indeed, the MEC encodes features such as direction by head direction cells (HD), and location and distance by grid cells, border cells, and nongrid spatial cells.
In response to environmental change, HD cells rotate their preferred firing direction, grid cells shift and rotate or reshuffle firing rates across fields, spatial cells reorganise their firing patterns, whilst downstream place cells “remap”, thus defining a unique neural representation of space. The cellular mechanism underlying spatial memory is thought to involve N-methyl-D-aspartate receptor (NMDAR)-dependent plasticity. Interestingly, place cell remapping in rats exposed to novelty does not require NMDARs, but long-term stabilization of those firing patterns does. It is still unknown whether spatial representations upstream in the MEC also rely on NMDAR-dependent plasticity.
Here, we addressed this question by recording single units in mouse MEC and pharmacologically blocking NMDARs using (±)-3-(2-carboxypiperazin-4-yl)propyl-1-phosphoric acid (CPP). MEC activity was recorded while mice explored a familiar environment (F1), after which they received an injection of either CPP or saline. One hour post-injection, they were re-introduced to the familiar environment (F2) before being exposed to a novel environment (N1). After a 6-12 hour delay, once the drug no longer had an effect, mice were re-exposed to both environments, allowing us to monitor the stability of newly formed maps in N2 whilst checking cell stability in F3.
First, our results show that the presence of CPP does not prevent remapping of HD and spatial cells when exposed to a novel environment (N1). Second, in mice having received a CPP injection prior to N1, both HD and spatial cells remap by coherent rotation of directional tuning and changes in positional firing patterns, respectively, when re-exposed to the novel environment in N2. In contrast, in mice having undergone a saline injection, firing properties were

consistently maintained from N1 to N2. In agreement with previous work on hippocampal place cells, our findings suggest a critical role of NMDAR-dependent plasticity in the consolidation of novel MEC spatial and directional representations that may be required to stabilize hippocampal firing patterns following remapping.

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Poster

694. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 694.28/Z42

Topic: H.01. Animal Cognition and Behavior

Support: University of Washington Innovation Award
University of Washington Graduate Opportunities and Minority Achievement Program Presidential Fellowship

Title: Hippocampal correlates of optimal route planning during open field foraging

Authors: *B. J. JACKSON, D. H. GIRE;
Psychology, Univ. of Washington, Seattle, WA

Abstract: Brains have evolved to efficiently solve complex real-world optimization problems such as finding the shortest routes while searching for food. During these searches animals rapidly identify constraints of the problems they face and adaptively employ appropriate cognitive strategies and heuristics to solve these problems, resulting in solutions that while not always optimal, are quickly and efficiently implemented. Previous research in our lab has shown that rats are able to adaptively shift cognitive resources between sensory and memory systems during semi-naturalistic foraging to optimize performance under uncertainty. In these experiments we found evidence that rats often employ a "nearest-neighbor" heuristic when searching for food across multiple possible locations. That is, they proceed first to the nearest likely location of food and iteratively execute this strategy until all pellets have been found. In the present study we directly test the limits of the heuristics that rats employ when solving a particularly difficult, foraging-based optimization scenario, the probabilistic "traveling salesman" problem. In this scenario, rats are trained to search for food pellets across 6-9 possible locations within a large (2.5m x 1m) foraging area, creating as many as 362,880 possible paths to collecting all of the pellets. Rats search without visual cues and must rely only on local cues to detect the pellets, such as whisker contact or olfaction. This forces them to plan foraging routes without reliable distal guidance cues. We used a computer-controlled pellet placement system to create distributions in which nearest-neighbor searches were either optimal or sub-optimal.

Under these conditions we find that rats perform significantly worse on trials in which a nearest-neighbor search is sub-optimal ($p = 0.0017$, Wilcoxon rank-sum test, n=12 rats), suggesting that they may employ this relatively simple heuristic. To further test this, we have created distributions in which a nearest-neighbor search would be strongly sub-optimal. Using these more challenging distributions we will test whether rats routinely use the nearest-neighbor heuristic or whether they shift to perform more complex, multi-step path planning when it is advantageous. We will investigate the neural correlates of route planning by recording from the hippocampus during this more challenging optimization problem. We predict that theta and gamma power and coherence across the hippocampus will vary as a function of the complexity of the route planning for a given path.

Disclosures: B.J. Jackson: None. **D.H. Gire:** None.

Poster

694. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 694.29/AA1

Topic: H.01. Animal Cognition and Behavior

Support: Kavli - KIBM #2019-1608

Title: Subiculum firing fields shift systematically to differentiate similar route shapes distributed across environmental locations

Authors: *R. J. PLACE[1], D. A. NITZ[2];
[1]Cognitive Sci., UCSD, La Jolla, CA; [2]Univ. of California San Diego, La Jolla, CA

Abstract: Recent findings reveal the subiculum (SUB) represents networks of intersecting paths with multiple activity fields, such that single neurons spike as rats navigate features shared across spatially distinct routes. These spiking patterns have been shown to track topographic structures, including the animal's axis of travel within an environment or its relative distance traversed along routes with common framework [1,2]. This signal could serve to extract common components across path structures or link multiple routes distributed across environmental space. To expand upon these results, we performed electrophysiological recordings in SUB as rats traversed a series of interconnected paths. This novel task required rats to navigate learned routes defined amongst a network of three path axes that intersect to form a triangular grid. For each trial, the rat was cued to start at any 1 of 12 positions along the network's perimeter, with each starting location dictating the given trial's rewarded route. The distribution of turn degrees and relative edge sizes was preserved across routes, but the route's orientation and absolute length depended upon the starting position. This path arrangement allowed us to test neuron spiking responses driven by room space (e.g. environmental location and orientation) versus route space

(e.g. path structures and scale).
We observed here that SUB neurons exhibited multiple firing fields within the complete path network, such that single neuron activity mapped individual route spaces by their relative relationship to the environment's perimeter. Neural ensemble analysis revealed that similar routes with different lengths, were systematically mapped along the same scale of room coordinates. This signal suggests SUB activity could serve to link individual paths within a network by defining single path substructure relative to its environmental position. In contrast to CA1 neurons, which often display singular spatially tuned activity fields, these findings highlight SUB's unique position to transform information between CA1 and cortical areas, including retrosplenial (RSC) and posterior parietal cortex (PPC), for which spiking patterns have been found to represent multiple spatial and movement features during route navigation [3,4].
(1) Olson et al. (2017). Nat. Neurosci. 20, 170-172.
(2) Johnson et a. Program No. 508.10. 2018 Neuroscience meeting planner. SD, CA: SFN, 2018.
(3) Alexander et al. (2015). Nat. Neurosci. 18, 1143-1151.
(4) Nitz, D. (2012). Nat. Neurosci. 15, 1365-1367.

Disclosures: R.J. Place: None. **D.A. Nitz:** None.

Poster

694. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 694.30/AA2

Topic: H.01. Animal Cognition and Behavior

Support: WT 110157/Z/15/Z

Title: Spatial view cells and the primate retrosplenial cortex

Authors: *A. S. MITCHELL, S. MASON, E. LOMI, B. PERRY;
Univ. of Oxford, Oxford, United Kingdom

Abstract: In primates and humans, the retrosplenial cortex is part of the default mode network, a collection of cortical brain structures that form a principal neural network, which is particularly activated when at 'rest' during neuroimaging. In addition, damage to the retrosplenial cortex disrupts the retention of previously acquired object-in-place scene discriminations in primates, and in humans, causes topographic disorientation and difficulties navigating, even in familiar surroundings. In the current study, retrosplenial cortex function was assessed across multiple sessions while recording from multi-channel stereotrodes temporarily inserted into the retrosplenial cortex of two male rhesus macaque monkeys. During electrophysiological recordings, the monkeys were positioned vertically in their primate chair and rotated clockwise and counter-clockwise within their familiar research lab environment. The room was full of

various allocentric cues. ‘Spatial view cells’, which respond when the monkey looks at a certain part of the allocentric environment, were analysed. Neuronal recordings were also collected and analysed when the monkeys were at ‘rest’. We report on differences in retrosplenial neuronal responses during active viewing compared to periods of 'rest'.

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Poster

695. Human Perception and Imagery II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 695.01/AA3

Topic: H.02. Human Cognition and Behavior

Support: NSF BCS-1658560

Title: Functional connectivity during action recognition modulated by top-down goals

Authors: ***X. ZHOU**[1], D. STEHR[2], P. HWU[2], J. A. PYLES[3], E. D. GROSSMAN[1]; [1]Cognitive Sci., [2]Univ. of California Irvine, Irvine, CA; [3]Dept. of Psychology, Ctr. for the Neural Basis of Cognition, Carnegie Mellon Univ., Pittsburgh, PA

Abstract: The posterior superior temporal sulcus (pSTS) is a key component of action observation network (AON) and a putative input into mirror neuron system (MNS). The pSTS is engaged in perceiving faces and actions, detecting cues that signal animacy and agency, and interpreting these events as goal-directed behaviors. In human, neural activity on the pSTS reflects both perceptual and non-perceptual features, including task instructions during action observation (Grafton, 2009), current demands in the tasks (Tavares et al., 2008; Morris et al., 2008), and the extent to which actions are congruent with current expectation (Jastorff et al., 2011; Shultz et al., 2011; Wyk et al., 2009). We therefore propose that the pSTS encodes sensory cues in the context of expectations as constructed by the observer, with the implication that these top-down influences derive from higher levels of processing in action understanding originating from the prefrontal cortex. To test this hypothesis, we computed functional connectivity between bilateral STS, inferior frontal gyrus (IFG), the lateral occipital complex (LOTC), and hMT+ when participants viewed actions under three different task instructions: attend to the action, attend to the actor’s identity or attend to the actor’s goal. We found that when participants were instructed to direct attention to actions as opposed to the identity of the actor, functional connectivity increased between IFG and pSTS, and between IFG and hMT+. The same was true when observers were instructed to direct attention to action goals. We conclude that functional connectivity within the action observation network in strengthened when observers direct to features that promote action understanding, implicating IFG as a mechanism by which inference in action understanding may shape perceptual encoding.

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Poster

695. Human Perception and Imagery II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 695.02/AA4

Topic: H.02. Human Cognition and Behavior

Support: NSF BCS-1658560

Title: Top-down attention guidance shapes action encoding in the pSTS

Authors: ***D. A. STEHR**[1], X. ZHOU[1], P. HWU[1], J. A. PYLES[2], E. D. GROSSMAN[1]; [1]Dept. of Cognitive Sci., Univ. of California, Irvine, Irvine, CA; [2]Dept. of Psychology, Ctr. for the Neural Basis of Cognition, Carnegie Mellon Univ., Pittsburgh, PA

Abstract: The posterior superior temporal sulcus is a key brain region within the action observation network linked to the perceptual encoding of visual events that promote the understanding of actions and their goals. Mounting evidence reveals that the univariate BOLD response in pSTS is strongly influenced by top down attention during action observation (Tavares et al., 2007; Jastoff et al., 2011). This implies that top-down attentional guidance shapes feature-tuning in the pSTS during action encoding. To test this hypothesis, we evaluated the impact of top down modulatory signals on the multivariate spatial activation patterns in the pSTS while participants viewed avatars performing two actions (jumping or crouching) under three different task instructions (attend to action, attend to goal, attend to identity). For each of these tasks, support vector machine (SVM) classifiers were trained to predict the action class from trial-specific spatial patterns of beta estimates within the pSTS during action viewing. Action decoding was evaluated by mean classification accuracy using leave-one-run out cross-validation. Results showed that the ability to decode the action's class from multivoxel activity patterns varied with the attentional demands placed on the participant. The action's class was more easily decoded when participants attended to the action itself or its expected goal compared to when they attended to the identity of the avatar. This finding is evidence that attention to action features or their goals sharpens neural tuning in the pSTS. Our results support the hypothesis that the pSTS serves as an interstitial zone mediating top down goal-directed signals and bottom-up perceptual cues.

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Poster

695. Human Perception and Imagery II

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Title: Distinct neural mechanisms of speech imagery differentially modulate auditory perception

Authors: *O. MA[1,2], X. TIAN[2,3];
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Abstract: The neural representation can be induced without external stimulation in top-down processes, such as mental imagery. The previous study found that imagined speaking (AI) and imagined hearing (HI) modulated perceptual neural responses in different directions, suggesting motor-to-sensory transformation and memory retrieval as two possible neural pathways for internally activating auditory representation (Tian & Poeppel, 2013). However, the functional characteristics of this top-down process are unclear. We hypothesized that motor-to-sensory transformation could evoke more precise representation than memory retrieval. We built a neural network model and conducted a behavioral and fMRI experiment to test this hypothesis. In the neural network, precision and its top-down function were modeled as the modulation of connection strength between layers. The simulation captured previous MEG imagery repetition effects. Moreover, we tested this model's novel prediction -- two types of speech imagery would affect hearing differently - by conducting a behavioral imagery-adaptation experiment (19 participants, 9 males, the average age of 22.58). Participants judged the /ba/-/da/ continuum auditory stimuli after they either performed AI or HI. The psychometric curve showed positive shifts toward the preceding imagined syllables, but the shift was more prominent after AI than HI, quantitatively in line with the prediction generated by the model. To further investigate the neural origins that lead to auditory representation with different degrees of precision, we conducted an fMRI experiments (25 participants, 13 males, the average age of 21.28). Participants were asked to watch silent videos that contained moving objects, while either imagined speaking sentences about the events (AI condition) or imagined hearing the objects' sounds that cannot easily be mimicked by human articulation (HI condition). The univariate and

region-of-interest (ROI) analyses revealed that auditory cortex was activated in both imagery conditions and AI induced greater activity in the superior temporal gyrus compared to HI. Moreover, the speech production system (including the precentral cortex and inferior frontal gyrus) and memory retrieval network (including the inferior parietal cortex and precuneus) were preferentially activated in AI and HI, respectively. These consistent simulations, behavioral and neuroimaging results support our hypothesis that distinct neural mechanisms of speech imagery can internally generate auditory representation with different degrees of precision and differentially influence auditory perception.

Disclosures: O. Ma: None. **X. Tian:** None.

Poster

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Topic: H.02. Human Cognition and Behavior

Support: China Postdoctoral Science Foundation

Title: Neural tracking of speech mental imagery: Evidence from magnetoencephalography and intracranial electroencephalogram

Authors: *L. LU[1,2], J. SHENG[2], J.-H. GAO[1,2];
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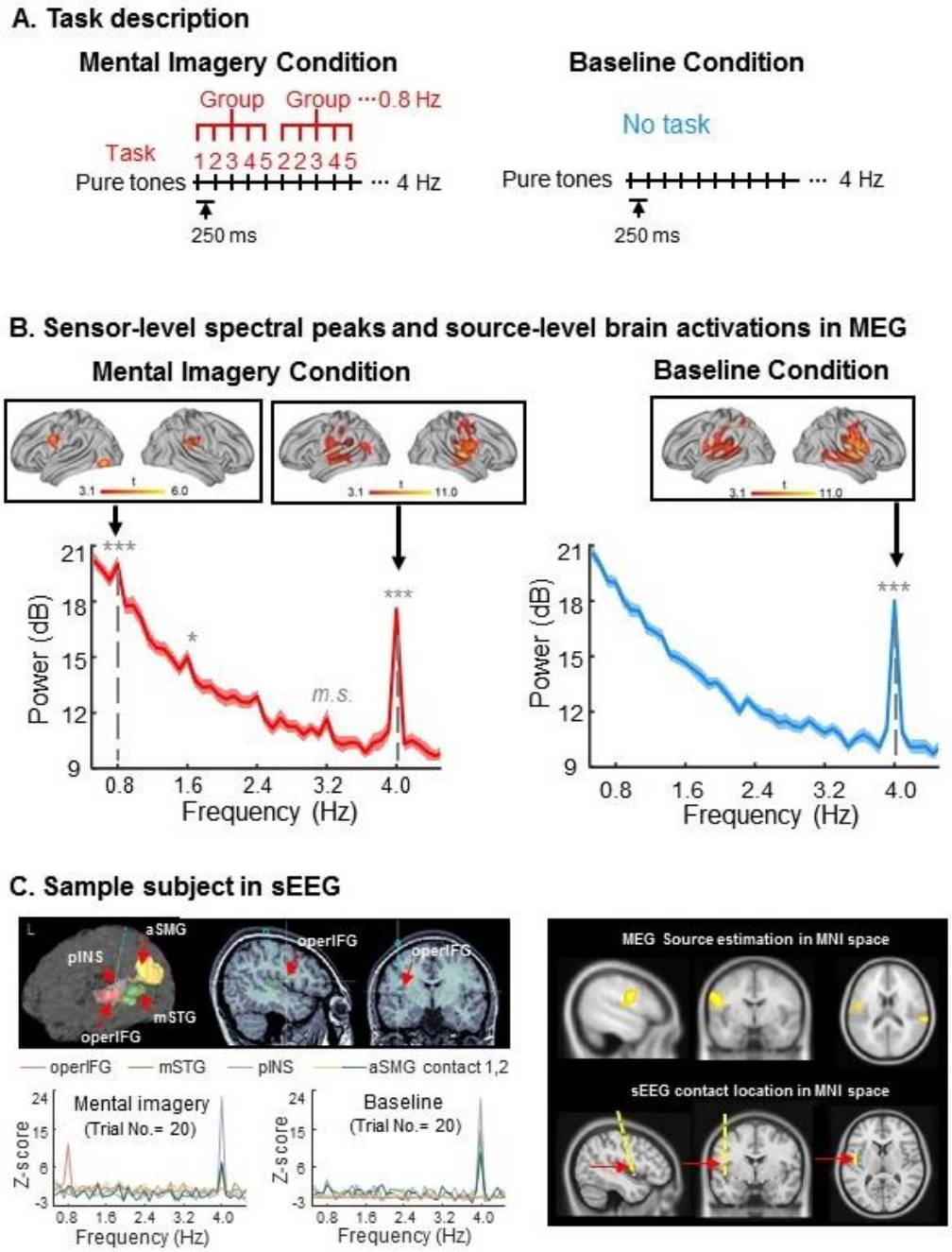
Abstract: Mental imagery is the unique subjective experience when our brain internally creates representations in absence of external stimulations. Although many neuroimaging studies have reported distributed neural networks that can be activated by speech mental imagery, the neural dynamics of speech mental imagery have been mostly overlooked. Therefore, it is necessary to establish a neurophysiological model of speech mental imagery to elucidate the spectral-temporal features of imagery-induced neural activities. To address this issue, we applied a unique frequency-tagging method to experimentally isolate the top-down process of speech mental imagery from bottom-up sensory-driven activities, and concurrently tracked the neural processing time-scale corresponding to the two processes. A total of twenty young adults (12 males, 24.6 ± 3.6 yrs) participated in the magnetoencephalography (MEG) experiment in which they received an imagery block with the task to internally count in groups following a sequence of sounds and a baseline block with the same auditory stimulation but without the task. As a result, significant spectral peaks were observed at the imagery-rate and stimulus-rate frequencies that were precisely tagged ($p < 0.001$). Further, minimum L1-norm source estimation for the significant frequency bins revealed isolated brain networks activated at the imagery-rate frequency, including the left central-frontal lobe, the left inferior occipital lobe and the right

inferior parietal lobule. In contrast, more extensive brain regions in the auditory temporal cortex were activated at the stimulus-rate frequency. The MEG results were replicated by stereotactic electroencephalogram (sEEG) data recorded from five subjects (two males, 27.6 ± 12.0 yrs) with implantation of intracranial electrodes who performed the same task. Our study for the first time tracked the neural processing time-scale induced by speech mental imagery and uncovered a disassociated neural network underlies the dynamic construction of speech mental imagery independent of auditory sensory perception.



Disclosures: **L. Lu:** None. **J. Sheng:** None. **J. Gao:** None.

Poster

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Topic: H.02. Human Cognition and Behavior

Support: Wellcome Trust (203147/Z/16/Z)

Title: Prior expectations bias early visual processing: A magnetoencephalography study

Authors: G. TURNER, F. AITKEN, ***P. KOK**;
Wellcome Ctr. for Human Neuroimaging, Univ. Col. London, London, United Kingdom

Abstract: Perception can be cast as a process of inference, wherein external sensory inputs are combined with our prior knowledge and expectations. In line with this, many recent studies have found that prior expectations can influence processing in the visual cortex. However, very little is known regarding the temporal dynamics of the integration of sensory inputs with prior expectations. For instance, recent work suggests that expectations may set up pre-stimulus templates of expected stimuli in visual cortex, which can then bias the processing of external sensory inputs from the moment they arrive. Alternatively, it has been suggested that early stages of sensory processing are free from modulations by expectations, and only later, during perceptual decision-making, do prior expectations exert their influence. In the current study, we dissociated between these hypotheses by exposing human participants (N=22) to auditory cues that predicted the likely direction of upcoming noisy moving dot patterns while recording neural activity with millisecond resolution using magnetoencephalography (MEG). First, we found that participants' perceptual reports of the moving dot directions were biased towards the direction predicted by the auditory cues. To investigate whether prior expectations led to early modulations of sensory processing, we used inverted encoding models to decode the direction of moving dot patterns from the MEG signal in time-resolved manner. Strikingly, this approach revealed that the auditory cues affected the motion direction represented in the MEG signal as early as 150 ms after onset of the moving dots patterns. Furthermore, this early neural modulation was related to perceptual effects of expectation: participants with a stronger perceptual bias towards the predicted direction also revealed a stronger reflection of the predicted direction in the early MEG signal. In fact, for these participants, the motion direction decoded from the MEG signal correlated more strongly with the motion direction they reported perceiving than with the motion direction actually presented on the screen. This correlation between neural decoding and perception already emerged prior to onset of the moving dots (~-150 ms), suggesting that the pre-stimulus state of visual cortex influences how we process sensory inputs, and thereby partly determines perception. Together, these results suggest that

prior expectations can modulate sensory processing at very early stages, making expectation a fundamental component of the neural calculations underlying the contents of our perception.

Disclosures: **G. Turner:** None. **F. Aitken:** None. **P. Kok:** None.

Poster

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Support: Research Council of Norway - grant number 240389/F20.
NIH R37NS21135 and NIMH Silvio O. Conte Center 1PO MH109429-01

Title: Human brain network involved in auditory deviance detection: Evidence from intracranial EEG recordings

Authors: *A. O. BLENKMANN[1], A.-K. SOLBAKK[2], S. LESKE[1], J. LUBELL[3], A. LLORENS[4], S. COLLAVINI[5], I. FUNDERUD[1], P. G. LARSSON[7], J. IVANOVIC[7], T. BEKINSCHTEIN[8], S. KOCHEN[6], R. T. KNIGHT[9], T. ENDESTAD[1];
[1]Univ. of Oslo, Oslo, Norway; [2]Univ. of Oslo, Bekkestua, Norway; [3]Univerty of Aarhus, Aarhus, Denmark; [4]Dept. of Psychology, Helen Wills Neurosci. Institute, UC Berkeley, Berkeley, CA; [5]Conicet, Buenos Aires, Argentina; [6]Conicet, Capital Federal, Argentina; [7]Oslo Univ. Hosp., Oslo, Norway; [8]Univ. of Cambridge, Cambridge, United Kingdom; [9]Univ. of California Berkeley, Berkeley, CA

Abstract: The neural network underlying human auditory deviance detection is not fully understood. To address this, we recorded intracranial EEG from 22 adult patients with drug resistant epilepsy undergoing presurgical monitoring who had depth electrodes implanted in all brain lobes (1193 channels in total). Patients passively heard a stream of bilaterally presented tones while reading. We used the Optimum-1 paradigm, that consisted of 300 standard tones interleaved with 300 randomly presented deviant tones per block. Patients completed between 3 to 10 blocks. Deviant tones differed from standards in: 1) intensity (louder or softer), 2) frequency (higher or lower), 3) sound source location (right or left), 4) a shorter duration, or 5) a silent gap in the middle of the tone (Näätänen et al., 2004). Electrode coordinates were obtained from coregistered MRI and CT images using iElectrodes toolbox (Blenkmann et al., 2017). Channels were bipolar referenced and high frequency band activity (HFA) analytic amplitude signal was obtained using the Hilbert transform (75-145 Hz).
Compared to the baseline period, significant HFA responses to tones in general were observed in 31% of the channels.
We used an ANOVA to quantify the HFA response variance across trials that could be explained

by the different factors of the stimuli: Intensity, Laterality, Frequency, Duration and Gap. We estimated the amount of explained variance by using ω2 (Siegel et al., 2015). Eighteen % of the channels showed a significant increase of the condition-specific explained variance. Some channels showed condition-specific activations to one particular deviant, while others showed activations to a combination of two or more deviants.
The channels showing responses to tones in general and condition-specific effects were mostly observed bilaterally in temporal cortex. Frontal, anterior cingulate, and parietal cortices were also involved to a lesser extent. Our results, in line with the predictive coding framework, reveal that a distributed brain network is involved in auditory processing and deviance detection.

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Poster

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Title: Local parts lost itself in the whole: A MEG study

Authors: *L. LIU, H. LUO;
Peking Univ., Beijing, China

Abstract: Grouping local parts into coherent shapes is a central function in vision. It has been suggested to be a generative process that feedback signals carry predictions and feedforward signals represent prediction errors. Although recent fMRI studies provide evidence supporting the predictive coding hypothesis in illusory shape perception, the neuronal temporal dynamics underlying this generative process remains largely unknown. To address the issue, we recorded magnetoencephalography (MEG) signals while human subjects were presented with three Pac-Man figures, the combination of which is either or not able to induce an illusory shape perception (‘Kanizsa triangle’), corresponding to grouping and ungrouping conditions respectively. Critically, here we employed a novel information theoretic measure, which is called Partial

Information Decomposition technique (PID), combine with randomly modulated the luminance of each Pac-Man to extract neuronal response specific for each of the three Pac-Man figures. First, the PID responses for grouping condition showed decreased activities compared to the ungrouping condition, consistent with predictive coding account. Second, the PID responses which represent three Pac-Man figures in grouping condition showed an early enhancement in illusory shape location. Specifically, within 0-100 ms, the PID responses for three Pac-Man figures increase was originated in regions of V1 that have a receptive field on the illusory shape, within 100-200 ms, the PID responses inhibition was found to arise from regions of V1 that have the receptive field on three Pac-Man figures. We propose that the representation of local parts in illusory shape perception consists of two stages: an early one that quickly encodes updated prediction about the new illusory shape and a late one that represents decreased prediction error that performs inhibition in individual local parts.

Disclosures: L. Liu: None. **H. Luo:** None.

Poster

695. Human Perception and Imagery II

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Topic: H.02. Human Cognition and Behavior

Support: NSF BCS-1439237

Title: A representational similarity analysis examining scene categorization in the brain

Authors: *E. M. AMINOFF, A. YOUNG;
Fordham Univ., Bronx, NY

Abstract: There are multiple goals achieved in visual recognition: some consist of recognizing a specific stimulus, and others consist of recognizing the category of the stimulus (e.g., Toto vs. dog). When processing a visual scene, which brain regions mediate the processing of the general category (e.g., office), rather than the specific exemplar (e.g., my office)? How does the answer to this question elucidate the mechanisms underlying scene perception? To answer these questions, we used the BOLD5000 dataset (Chang et al., 2019) to investigate similarities in fMRI voxel activity for when participants viewed the same exact scene, compared to when they viewed a scene of the same category. We examined five visual processing regions, three of which are considered scene processing regions: the parahippocampal place area (PPA), the retrosplenial complex (RSC), and the occipital place area (OPA). In addition, we examined an early visual region and the lateral occipital complex (LOC). The logic was if a region exhibited the same extent of similarity when a scene was repeated to when a different exemplar of the same category was presented, we concluded that region processed the scene with respect to the

generalized scene category rather than the specifics of the stimulus itself. Preliminary results demonstrated the right hemisphere RSC showed this pattern of results. In addition, the LOC demonstrated a sensitivity to the categorical processing of scenes, presumably due to the object recognition entailed. All other regions showed a greater similarity for when the same stimulus was repeated compared to when the category was repeated. We discuss these results in a contextual associative framework of scene processing and representation.

Disclosures: E.M. Aminoff: None. **A. Young:** None.

Poster

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Topic: H.02. Human Cognition and Behavior

Support: oard of Regents - RCS grant to S.G.G.

Title: Fear conditioning to imagined percepts and its relationship to standard visual conditioning

Authors: *L. M. BURLEIGH[1], J. OWENS-FRENCH[1], F. CHAISSON[1], A.-B. MADDEN[2], X. JIANG[1], L. RAGGIO[1], S. G. GREENING[1];
[1]Louisiana State Univ., Baton Rouge, LA; [2]Texas State Univ., Austin, TX

Abstract: Mental images can provoke intense emotional states (Holmes & Matthews, 2010). Imagery and perception have common neural and physiological mechanisms, including activation of the early visual areas (Albers et al., 2013). We tested the prediction that individuals can acquire fear to imagined percepts and if this fear transfers to viewing percepts, using fMRI and self-reported measures to determine participants' fear. The participants completed a task in which they viewed and imagined two stimuli, and were fear conditioned when imagining the CS+. Participants are only told that mild electrical stimulation will be paired with one of the stimuli, but not which stimulus, viewed or imagined. Participants completed 6 runs of each task after completing 6 runs of a habituation form of each task. Behaviorally, participants report greater fear when imagining the CS+ than imagining the CS-. When acquiring fear to an imagined stimulus, we found significant activation in the right insula. These findings are consistent with previous literature indicating that this region is involved in processes related to emotional memory, autonomic arousal, and emotion-related motivation. Behaviorally, participants also report greater fear when viewing the CS+ than when viewing the CS-, though neither is ever paired with shock. When fear is generalized from an imagined precept to a viewed one (i.e., CS+ view > CS- view), we found no significant activation. We can conclude that participants generalize the fear acquired when imagining the stimulus to viewing the stimulus, though no underlying neural mechanisms were uncovered. Finally, participants also show a

similar level of self-reported fear to fear conditioning acquired to imagining a stimulus as to when fear is acquired to viewing a stimulus. We found insular cortex and precentral gyrus activation when investigating the similarities between these processes. These results indicate that humans can fear condition to imagined percepts, which involves activation of anterior insula; that this fear conditioning generalizes to instances of viewing the conditioned percept; and that differential conditioning to both imagined and viewed percepts produced a similar magnitude of subjective fear along with activation of the right anterior insula.

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Poster

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Topic: H.02. Human Cognition and Behavior

Support: Board of Regents - RCS grant to S.G.G.

Title: Fear extinction via mental imagery

Authors: *X. JIANG[1], R. L. LANDRY[1], P. M. MIZELL[1], H. J. CRULL[2], L. M. BURLEIGH[1], S. M. SALTZMANN[1], S. G. GREENING[1];
[1]Psychology, [2]Biol. Sci., Louisiana State Univ., Baton Rouge, LA

Abstract: Mental imagery is the perceptual-like experience of previously perceived stimuli without sensory input from external stimuli. It plays an important role in various affective conditions, in relation to both their symptom presentations (e.g., flashbacks in post-traumatic stress disorder) and clinical treatments (e.g., imaginal exposure therapy). Although widely used, this assumption of interactions between mental imagery and emotion is not well researched. The current study was designed to assess the relationship between mental imagery and emotion. Specifically, whether fear conditioned perceptual images can undergo extinction via exposure to their mental imagery. This is a two-day study with day 1 as the screener and day 2 as the functional magnetic resonance imaging (fMRI) day. In day 1, participants completed fear conditioning while their skin conductance responses (SCRs) were recorded. Two English letters were selected as the conditioned stimuli (CS) and electrical stimulation was used as the unconditioned stimulus (US). The US was adjusted for each participant so that it was "uncomfortable but not painful." One of the CS's was paired with the US (CS+) and the other one was not (CS-). In day 1, 49 out of the 147 participants collected exhibited SCR evidence of fear acquisition (i.e., greater SCR for the CS+ than CS-) and 26 of them completed day 2. Three English letters were selected for day 2, which was composed to three study phases. First, the fear

acquisition phase in which two of these letters were paired with shock (CS+) while a third letter was not (CS-); second, the first extinction phase involving exposure to mental images of one of the CS+'s (CS+I) and the CS-; third, the second extinction phase involving the viewing of all three letters.
The anterior insula (aIn) and anterior cingulate cortex (ACC) were selected as regions-of-interest (ROIs) using a separate functional localizer task during which participants viewed fearful and neutral images selected from the International Affective Picture System and the Nencki Affective Picture System. Following acquisition, there were significantly greater activations in left aIn and bilateral ACC and self-reported fear for the perceptual images of both CS+'s than CS- ($p < 0.05$ with Bonferroni correction). These preliminary findings provide evidence that fear conditioning took place in the current sample. A completed sample with analyses on the fMRI, SCR, and self-report data across all three experimental phases (acquisition, extinction 1, and extinction 2) will be presented in the poster.

Disclosures: X. Jiang: None. **R.L. Landry:** None. **P.M. Mizell:** None. **H.J. Crull:** None. **L.M. Burleigh:** None. **S.M. Saltzmann:** None. **S.G. Greening:** None.

Poster

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Program #/Poster #: 695.11/AA13

Topic: H.02. Human Cognition and Behavior

Support: Board of Regents - RCS grant to S.G.G.

Title: Internal distraction in emotion regulation: Efficacy and neural mechanisms of imagined distractors

Authors: *T. D. ROBINSON[1], L. GREGOIRE[2], K. JACKSON[1], S. GREENING[1];
[1]Louisiana State Univ., Baton Rouge, LA; [2]Texas A&M Univ., College Station, TX

Abstract: This study aimed to both verify the effectiveness and examine the neural underpinnings of internally generated distracters in the regulation of negative emotional stimuli. Distraction has well-established regulatory effects on affect and other regulatory techniques such as reappraisal appear underpinned by mechanisms of internal distraction. We tested the prediction that an internally generated distracter would reduce the effects of a negative stimulus as effectively as an externally presented distracter, and that neural activity would show this effect in emotion processing regions of interest. Participants were fear conditioned to one of two neutral face stimuli (CS+ vs. CS-) prior to viewing a series of composite face/distracter images (i.e., places: houses and buildings). During viewing, they were instructed to attend to either the face, (CS+ or CS-), or the place, which involved either attending to an external visual distracter

or to an internally generated (imagined) distracter. Likert-ratings revealed that the internal distracter paradigm lowers reported fear with the same effectiveness as the traditional external visual distracter. Emotional processing, evidenced by elevated fMRI BOLD activity in the anterior insula (aIn), was significantly different between CS+ and CS- faces during the attend face conditions, but not when distracting either externally or internally, which reflect by a significant interaction. This indicates that both the external and internal distraction tasks counteract the effects of the fear stimulus. Analysis of the parahippocampal place area (PPA) indicated elevated activity during both attend and imagine distracter tasks. To test the prediction that PPA activity was related to the observed changes in fear, correlational comparison of the differences in activity between attend minus distract CS+ was compared to aIn activity and self-reported fear. Higher PPA activity correlated with greater reductions in aIn activity and greater decreases in self-reported fear. These findings not only support the hypothesis that the internal distraction paradigm effectively reduces the effects of the fear stimulus, but also suggests that the regulatory effect is directly related to visualization of the imagined distracter stimulus.

Disclosures: T.D. Robinson: None. **L. Gregoire:** None. **K. Jackson:** None. **S. Greening:** None.

Poster

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Title: Decoding prestimulus EEG alpha activity reveals expectancy in the direction of stimulus changes

Authors: *B.-K. MIN[1,3], **J. KIM**[2], D. PANTAZIS[3], H. KIM[2];
[1]Dept. of Brain and Cognitive Engin., [2]Inst. for Brain and Cognitive Engin., Korea Univ., Seoul, Korea, Republic of; [3]McGovern Inst. for Brain Res., MIT, Cambridge, MA

Abstract: Since prestimulus EEG alpha activity is considered to convey prestimulus top-down processing, we investigated whether expectancy of upcoming stimulation can be decoded from prestimulus alpha oscillations under a changing direction paradigm. EEG was measured from 24 participants performing the changing direction task, which included expected and unexpected conditions, depending on whether a sequence of annulus-shaped stimuli expanded/contracted in

an ordered or random manner. Prestimulus alpha power (500 ms prestimulus to stimulus onset) was estimated by band-pass filtering the EEG signals in alpha band and applying a Hilbert transform. The expected condition yielded significantly shorter reaction times than the unexpected condition ($t(23) = -10.928$, $p < 0.001$; expected 246.3 ms, unexpected 384.2 ms), indicating more efficient preparation for upcoming stimuli during the expected sequence in the direction of changes. Using the prestimulus alpha power, the decoding performance between expected and unexpected sequences was significantly higher than chance level ($t(23) = 8.546$, $p < 0.001$). The maximum of decoding accuracy (86.7%) in the prestimulus period was observed just before stimulus onset. In the expected sequence, the prestimulus alpha power of the second inter-stimulus interval (ISI) was significantly higher than that of the first ISI, which was also used for prediction of the next stimulus type with a high accuracy of 70.0% ($t(23) = 2.622$, $p < 0.05$). Taken together, our results provide evidence that ongoing alpha activity encodes top-down information about the expected changes of upcoming visual stimuli.

Disclosures: B. Min: None. **J. Kim:** None. **D. Pantazis:** None. **H. Kim:** None.

Poster

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Topic: H.02. Human Cognition and Behavior

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KAKEN-HI 19H01771

Title: Testing the reproducibility of tDCS effect: Modulating beauty perception by brain stimulation

Authors: *K. TAKAHASHI, Y. YOTSUMOTO;
Dept. of Life Sci., The Univ. of Tokyo, Tokyo, Japan

Abstract: Transcranial direct current stimulation (tDCS) has been used in a large number of neuroscientific studies as a promising tool to test the causal relationship between brain areas of interest and behavior. However, its reproducibility is now questioned due to failures in replication reported by recent studies. In the present study, we focus on tDCS effect on one cognitive domain, beauty perception. To date, modulation of beauty perception by tDCS has been shown in the two studies: Cattaneo et al. (2014) and Nakamura & Kawabata (2015). While Cattaneo et al. reported increase of beauty perception following anodal tDCS over the prefrontal cortex, Nakamura & Kawabata (2015) showed the opposite outcome resulted by cathodal tDCS over the same brain area. Here, we aimed to replicate their studies and to investigate tDCS effect

on beauty perception with the parameters they used: (1) cathodal stimulation over the medial prefrontal cortex (mPFC) (Nakamura & Kawabata, 2015); (2) anodal stimulation over the left dorsolateral prefrontal cortex (lDLPFC) (Cattaneo et al., 2014). Also, besides attempting to replicate those studies, we performed more focal anodal stimulation targeting the orbitofrontal cortex (OFC) to explore an optimal stimulation site for modulating beauty perception (3). Participants rated the subjectively perceived beauty of images before and after tDCS. Furthermore, we divided images according to the obtained rating scores in our preliminary study: high, middle- high, middle-low and low image clusters. To exclude confounding factors such as stimuli attributions or individual preference, we examined the effect of tDCS on beauty perception in each image cluster separately. The results showed no strong effect of tDCS with the same parameters as of previous studies on beauty rating scores in any image cluster. Likewise, anodal stimulation over the OFC, the current simulation software derived parameter, did not lead to change in scores. In sum, we were not able to replicate the findings of previous tDCS studies. More focal stimulation (tDCS over the OFC) also failed to modulate beauty perception. These results provide evidence concerning the recent reproducibility issue of tDCS effect and might suggest the possible inflation of its effect on human cognition.

Disclosures: K. Takahashi: None. **Y. Yotsumoto:** None.

Poster

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Topic: H.02. Human Cognition and Behavior

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Title: Intracranial electrophysiological correlates of binocular rivalry in the human brain

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Abstract: Binocular rivalry is a striking form of multistable perception where different images are presented concurrently to each eye and conscious perception alternates between the images. This provides a unique opportunity to disentangle conscious perception and sensory processing since perception alternates between the two possible percepts, while the sensory input remains

static. Electrophysiological and neuroimaging work in humans and nonhuman primates indicate that local competitive interactions between neuronal populations in visual areas under "top-down" influences from fronto-parietal (F-P) regions support binocular rivalry.
This study leveraged intracranial recordings in patients with refractory epilepsy to study how F-P regions support rapid shifts in conscious perception during binocular rivalry. Subjects (n=5) were implanted with intracranial electrodes over frontal, parietal, and occipito-temporal cortices. Subjects participated in 2 experiments. Experiment 1 was a category localizer in which subjects saw faces, houses, words, bodies, and scrambled images and were instructed to press a button when a scrambled image appeared (odd-ball paradigm). Experiment 2 was a face/house binocular rivalry paradigm in which red/blue stimuli were presented independently, but simultaneously to each eye. Subjects reported when a perceptual switch occurred during 2 main conditions: the rivalry condition in which perceptual switches were endogenous or self-driven and the replay condition in which switches were exogenously or externally controlled.
We first identified face- and house-selective electrodes in ventral temporal cortex (Exp 1), primarily located anatomically over the fusiform and parahippocampal gryi, respectively. We then examined the profile of responses during rivalry (Exp 2). Behaviorally, subjects reported subjective alternations between percepts every 2-6 seconds. We found that high-frequency broadband activity (HFB: 70-150 Hz) was significantly active above baseline during 3 main temporal response windows: (i) at the onset of stimulus presentation, and (ii) preceding or (iii) time-locked to the perceptual switch. Electrodes time-locked to the onset were located primarily in ventral occipito-temporal cortices and corresponded with the category-selective electrodes identified in Exp 1; In contrast, electrodes preceding or time-locked to the perceptual switch were primarily located in lateral frontal and parietal regions. We found that subregions of the F-P attention network support endogenous rivalry and contrasted their response patterns with the neural responses during replay.

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Poster

695. Human Perception and Imagery II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 695.15/AA17

Topic: H.02. Human Cognition and Behavior

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Title: COALIA: A virtual human brain model of EEG for consciousness research

Authors: *P. BENQUET[1], J. MODOLO[2], S. BENSAID[2], I. MERLET[2], F. WENDLING[3]; [1]INSERM U1099 -LTSI, Rennes, France; [2]INSERM U1099, Rennes, France; [3]INSERM U1099 LTSI, Rennes Cedex, France

Abstract: Understanding the origin of the main physiological processes involved in consciousness is a major challenge of contemporary neuroscience, with crucial implications for the study of Disorders of Consciousness (DOC). One possibility of integrating the main results from the experimental literature into a cohesive framework, while accounting for nonlinear brain dynamics, is the use of physiologically-inspired computational models. In this study, we present a physiologically-grounded computational model, attempting to account for the main micro-circuits identified in the human cortex, while including the specificities of each neuronal type. More specifically, the model accounts for thalamo-cortical (vertical) regulation of cortico-cortical (horizontal) connectivity, which is a central mechanism for brain information integration and processing. The distinct neuronal assemblies communicate through feedforward and feedback excitatory and inhibitory synaptic connections implemented in a template brain accounting for long-range connectome. The EEG generated by this physiologically-based simulated brain is validated through comparison with brain rhythms recorded in humans in two states of consciousness (wakefulness, sleep). Using the model, it is possible to reproduce the local disynaptic disinhibition of basket cells (fast GABAergic inhibition) and glutamatergic pyramidal neurons through long-range activation of VIP interneurons that induced inhibition of SST interneurons. The model (COALIA) predicts that the strength and dynamics of the thalamic output on the cortex control the local and long-range cortical processing of information. Furthermore, the model reproduces and explains clinical results regarding the complexity of transcranial magnetic stimulation TMS-evoked EEG responses in DOC patients and healthy volunteers, through a modulation of thalamo-cortical connectivity that governs the level of cortico-cortical communication. This new model provides a quantitative framework to accelerate the study of the physiological mechanisms involved in the emergence, maintenance and disruption (sleep, anesthesia, DOC) of consciousness.

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Poster

695. Human Perception and Imagery II

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Program #/Poster #: 695.16/AA18

Topic: H.02. Human Cognition and Behavior

Support: BFU2017-82375-R

Title: Cognitive processing of viewers while watching different styles of editing in media contents

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Abstract: How brain manages the perception of the audiovisual content is something that started to be developed in the 1950s. Studies about cognitive processing of media content are of interest since we have found some differences between different types of audiovisual editing. In the present study, we asked what the cognitive processing of the spectators would be while they observe editing cuts in audiovisual narratives and if there would be differences when inserting them in different editing styles. We presented two videos with the same narrative, content, and duration, but different style of edition to 36 subjects (aged 25-56). One stimulus was a movie with 33 shots and an average shot length (ASL) of 5.9 s, with a classical style of edition, based on the Hollywood-style, with smooth transitions among shots, clear presentation of the visual information, and a great continuity. The other stimulus was a movie with 79 shots and an ASL of 2.4 s, based on MTV-videoclips style, very discontinuous, chaotic, and fast. Continuous EEG was recorded and event-related potentials (ERPs) and the spontaneous eyeblink rate (SBR) were analyzed. We found that cuts decrease spectators' SBR during the following second to their end in a significant way ($t_{(35)} = -2.719$, $p = 0.01$, Student's paired t test). This significant decrease was obtained in the Hollywood-style movie, but not in the MTV-style movie. We computed ERPs associate to cuts from 500 ms before the cut to 1000 ms after it and found that as the time after the cut progresses, a spread of potential goes from the occipital area to the frontal area. We also found significant differences in the potential of brain responses to the different styles of edition studied here. While cuts inserted in a Hollywood-style movie evoked larger ERPs in the medial, and mostly, in the frontal areas, those inserted in an MTV-style movie evoked a larger ERP activation in the occipital area. According to our results, cuts manage viewers' attention. A cognitive process of visual perception of media content is reset after each cut. This is coherent with previous studies of visual perception of any visual stimulus change. However, the style of edition for presenting cuts is very important. Clear and continuous presentation of the content has a lower impact on the visual cortex but a greater effect on higher areas involved in conscious processing. The opposite happens in the case of more chaotic audiovisuals, video clip type. These results can be applied to create media works able to manage viewers' attention and cognitive processing.

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Poster

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Topic: H.02. Human Cognition and Behavior

Support: KAKEN-HI 17K18693
KAKEN-HI 16H03749
KAKEN-HI 19H01771

Title: Response characteristics of one's own voice in the human auditory cortex

Authors: *T. HOSAKA, Y. YOTSUMOTO;
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Abstract: It is strange to hear the recorded version of one's own voice. Recorded voice is perceived differently from the actively spoken voice (own voice) because the pathways of these two types of vocal sounds to our hair cells are different. Most studies that investigated neural mechanisms of voice recognition compared neural activities while the participant listened to their own voice with those while the participant listened to others' voices. However, humans show keen sensitivity when it comes to the perception of their own voices, and they are able to detect not only the differences between themselves and others but also the slight modulations of their own voices. Here, we examined the neural mechanisms underlying such sensitive perception of one's own voice. Our experiment consisted of three sessions. First, we recorded the participants' voices, and their voices were processed using five different filters that were used to simulate the participants' own voices in earlier studies. In the second session, the participants rated the similarity of the presented voice to their own. In the third session, the participants rated the presented voice again while they underwent functional magnetic resonance imaging (fMRI). The behavioral results from the second and the third sessions indicated that the filters induced a range of responses with regard to the likelihood of perception of one's own voice. We first calculated the contrast between the voices that were judged to be the least like the participants' own voice and the voices that were judged to be the most similar to their own from the fMRI data. The contrast revealed that the bilateral superior temporal gyrus showed greater activation while listening to the voice least similar to the participant's own voice and was activated to a lesser degree while listening to the voice most similar to their own. The superior temporal gyrus is known to be involved in the identification of a person by their voice and in long-term neural sharpening. With neural sharpening, the stimuli that are more typical for an object elicit reduced neural responses. Our results indicated that the superior temporal gyrus showed neural sharpening on presentation of voices and showed decreased activation to their own voice. To

summarize, we showed that the superior temporal gyrus is involved in detecting slight modulations of one's own voice and in self-recognition.

Disclosures: **T. Hosaka:** None. **Y. Yotsumoto:** None.

Poster

695. Human Perception and Imagery II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 695.18/AA20

Topic: H.02. Human Cognition and Behavior

Support: KAKEN-HI 17K18693
KAKEN-HI 16H03749
KAKENHI 19H01771

Title: Shared frequency-specific coding between auditory perception and auditory imagery revealed by multi-voxel pattern analysis

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Abstract: Human auditory cortex has tonotopic representation because of which the spatial activity pattern depends on the frequency of the sounds. On the other hand, it is also known that human auditory cortex responds to top-down processing such as auditory imagery. Visual imagery activates the early sensory cortex in a manner similar to visual perception, but the mechanism of auditory imagery and its relationship with auditory perception remains largely unknown. The present study examined whether an activated pattern in the primary auditory cortex can be used to distinguish not only the frequency of sounds heard but also that of imagined sounds. In this experiment, we used functional magnetic resonance imaging (fMRI) to measure the neural activations during listening and imagining of three different pure tones. In addition to a conventional univariate mapping method, we applied multi-voxel pattern analysis (MVPA) for the purpose of dealing with the difficulty of detecting cortical representation in the primary auditory cortex. A support vector machine (SVM) was used for the classification of multivariate analysis. The accuracy of intra-subject classification was compared with a chance level, to judge whether the different tones could be distinguished using the activated pattern. The results indicated that the classification was successful for both perception and imagery. This result suggested that the spatial pattern of activation in the human primary auditory cortex contains information regarding the frequency of imagined sounds as well as that of heard sounds. Moreover, cross-classification between perception and imagery was also successful, indicating similar activation patterns between perception and imagery. Our findings imply that the top-down process for auditory imagery and the bottom-up process for auditory perception partially

share neural mechanisms in the primary auditory cortex. Our results further suggest that auditory imagery and its processing are comparable to those in the visual domain.

Disclosures: S. Katsui: None. **Y. Yotsumoto:** None.

Poster

695. Human Perception and Imagery II

Location: Hall A

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Program #/Poster #: 695.19/AA21

Topic: H.02. Human Cognition and Behavior

Title: The effect of distorted temporal-spatial visual feedback on robot hand illusion

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Abstract: We can make a distinction between our own body and others through self-body recognition. Robot Hand Illusion (RoHI) is an illusion regarding visuo-motor integration on a fake hand, which is relevant to both the sense of ownership and the sense of agency. A previous study investigated how delayed visual feedback influences self-body recognition in RoHI when participants use a data glove and manipulate a virtual hand projected on a monitor. As a result, the sense of agency was induced in less than 490ms delay conditions and the sense of ownership was induced in less than 190ms delay. In this study, we investigated how RoHI is induced when virtual hand's position and palm direction are distorted from the participant's hand posture, with visual feedback delay. Sixteen healthy right-handed participants (mean age 21.6 ± SD 1.1; 6 females) took part in this study. Participants conducted 12 sessions. In each session, participants make hand opening and closing movements with a sensor glove for 30s and watched the movement of a virtual hand which was projected on a monitor. The visual feedback delay was inserted in 3 conditions (100ms, 300ms, 500ms). Virtual hand's posture were altered in 4 conditions (Forward-Obverse: FO, Forward-Reverse: FR, Opposite-Obverse: OO, Opposite-Reverse: OR): Forward means that virtual hand's position is anatomically correct to the participant's torso, while Opposite means that it is rotated 180°. Obverse means that virtual hand's palm direction is the same as the participant's hand, while Reverse means that it is reversed. After each session, participants answered questionnaires associated with self-body recognition. We found the sense of ownership was induced only in the FO-100 (FO, 100ms delayed) condition (t-test, $t(15) = 2.7$, $p < 0.01$), and it was significantly decreased to less than zero in the 300ms delayed and 500ms delayed conditions (FR-300, $t(15) = -4.0$, $p < 0.001$; OO-300, $t(15) = -5.2$, $p < 0.001$; OR-300, $t(15) = -3.4$, $p < 0.005$; FO-500, $t(15) = -5.4$, $p < 0.001$; FR-500, $t(15) = -5.3$, $p < 0.001$; OO-500, $t(15) = -7.2$, $p < 0.001$; OR-500, $t(15) = -6.8$, $p < 0.001$). The sense of agency was induced in the 100ms delayed conditions, the FO-300 and the OR-300 conditions (FO-100, $t(15) = 8.7$, $p < 0.001$; FO-300, $t(15) = 3.4$, $p < 0.05$; FR-100, $t(15)$

= 5.6, $p < 0.001$; OO-100, $t(15) = 14.6$, $p < 0.001$; OR-100, $t(15) = 5.0$, $p < 0.001$; OR-300, $t(15) = 3.1$, $p < 0.005$). These findings indicate the sense of ownership is decreased when virtual hand's position and/or direction is greatly different from the participant's real hand posture. In contrast, the sense of agency can be induced by visuo-motor integration even if the posture is not matched.

Disclosures: Y. Ioka: None. **S. Shimada:** None.

Poster

695. Human Perception and Imagery II

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Topic: H.02. Human Cognition and Behavior

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Emory University SIRE program

Title: Consistency and strength of grapheme-color associations may be separable aspects of synesthetic experience: Evidence from an individualized implicit association test

Authors: N. STEINER[1], M. MARTINEZ[2], *S. A. LACEY[3], L. NYGAARD[1], K. SATHIAN[4]; [1]Emory Univ., Atlanta, GA; [2]Rowan Sch. of Osteo. Med., Stratford, NJ; [3]Penn State Col. of Med., Hershey, PA; [4]Dept. of Neurol., Milton S. Hershey Med. Ctr. & Penn State COM, Hershey, PA

Abstract: Synesthesia is a phenomenon in which experiences in one sensory or cognitive domain are accompanied by involuntary experiences in a second domain. Grapheme-color synesthesia, in which seeing a particular letter or number induces a secondary experience of color, is the most common form. Such synesthetic associations are characterized by their arbitrary (there is no obvious connection between the letters and colors) and idiosyncratic (different synesthetes may experience different colors for the same letter) nature. The Synesthesia Battery (SB: Eagleman et al., J Neurosci Meth, 2007) measures the consistency with which individuals choose the same color for the same grapheme and returns a standardized score: < 1 indicates a genuine synesthete, > 2 indicates a non-synesthete, 1 - 2 indicates that synesthetic status cannot be unambiguously determined. However, the SB does not measure the strength of synesthetic associations. Using the Implicit Association Test (IAT: Greenwald et al., J Pers Soc Psychol, 1998), we have previously shown that synesthetes have greater sensitivity to some crossmodal correspondences than non-synesthetes (Lacey et al., Eur J Neurosci, 2016). Here, we used the IAT to measure association strength. In the IAT, two stimuli are associated with the same response key. A single stimulus is presented on each trial and participants make speeded responses, which are faster when the key associations are congruent and slower when

incongruent, i.e., there is a congruency effect (Parise & Spence, Exp Brain Res 2012). Grapheme-color synesthetes (n =18) completed the SB and an individualized IAT in which two response keys were associated with a grapheme and its correct synesthetic color for congruent trials (e.g., A + red, B + green) or its incorrect color for incongruent trials (i.e., A + green, B + red). Age- and gender-matched non-synesthetic controls (n = 18) also completed the IAT, using the grapheme-color associations of their matched synesthete. We expected that synesthetes would have larger IAT congruency magnitudes than non-synesthetes. For synesthetes, a positive correlation between SB scores and congruency magnitudes would indicate that strong associations are also consistent. However, while congruency magnitudes were larger for synesthetes than non-synesthetes, strength (IAT magnitudes) was uncorrelated with consistency (whether SB scores or Euclidean distances in RGB color space). We conclude that the consistency and strength of associations may be separable aspects of synesthetic experience.

Disclosures: **N. Steiner:** None. **M. Martinez:** None. **S.A. Lacey:** None. **L. Nygaard:** None. **K. Sathian:** None.

Poster

695. Human Perception and Imagery II

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Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 695.21/AA23

Topic: H.02. Human Cognition and Behavior

Title: Brain tissue electrical conductivity estimation for epilepsy diagnosis

Authors: ***F. WENDLING**[1], A. CARVALLO[1], P. BENQUET[1], S. LAGARDE[2], F. BARTOLOMEI[2], J. MODOLO[1];
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Abstract: Rationale. Many studies reported the potential clinical value of electrical conductivity in the field of oncology and muscular diseases. In contrast, there were only few attempts to evaluate the potential clinical/diagnostic value of electrical conductivity to characterize brain tissue in neurological disorders. In the context of epilepsy, bioelectrical impedance and conductivity have been reported as possible indicators of brain tissue epileptogenicity, but conflicting data has limited their use for diagnosis. Objective: We developed a low-intensity pulsed stimulation method providing a fast and reliable estimation of brain tissue electrical conductivity, to identify potential changes in conductivity due to underlying pathophysiological processes induced by epilepsy. Methods: Using the quasi-static approximation of Maxwell equations, we derived an analytical model of the electric field generated by intracerebral stereotactic-EEG (SEEG) electrodes used for pre-surgical evaluation of patients with drug-resistant epilepsy. We coupled this electric field model with a model of the electrode-electrolyte interface to provide an explicit analytical expression of brain tissue conductivity based on the

recorded brain tissue response to pulse stimulation. Results: We validated our biophysical model using i) saline solutions calibrated in electrical conductivity, ii) rat brain tissue, and iii) electrophysiological data recorded from epileptic patients during SEEG exploration (n=7). Estimated conductivity values in saline solutions and post-mortem rat brains were close to actual values (typically < 1% error). More importantly, in patients, conductivity values were significantly different between healthy and epileptogenic regions, as assessed by the analysis of locally-generated epileptiform markers observed in SEEG signals. Conclusion: This new model-based method offers a fast and reliable estimation of brain tissue electrical conductivity while correcting for electrode-electrolyte interface effects. Significance: This method outperforms standard bio-impedance measurements since it provides absolute (not relative) changes in brain tissue conductivity. Novel diagnostic applications can be envisioned based on quantified differences in electrical conductivity between healthy and hyper-excitable regions.

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Poster

695. Human Perception and Imagery II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 695.22/AA24

Topic: H.02. Human Cognition and Behavior

Title: Neurofunctional relevance of genome-wide supported neuroticism loci

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Abstract: Neuroticism is a heritable personality trait, genetically related to mental disorders such as anxiety and major depression. The study of its genetic basis is hence proposed as a means to gain insights into the biological underpinnings of these etiologically intractable illnesses. Recently, a large-scale study in more than 329,000 UK Biobank participants reported 116 independent variants influencing neuroticism as measured by a well-established self-report questionnaire that includes items related to negative emotionality such as feelings of worry, guilt, loneliness, irritability, and nervousness. Yet, the nature of this phenotypic assessment limits our ability to link the discovered genetic loci with tractable biological mechanisms involved in physiological and pathological conditions.
In this study, we investigated the relevance of these genome-wide supported findings by

imposing on the reported variants a layer of functional measurements of neuroticism-related neural circuitry. Specifically, a total of N=1,389 healthy young adults underwent genotyping assessment and an emotional processing task. A polygenic score (PRS) derived from the 116 reported neuroticism loci was subsequently tested for association with negative emotion processing-related fMRI activation at candidate regions previously reported as linked to neuroticism. This revealed a significant association between the neuroticism PRS and thalamic activation, adjusted for age and sex effects (p = 1.3e-03). Single-marker analysis further allowed the identification of one single-nucleotide polymorphsim, rs6773869, located within *PLCL2* - encoding for phospholipase C like 2 - significantly associated with thalamic activation (p = 1e-04). In a subsample of n=568 participants, this locus was also identified as a methylation quantitative trait locus (mQTL), as it correlated with whole-blood methylation levels of two distinct CpGs, intronic to *PLCL2*. Finally, rs6773869 also showed significant association with whole-blood expression levels of *PLCL2* in a subsample of n=403 subjects.
Altogether, capitalizing on large-scale GWAS for neuroticism and neurofunctional correlates of neuroticism, we identified a genetic marker associated with emotional processing activity in a thalamic region. Exploratory molecular traits analysis also suggest that this locus is likely functional.

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Poster

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Title: Neural habituation enhances novelty detection: An EEG study of rapidly presented words

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Abstract: Huber and O'Reilly (2003) proposed that neural habituation serves an important function in perceptual processing, separating the current object from recently viewed objects that would otherwise blend with the current object. However, neural habituation comes at a cost, producing repetition deficits. Prior work confirmed the predicted transition from repetition benefits to deficits with increasing prime duration, but the concomitant prediction of enhanced

novelty detection was not tested. The current study examined this prediction with a same/different word priming task, using SVM classification of EEG data, ERP analyses focused on the N400, and an artificial neural network implementing the habituation theory, which was fit to the behavioral data to provide a priori predictions of the full-trial ERP waveforms. Subjects made same/different judgements to a test word in relation to an immediately preceding briefly presented target word; neural habituation was manipulated by varying the duration of the preceding prime word. With increased prime duration, correct "different" responses increased, evidencing enhanced novelty detection, and P100/N170 amplitudes to repeated targets decreased, evidencing neural habituation. A between-subject SVM classifier predicted trial-by-trial behavior with 66.34% accuracy on held-out data, with greatest predictive power at a time and topographic pattern consistent with the N400. The neural habituation model was augmented with a working memory layer, and a second experiment used response-locked ERPs to confirm the model's predictions regarding decision processes. These results support the hypothesis that synaptic depression enhances novelty detection, and the auxiliary assumption that the N400 reflects the encoding of new content into working memory.

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Poster

695. Human Perception and Imagery II

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Program #/Poster #: 695.24/AA26

Topic: H.02. Human Cognition and Behavior

Title: Approach biases in cannabis and pornography users

Authors: *S. M. SKLENARIK[1], K. JENKINS[1], M. FERNANDEZ[1], R. LIVOTI[1], S. PELLEGRINO[1], E. BULKLEY[1], A. PURINS[1], K. MILLER[1], E. LECKY[1], M. MOURMOURAS[1], M. GOLA[2], M. POTENZA[3], R. ASTUR[1];
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Abstract: Addicted individuals often demonstrate relatively automatic action tendencies in response to addiction-related stimuli, whereby they approach rather than avoid addictive stimuli. For instance, Wiers et al. (2011) found that alcohol-dependent individuals are quicker to approach and slower to avoid pictures of alcohol compared to neutral stimuli; this approach bias is not present in people without problematic drinking behaviors. Importantly, studies indicate that such cognitive biases can be manipulated to decrease problematic behavior and improve treatment outcome (Wiers et al., 2013). The purpose of the current studies was to replicate this approach bias effect in individuals at risk for problematic cannabis use and problematic pornography use using computerized Approach-Avoidance Tasks (AAT).

65 undergraduates (20 male, 45 female) who reported using cannabis in the past 6 months were recruited from the University of Connecticut for a 30-minute study assessing cognitive biases for cannabis pictures. 224 additional undergraduates (58 male, 166 female) who reported using pornography were recruited for 30-minute studies measuring cognitive biases for erotic pictures. All participants completed questionnaires assessing cannabis and pornography use. Participants then completed the AAT, which differed only in the type of addictive stimuli presented (i.e. cannabis or erotic images). Using a standard gaming joystick, participants were instructed to pull a joystick in response to an irrelevant property of the pictorial stimuli (e.g., vertical orientation of the picture) and push in response to the opposite property (e.g., horizontal orientation). Pulling the joystick caused the images to enlarge as if moving closer (simulating approach movement), and pushing caused the images to shrink as if moving away (avoidance). Median reaction times were analyzed to calculate a cognitive bias score.
A one-sample T-test showed that there was no approach bias for the cannabis images (approach bias = 5.69 ms, SD= 68.7 ms, $t(64) = 0.67$, *ns*) compared to neutral images, although cannabis use was significantly positively correlated with pornography use, depression, and online gaming. However, males showed a significant approach bias of 81.81 ms (SD = 93.07) for the erotic images, $t(57) = 6.69$, $p < 0.001$, compared to the neutral images; males with problematic pornography use showed more than double this approach bias. Females showed a much weaker approach bias for erotic stimuli. Both clinical implications and intervention studies using a cognitive retraining paradigm to reverse approach biases and decrease problematic behaviors are discussed.

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Poster

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Topic: G.03. Emotion

Support: Department of Science and Technology, Govt of India

Title: The neural correlates of navarasa. Essence of 9 emotions

Authors: *R. P. REDDY, J. RAJESWARAN;
Clin. Psychology, NIMHANS, Bangalore, India

Abstract: The aim of the study was to compare the neural correlates of Navarasa (9 emotions) with Mental Health Professionals versus other professionals (n=6). All were screened on Mini-

International Neuropsychiatric Interview (MINI), Standard Progressive Matrices, Interpersonal Reactivity Index (Davis,1980), Questionnaire of Cognitive and Affective Empathy (Renate at al, 2011), Emotional Quotient (Chadda) Social Stories Questionnaire (Autism Research Centre, 2002), Faux Pas Recognition Test (Simon Baron- Cohen, 1998).
fMRI Design: Navarasa Face Paradigms (9 emotions- Śṛngāram:Love, Hāsyam: Happiness, Raudram: Anger, Kāruṇyam: Compassion, Bībhatsam: Disgust, Bhayānakam: Fear, Vīram: Brave, Adbhutam: Amazement). fMRI scanning: MRI scanning was conducted in a 3 Tesla Siemens Magnetom Skyra scanner. Anatomical scan was acquired with a T1 MPRAGE sequence, with FOV w240mm, slice thickness 0.9mm, slices per slab176, voxel size 0.9*0.9*0.9mm. fMRI was acquired with an EPI sequence. The FOV was 192mm, slice thickness 4mm, slices obtained 36, voxel size 3*3*4mm, matrix 64*64, TR 4 seconds, TE .03 seconds (E prime 1.1 / Block design paradigm/ Statistical Parametric Mapping on MATLAB). Preprocessing consisted of Realignment, Normalization and Smoothing. The first level analysis was General Linear Model with Family Wise Error (FWE), $p<0.05$. One sample t test was used in the 2nd level analysis without FWE & $p<0.001$
Results: When compared to MHP and OP there was nil significant statistical difference between the groups on behavioral data. Navarasa task activated medial, superior frontal gyrus, left inferior parietal lobule, right precuneus, right angular gyrus, left occipital, right fusiform, superior temporal gyrus, left cingulate gyrus, bilateral posterior cingulate, bilateral cingulate, and Bilateral cerebellum.
The total number of participants for the study is 60, analysis of the same is underway.

Disclosures: R.P. Reddy: A. Employment/Salary (full or part-time):; Faculty at National Institute of Mental Health and Neurosciences, an Institute of National Importance, Govt of India. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Department of Science and Technology, Govt of India. **J. Rajeswaran:** None.

Poster

695. Human Perception and Imagery II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 695.26/AA28

Topic: H.02. Human Cognition and Behavior

Title: Long-term piano training alters the functional connectivity of the core networks

Authors: *Y.-C. LIAO[1], C.-J. YANG[1,2], T.-Y. HONG[1,2], H.-T. YU[3], L.-F. CHEN[1], J.-C. HSIEH[1,2,4];
[1]Natl. Yang-Ming Univ., Inst. of Brain Sci., Taipei, Taiwan; [2]Integrated Brain Res. Unit, Taipei, Taiwan; [3]Taipei Natl. Univ. of the Arts, Grad. Inst. of Arts and Humanities Eduction, Taipei, Taiwan; [4]Brain Res. Ctr., Taipei, Taiwan

Abstract: Music performance is one of the most facinating creative behaviors (Heroux, 2016). Playing piano mandates a divergent contemplation one the musical storyline and the semantic context (Heroux, 2016). Pervious studies on general creativity have posited the interplay of the default mode network (DMN) and the executive control network (ECN) as pivotal for creativity (Beaty, et al, 2015; Heinonen, et al, 2016). The DMN is engaged in mind-wandering (Mason, et al, 2007), future thinking (Schacter, et al, 2012), and mental simulation (Bucker, et al. 2007). The ECN participates in working memory, attention, and relational integration (Beauty, et al, 2016). In this study, we specifically investigated the consolidated crosstalks in terms of functional connectivity (FC) between the DMN and ECN in university students majored in piano. We hypothesized that long-term piano training may be associated with heightgened FC between DMN and ECN. Thirty-three piano students (PIANISTs) and thirty-six age-matched non-musical controls (CONs) were enrolled. We utilized the resting-state functional magnetic resonance images (rs-fMRIs) to unveil the DMN- and ECN-seeded FCs. Abbreviated Torrance Test for Adults (ATTA) questionnaire to assess the general creativity. Behaviouraly, there were no significant differences in ATTA scores between two groups. PIANISTs showed hyperconnectivity of DMN-ECN FCs than CONs. DMN and ECN together play an important role in creativity. Performing music entails internal imagery and feeling to produce musical expressions as rooted in personal experience and memories as well as empathetic appreciation of the composer‘s musical ideas. Our data are indicative of the neurological underpinning of the core processing of musical creativity. Absence of ATTA findings may indicate that musical training would not substantially alter the general creativity. Pianist’s performing creativity is manifested via musical items rather than non-musical ones. The highgtened DMN-ECN FCs can serve as neural underpinnings of expressional creativity of music performance.

Disclosures: Y. Liao: None. **C. Yang:** None. **T. Hong:** None. **H. Yu:** None. **L. Chen:** None. **J. Hsieh:** None.

Poster

696. Human Motor and Sequence Learning I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 696.01/AA29

Topic: H.02. Human Cognition and Behavior

Support: SJH is supported by a NINDS Intramural Competitive Fellowship.
This work was supported by the NINDS Intramural Research Program.

Title: Cyclic consolidation of human motor memory

Authors: *S. J. HUSSAIN[1], M. K. VOLLMER[1], G. NORATO[1], C. ZRENNER[2], E. R. BUCH[1], U. ZIEMANN[3], L. G. COHEN[1];

[1]NIH, Bethesda, MD; [2]Ctr. for Neurol., Univ. Hosp. Tübingen, Tuebingen, Germany; [3]Eberhard Karls Univ., Tübingen, Germany

Abstract: Fluctuations in cognitive function are a fundamental property of the human brain. These fluctuations parallel brain oscillations, with cognitive and sensory abilities being enhanced during optimal oscillatory phases. We recently demonstrated that output from the human motor cortex (M1) is increased during trough compared to peak phases of sensorimotor mu (8-12 Hz) rhythms and that this relationship depends on mu power (Hussain et al. 2018). However, whether human motor learning exhibits cyclic fluctuations and if so, the neural mechanisms causing them, is not known. We reasoned that if the mu rhythm cyclically modulates the motor cortical (M1) mechanisms underlying skill consolidation, then disrupting M1 activity during different mu phases after skill learning should differentially impair consolidation. Healthy adults practiced a novel explicit motor sequence learning task on Day 1. Immediately after practice, we transiently and repeatedly disrupted M1 activity using sensorimotor oscillatory phase-dependent closed-loop transcranial magnetic stimulation (closed-loop TMS) during either mu peak phases (N=17) or mu trough phases (N=17). We first confirmed the accuracy of the real-time EEG analysis algorithm required for closed-loop TMS delivery, showing that it accurately targeted mu peak and trough phases ($p<0.001$ for both). We then evaluated Day 1 acquisition (online learning) and overnight consolidation (offline learning) of the new motor skill. As expected, day 1 training led to comparable skill acquisition in both groups (online learning; main effect of LEARNING STAGE only, $p<0.001$). Subjects in both groups showed significant overnight performance improvements, reflecting consolidation (offline learning; main effect of LEARNING STAGE, $p<0.001$). However, disruption of M1 activity produced different effects depending on whether it was delivered during mu peaks or troughs (LEARNING STAGE x GROUP interaction, $p=0.001$). Disrupting M1 activity during mu peaks resulted in poorer overnight consolidation compared to disrupting M1 activity during mu troughs. Corticospinal excitability and mu power measurements during closed-loop TMS did not explain differences in consolidation between groups. We therefore conclude that neural mechanisms of stable skill learning operate cyclically to produce successful consolidation.

Disclosures: S.J. Hussain: None. **M.K. Vollmer:** None. **G. Norato:** None. **C. Zrenner:** None. **E.R. Buch:** None. **U. Ziemann:** None. **L.G. Cohen:** None.

Poster

696. Human Motor and Sequence Learning I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 696.02/AA30

Topic: H.02. Human Cognition and Behavior

Support: NINDS competitive fellowship

Fyssen fondation

Title: Neural representation of the memory of errors

Authors: *R. QUENTIN[1], E. R. BUCH[1], I. ITURRATE[1], L. CLAUDINO[1], M. K. VOLLMER[1], J. STIMELY[1], M. VERNET[2], L. G. COHEN[1];
[1]Human Cortical Physiol. and Neurorehabilitation Section, NINDS, Bethesda, MD; [2]Lab. of Brain and Cognition, NIMH/NIH/DHHS, Bethesda, MD

Abstract: Background. We continuously use information from our previous errors to improve performance and learn. Computational models proposed how could this information contribute to improve future performance [1,2] but the neural representation of this memory of errors has not been identified [2]. Methods. To address this question, we recorded magnetoencephalographic (MEG) activity in thirty-two healthy volunteers while they performed a visuomotor adaptation learning task. The experimental design required subjects to adapt to a stable -30° or +30° visual feedback perturbation (*motor adaptation task*) and to observe a similar feedback in the absence of motor movement (*observation task*). We used multivariate pattern analysis (MVPA) to decode from the MEG brain activity the visuomotor adaptation error signal in each trial, defined as the distance in radian between the target and the visual feedback. We predicted that the brain would maintain a memory of the previous error until the following trial. Results. All subjects learned to adapt to the perturbation during the *motor adaptation task.* In both conditions, MVPA decoded a brief signal time-locked to the presentation of the visual feedback. Subsequently, the error signal was decoded over several seconds until the onset of the following trial only during the *motor adaptation task*. Decoding in the 500 ms time window preceding the onset of each trial further identified the error signal in the *motor adaptation task* but not in the control *observation task*. Time-frequency analyses showed that the error signal was decoded in different frequency bands of neural activity. Conclusions. During motor learning, the brain encodes and maintains a neural representation of the memory of errors, conceivably to correct errors in future movement. These results reveal a neural substrate of the maintenance of previous error during human motor learning.
References 1. Wei, K. & Körding, K. Relevance of Error: What Drives Motor Adaptation? *J. Neurophysiol.* **101**, 655-664 (2009). 2. Herzfeld, D. J., Vaswani, P. A., Marko, M. K. & Shadmehr, R. A memory of errors in sensorimotor learning. *Science* **345**, 1349-1353 (2014).

Disclosures: R. Quentin: None. **E.R. Buch:** None. **I. Iturrate:** None. **L. Claudino:** None. **M.K. Vollmer:** None. **J. Stimely:** None. **M. Vernet:** None. **L.G. Cohen:** None.

Poster

696. Human Motor and Sequence Learning I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 696.03/AA31

Topic: H.02. Human Cognition and Behavior

Support: NINDS IRP

Title: Neural replay during wakeful rest predicts skill learning

Authors: *E. R. BUCH, L. M. CLAUDINO, M. BÖNSTRUP, R. QUENTIN, L. G. COHEN; Human Cortical Physiol. and Neurorehabilitation Section, NINDS, Bethesda, MD

Abstract: Background: Motor skills are acquired and consolidated through online (during practice) and offline (in between practice sessions) processes. In animal models, offline learning is linked to neural replay events (Ramanathan et al., 2015). In humans, it is not known if wakeful replay exists in the context of skill learning. Methods: To address this question, we studied data previously acquired (Bonstrup et al., 2019) in 28 subjects who practiced a novel task that involved repetitive typing of a 5-item numeric sequence as fast and accurately as possible with their non-dominant, left hand. Task training consisted of 36 alternating practice and rest intervals (10 seconds each) lasting a total of 12 minutes (Day 1). 26 subjects returned for a retest session the following day (Day 2). Online skill learning was measured as the change in tapping speed (count/s) of correct sequences between the beginning and end of training on Day 1, while overnight offline learning was defined as the difference in tapping speed between retest on Day 2 and the end of Day 1 training. Simultaneous 275-channel magnetoencephalography (MEG) recordings were obtained on Day 1 to assess resting-state and task-induced MEG dynamics immediately before, during and after Day 1 training. Support vector machine (SVM) classifiers were constructed for individual key-press events during practice and then used to identify 25-2500ms duration neural replays of the trained sequence during wakeful rest. Accuracy remained stable along the experiment. Results: Subjects on average displayed significant online (0.613±0.049 [mean±SEM]; t_{27}=12.49, p<1x10-12) and offline (0.205±0.025 ; t_{25}=8.21, p<1x10-8) improvement in correct sequence speed. Replay events were identified during wakeful rest in the 12-min practice period and after the end of practice, but not before practice. The duration at which peak replay rates occurred in most subjects was 75 or 100ms. The rate of 75-500ms duration neural replay events in rest intervals during the 12min practice period correlated with online (r = 0.41-0.49; p<0.03), and at 375-500ms for overnight offline (r = 0.48-53; p < 0.01, FDR corrected) learning for individual subjects. Conclusions: Human neural replay during wakeful rest intervals while practicing a new task predicts early skill learning.
References: Bonstrup, M., et al., 2019. Curr Biol.; Ramanathan, D.S., Gulati, T., Ganguly, K., 2015. PLoS Biol.

Disclosures: E.R. Buch: None. **L.M. Claudino:** None. **M. Bönstrup:** None. **R. Quentin:** None. **L.G. Cohen:** None.

Poster

696. Human Motor and Sequence Learning I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 696.04/AA32

Topic: H.02. Human Cognition and Behavior

Support: SJH was funded by the NINDS Competitive Fellowship Program.
This work was supported by the NINDS Intramural Research Program.

Title: Sensorimotor mu phase-dependency of self-paced movement initiation

Authors: M. K. VOLLMER[1], S. J. HUSSAIN[2], R. QUENTIN[1], I. ITURRATE[1], *L. G. COHEN[1];
[2]Natl. Inst. of Neurolog. Disorders and Stroke, [1]NIH, Bethesda, MD

Abstract: Human brain function exhibits cyclic fluctuations that parallel endogenous brain rhythms, with cognitive and sensory abilities being increased during specific optimal phases (VanRullen 2016). Whether human motor behavior, specifically timing of movement initiation, exhibits such fluctuations is not known. One brain rhythm that could feasibly produce these fluctuations is the sensorimotor mu (8-12 Hz) rhythm, which originates from synchronous post-synaptic potentials of sensorimotor cortical pyramidal cells (Pineda 2005). Given that voluntary movements are initiated when M1 activity reaches an excitatory threshold (Hanes and Schall 1996), we reasoned that this threshold could be differently reached during different mu rhythm phases. To investigate this possibility, we evaluated whether voluntary self-paced finger movements are preferentially initiated during an optimal mu rhythm phase in 20 healthy adults. We first determined each subjects' cortex-to-muscle latency (CML) as the onset latency of motor-evoked potentials in the left first dorsal interosseous (L. FDI) muscle. Then, subjects completed a self-paced movement initiation task during which they viewed a series of pictures on a computer screen while EMG was recorded from the left first dorsal interosseous (FDI) muscle. Subjects viewed each picture for as long as they desired, pressing a button using their left index finger when they were ready to move to the next picture. During analysis, we identified the time of movement initiation by measuring EMG onset for each subject and each button press. We then calculated the time at which the motor command required to initiate each button press was released from M1, defined as each movement's EMG onset minus that subject's CML. Mu oscillatory phases over contralateral sensorimotor regions were identified at this time point for each trial, and we determined the proportion of movements during which this time point occurred during different mu phases. Preliminary analysis showed that movements were similarly initiated across mu phases and mu phase-power combinations. Additional analysis under way include measurement mu phases at different time intervals preceding voluntary movement onset and evaluation of other sensorimotor rhythms. Our preliminary results so far

suggest that self-paced movements are consistently initiated across sensorimotor mu rhythm phases.

Disclosures: M.K. Vollmer: None. **S.J. Hussain:** None. **R. Quentin:** None. **I. Iturrate:** None. **L.G. Cohen:** None.

Poster

696. Human Motor and Sequence Learning I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 696.05/AA33

Topic: H.02. Human Cognition and Behavior

Title: Motor practice elicits sustained neural replay during wakeful rest

Authors: *L. CLAUDINO[1], E. R. BUCH[2], M. BÖNSTRUP[3], R. QUENTIN[4], L. G. COHEN[4]; [1]Human Cortical Physiol. and Neurorehabilitation Section, NINDS/NIH, Bethesda, MD; [2]Human Cortical Physiol. and Neurorehabilitation Section, NINDS, Bethesda, MD; [3]Natl. Inst. of Neurolog. Disorders and S, Bethesda, MD; [4]NIH, Bethesda, MD

Abstract: Background: Neural replay, spatiotemporal brain activity patterns associated with task performance during rest, has been reported during sleep and linked to overnight memory consolidation. Wakeful replay contributes to memory formation in rodents (Genzel and Robertson, 2015) but its role or even presence in the context of human motor practice is not known. Methods: To address this question, we studied data previously acquired (Bonstrup et al., 2019) in 28 subjects who practiced a novel task that involved repetitively typing a 5-item numeric sequence as fast and as accurately as possible with their non-dominant left hand. Task training consisted of 36 alternating practice and rest periods (10s each) lasting a total of 12 minutes. Simultaneous 275-channel magnetoencephalography (MEG) recordings were obtained to assess resting-state and task-induced brain activity dynamics. Support vector machine (SVM) classifiers were constructed for individual key-press events during practice and then used to identify neural replays of the trained sequence during wakeful rest periods (Kurth-Nelson et al., 2016). Events were assessed over sixteen different timescales (25-2500ms) pertaining to biologically relevant replay durations previously established in the literature (Olafsdottir et al., 2018). Results: Neural replay events were not detected prior to training. They were observed as early as the first rest period (following only 10s of practice). Replay events remained present at an average rate of 0.732±0.097 events/s (mean±SEM; 28/28 subjects) over the 36 rest periods and at 0.142±0.032 events/sec (24/28 subjects) for at least 5-minutes after the end of practice. The range of optimal replay duration was 50-250ms, with a majority of subjects (17/28) showing peak replay rates at either 75ms (11 subjects) or 100ms (6 subjects) durations. Source analysis identified a distributed bilateral parietofrontal network underlying wakeful neural replay. Conclusions: We conclude that motor practice elicits sustained neural replay during wakeful rest.

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Kurth-Nelson, Z., et al., 2016. Fast Sequences of Non-spatial State Representations in Humans. Neuron. 91**,** 194-204.
Olafsdottir, H.F., Bush, D., Barry, C., 2018. The Role of Hippocampal Replay in Memory and Planning. Curr Biol. 28**,** R37-R50.

Disclosures: L. Claudino: None. **E.R. Buch:** None. **M. Bönstrup:** None. **R. Quentin:** None. **L.G. Cohen:** None.

Poster

696. Human Motor and Sequence Learning I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 696.06/AA34

Topic: H.02. Human Cognition and Behavior

Title: Distinct causal roles of DLPFC and M1 in long-term skill learning: A combined TMS-fMRI study

Authors: *T. G. LEE, T. J. ADKINS;
Univ. of Michigan, Ann Arbor, MI

Abstract: Our day-to-day life depends on the expression of high level motor skills (e.g. typing, driving, etc). Prior work has shown that local activity and the network connections of cognitive control regions in the dorsolateral prefrontal cortex (DLPFC) show marked reductions as expertise develops. In contrast, motor cortex (M1) activity and connectivity seems to steadily increase over the course of training. The few studies that have examined skill learning at longer time scales (weeks and months) have employed the use of functional magnetic resonance imaging (fMRI). However, neuroimaging data can only provide correlational evidence for the role of particular brain regions in a given task. Here, we sought evidence for the causal role of both the DLPFC and M1 at different stages of motor skill learning by using a combination of fMRI and continuous theta-burst (cTBS) transcranial magnetic stimulation (TMS).
Human participants trained on six separate motor sequences in a sequence learning task over the course of 8 weeks. In order to examine depth-of-training effects, two sequences were practiced extensively (1200 trials), two were practiced a moderate amount (300 trials), and two were minimally trained (25 trials). After training was complete, participants returned for three separate sessions during which we administered cTBS over right DLPFC, right motor cortex, or the vertex of the scalp (control condition) just prior to performance of the six motor sequences in an MRI scanner. Preliminary results revealed that sequence information could be decoded from brain activity across a large swath of frontal cortex including DLPFC, premotor cortex, and the

supplementary motor area. The effects of stimulation on behavior was highly dependent on depth of training. M1 stimulation led to deficits in the more extensively trained skills, with relatively minor deficits in novice skills. In contrast, DLPFC stimulation led to impairments in performance across all skill levels with larger deficits for novice skills relative to expert skills. These results provide evidence that cognitive control regions play a causal role in skilled performance at all stages of learning, but that their contribution diminishes as expertise develops.

Disclosures: T.G. Lee: None. **T.J. Adkins:** None.

Poster

696. Human Motor and Sequence Learning I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 696.07/AA35

Topic: H.02. Human Cognition and Behavior

Title: Incentives modulate fronto-striatal BOLD representations of skilled action

Authors: *T. J. ADKINS, T. G. LEE;
Univ. of Michigan, Ann Arbor, MI

Abstract: People proactively modify how they perform skilled actions when they are offered rewards**,** often moving more forcefully, quickly, and accurately as the size of a monetary incentive increases. While these behavioral effects are well documented, the neural mechanisms underlying incentive-motivated skill performance are not well understood. We aimed to shed light on these mechanisms by measuring people's brain activity with functional magnetic resonance imaging (fMRI) while they performed skilled actions with opportunities for reward. Thirty human participants trained to perform two motor sequences in a discrete sequence production (DSP) task. These participants returned 48 hours later to perform the newly learned skills with opportunities to earn rewards ($5, $10, or $30) for fast and accurate performance. Each trial began with cues representing the size of the reward and the identity of the action to be performed. We used a combination of univariate and multivariate techniques (MVPA) to localize brain regions that were modulated by reward and coded for the upcoming action. We found evidence of reward-modulated action codes in the dorsolateral prefrontal cortex (dlPFC), ventromedial prefrontal cortex (vmPFC), dorsomedial striatum (DMS), and anterior cingulate cortex (ACC). Importantly, the quantity of information about action in these regions was associated with greater effects of reward on performance. These results suggest that motivational signals alter the performance of skilled actions by modulating action codes in regions important for goal-directed control.

Disclosures: T.J. Adkins: None. **T.G. Lee:** None.

Poster

696. Human Motor and Sequence Learning I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 696.08/AA36

Topic: H.02. Human Cognition and Behavior

Support: GIF I-99-105.4-2016
NIH R01 MH069456

Title: Statistical learning shapes neural sequence representations

Authors: *S. HENIN[1], N. B. TURK-BROWNE[2], D. FRIEDMAN[1], A. A. LIU[1], P. DUGAN[1], A. FLINKER[1], W. DOYLE[1], O. DEVINSKY[1], L. MELLONI[3];
[1]New York Univ. Sch. of Med., New York, NY; [2]Psychology, Yale Univ., New Haven, CT; [3]Neurosci., Max Planck For Empirical Aesthetics, Frankfurt Am Main, Germany

Abstract: Although sensory input arrives continuously, humans organize that experience into digestible and punctuated events, such as words, objects, scenes and events that are used to speak, think and remember. How is experience parsed into meaningful units? Statistical learning is thought to underlay the ability to discover structure and segment the continuous input. An ability that, for instance, babies use to discover word boundaries in the continuous speech by tracking the statistical co-occurrences of syllables. To identify the cortical circuits responsible for statistical learning (SL), we exposed subjects to auditory and visual SL while collecting direct, intracranial recordings (23 patients, 3689 electrodes). We used neural frequency tagging (NFT) to first map the cortical circuits for SL and then representational similarity analysis (RSA) to determine which aspect(s) of the temporal regularities are learned. Acquisition of higher-order units clustered in two distinct anatomically and hierarchically segregated responses: one representing the input and the higher-order units localizing to earlier processing stages (e.g., STG) associated with shorter temporal receptive fields, and another representing the higher-order units only localizing onto later processing stages (IFG) with longer temporal receptive fields. Moreover, we found that learning of sequences concurrently shapes sequence representations at multiple levels, with a division of labor across lower- and higher-order brain areas in terms of encoding of simple and generic aspects of the sequences i.e., transitional probability vs. complex and specific regularities i.e., information about the ordinal position and their specific identity. The anatomical and representational segregation of information in those circuits was observed both for SL in the visual and the auditory modality, yet the cortical areas, with the exception of IFG and anterior temporal pole, showed anatomical specificity to the modality. These findings indicate the existence of multiple computational systems for sequence processing supporting learning across hierarchically segregated cortical circuits.

Disclosures: **S. Henin:** None. **N.B. Turk-Browne:** None. **D. Friedman:** None. **A.A. Liu:** None. **P. Dugan:** None. **A. Flinker:** None. **W. Doyle:** None. **O. Devinsky:** None. **L. Melloni:** None.

Poster

696. Human Motor and Sequence Learning I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 696.09/AA37

Topic: H.02. Human Cognition and Behavior

Support: IBS-R015-D1 from the Institute for Basic Science

Title: Dissociation of fMRI activities in the caudate nucleus supports reinforcement learning of motor skills

Authors: *Y. CHOI[1,2], E. Y. SHIN[1,2], S. KIM[1,2];
[1]Ctr. for Neurosci. Imaging Res., Inst. of Basic Sciences, Sungkyunkwan Univ., Suwon, Korea, Republic of; [2]Sungkyunkwan Univ., Suwon, Korea, Republic of

Abstract: Motor skill learning involves a complex process of adopting novel movement patterns guided by evaluative feedbacks such as reward. For the study of reward-based motor skill learning, the basal ganglia (BG) is of particular interest, with the crucial role it plays in motor control and reinforcement learning. Recent primate studies have suggested that two separate circuits in the BG, rostral and caudal, are implicated in different stages of learning—early (voluntary) and late (automatic) learning, respectively. However, there remains much to be known about the respective involvement of the regions consisting of the BG throughout the course of reward-based motor skill learning in human. To investigate this issue, we conducted a novel human fMRI experiment, in which the subjects learned to control a computer cursor over a 5-by-5 grid by manipulating their right fingers, wearing an MR-compatible data-glove. By performing this task, the subjects learned the mappings between a high-dimensional motor space and a low-dimensional task space. The experiment consisted of 2 fMRI sessions ("Early" and "Late") separated by 5 behavioral training sessions, as we aimed to investigate the behavioral and neural changes over the course of extensive training. In line with existing primate studies, we identified distinct, rostrocaudally separated neural substrates in the caudate nucleus for the early and late stages of motor skill learning, using a parametric reward-modulating regressor. In addition, in the BG, significant changes in reward modulation occurred with the extensively trained mapping, but not with the untrained mapping. To our best knowledge, we first demonstrated the motor-learning-induced transition of reward-modulating regions in the human caudate nucleus.

Disclosures: **Y. Choi:** None. **E.Y. Shin:** None. **S. Kim:** None.

Poster

696. Human Motor and Sequence Learning I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 696.10/AA38

Topic: H.02. Human Cognition and Behavior

Support: ARO Grant W911NF-16-1-0274

Title: Using a massive behavioral dataset to investigate the synaptic maintenance of implicit learning

Authors: *M. R. KRAMER, P. H. COX, S. R. MITROFF, D. J. KRAVITZ;
George Washington Univ., Washington, DC

Abstract: Humans have a remarkable ability to leverage prior experience to anticipate and respond to subsequent events. When this adaptation occurs without conscious awareness, it is known as implicit learning, a complex process whose neural mechanisms remain unclear. While evidence suggests an important role for the striatum (e.g., Fernandez-Ruiz et al., 2001), the relative sparing of consolidated implicit memories with striatal damage suggests that they are ultimately stored in cortex, likely via changes in synaptic strength (see Reber, 2013). This local cortical plasticity model makes several direct behavioral predictions that we test here using a massive behavioral dataset from the mobile application Airport Scanner. If implicit learning is subserved by changes in local synaptic strength it should be: 1) systematic, taking place at every event and capturing the strength and amount of statistical evidence in favor of one behavior over another, 2) domain-general, with the same function defining the relationship between evidence and behavior across tasks, and 3) persistent across delays consistent with known mechanisms of synaptic plasticity. Specifically, synaptic change can involve *short-term* changes in membrane conductance (lasting minutes; Zucker & Regehr, 2002) and *long-term* changes in gene and protein expression (taking hours to arise; Kelleher, Govindarajan & Tonegawa, 2004). However, there is an intermediate period in which neither mechanism is active, which strongly predicts that implicit learning will be stable over short and long, but not intermediate, delays. Experiment 1 quantified the effect of prior evidence on behavior in a simple two-choice object-sorting task; implicit learning reflected both the strength and amount of prior evidence in a manner almost perfectly consistent with the binomial z-test (n=50,891; R^2=0.95, p=1.02*10^{-23}). Experiment 2 demonstrated domain-generality, showing that that the binomial z-test also strongly predicted implicit learning in an orthogonal visual search task (n=1,000,000; R^2=0.81, p=1.38*10^{-13}). Experiment 3 showed that when a delay is short (0-60 minutes) or long (12 to 48 hours), prior evidence influences behavior (n=11,028; R^2=0.97, p=6.25*10^{-5} and n=2,880; R^2=0.84, p=0.028, respectively), but with intermediate delays (1 to 12 hours), when neither short- nor long-term mechanisms of synaptic change are active, there was no effect of prior evidence on behavior

(n=2,031; R^2=0.10, p>0.60). These human behavioral results verify precise predictions stemming from known mechanisms of synaptic plasticity, suggesting that implicit learning is supported by local cortical synaptic changes.

Disclosures: M.R. Kramer: None. **P.H. Cox:** None. **S.R. Mitroff:** None. **D.J. Kravitz:** None.

Poster

696. Human Motor and Sequence Learning I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 696.11/AA39

Topic: H.02. Human Cognition and Behavior

Support: NSERC Discovery Grant

Title: Visual shift and hand compatibility enhance spatial realignment during visuomotor adaptation

Authors: *C. L. STRIEMER[1], A. MORRILL[1], B. ANGUS-COOK[1], R. WHITWELL[2]; [1]Psychology, Macewan Univ., Edmonton, AB, Canada; [2]Psychology, The Univ. of British Columbia, Vancouver, BC, Canada

Abstract: When a participant reaches to a target while wearing optically displacing prisms, they will initially miss in the direction of the prism shift. However, within a few trials the participant will "recalibrate" their reach in the opposite direction to compensate for the visual perturbation. If the participant continues to reach to targets while wearing the prisms over many more trials their visuomotor system will gradually realign the reference frames for the eye and the hand to adjust for the altered visual input. This "spatial realignment" is typically demonstrated through the presence of adaptation after-effects such that, when the prisms are removed, the participant will reach in the direction opposite the prism shift. Previous lesion studies have consistently demonstrated that damage to the cerebellum impairs visuomotor adaptation. In addition, it is well-known that the cerebellum exerts ipsilateral control over the limbs. However, a previous patient single-case study demonstrated that the cerebellum may also process ipsidirectional visual errors that are induced during prism adaptation such that the right cerebellum processes rightward visual errors and vice-versa. If this hypothesis is correct, then one might expect so see differences in the magnitude of the after-effects observed when the hand used during adaptation and the direction of visual shift employed are processed by the same cerebellar hemisphere (i.e., congruent) compared to opposite cerebellar hemispheres (i.e., incongruent).
Using a within-subjects design, we had participants (n=17) complete reaches with or without visual feedback prior to and following adaptation to 17° leftward or rightward optically displacing prisms using either their left or right hand (tested in separate sessions, counterbalanced). Our results revealed a "congruency effect" such that adaptation after-effects

were significantly larger for reaches performed without visual feedback (i.e., straight-ahead pointing) when the direction of prism shift and the hand used were congruent compared to incongruent. In contrast, no significant congruency effects were observed for pointing error reduction during adaptation. These results suggest that the cerebellum may play an important role in the processing of ipsidirectional visual and/or proprioceptive reach errors during visuomotor adaptation.

Disclosures: C.L. Striemer: None. **A. Morrill:** None. **B. Angus-Cook:** None. **R. Whitwell:** None.

Poster

696. Human Motor and Sequence Learning I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 696.12/AA40

Topic: H.02. Human Cognition and Behavior

Title: Increased task difficulty accelerates implicit perceptual-motor sequence learning

Authors: *P. SHU, Y. C. HAN, P. J. REBER;
Northwestern Univ., Evanston, IL

Abstract: The idea of "desirable difficulty" has been advanced to explain memory phenomena where increasing task difficulty leads to better explicit learning (Bjork, 1994). This effect has not been explored from a memory systems perspective and it is unknown whether it applies to implicit learning, where errorless (easier) learning may be more effective. Here, we report the effect of increasing task difficulty in an implicit perceptual-motor sequence learning task by modifying the spatial-response compatibility between perceptual cues and motor responses.
In the Serial Interception Sequence Learning (SISL) task, participants observe circular cues that move vertically towards one of 4 target zones and attempt a precisely timed motor (keyboard) response the moment the cue intercepts the target via the D, F, J or K keyboard keys. The speed of the moving cue is individually adaptively adjusted to keep overall task performance near 80% accurate (correct key pressed at the correct time). Sequence knowledge of a covertly embedded 12-item repeating sequence is expressed through a sequence-specific performance advantage (SSPA), higher response accuracy on the trained sequences compared to unfamiliar. For half the participants, task difficulty was increased by using an incongruent spatial cue-response mapping, with cues moving left to right towards target zones arranged vertically (but same response keys). All participants completed 4 training blocks (2880 trials) prior to a sequence-knowledge test (540 trials) containing repetitions of the trained sequence and two novel repeating foils.
Since the speed was adjusted to maintain 80% accurate responding in all conditions, the increased difficulty for the spatially incongruent test was reflected in a slower average task speed for these participants (M=1.0s, SE=.04s) compared to typical (M=.7s, SE=.02s), t(45)=5.3,

p<.001. However, SSPA in the incongruent condition test (M=18.5%, SE=2.0%) was significantly higher than the typical training condition (M=7.7%, SE=2.2%), t(45)=3.6, p<.001. Increasing training condition difficulty appears to have increased the rate at which participants learned covert sequential information. It is also possible that increased difficulty led to better sequence expression even with similar learning. Simple statistical or reinforcement learning mechanisms thought to support implicit learning do not easily account for this result but is added to a growing set of findings (e.g., Chon et al., 2018) suggesting a role for attentional or strategic effects on implicit learning.

Disclosures: **P. Shu:** None. **Y.C. Han:** None. **P.J. Reber:** None.

Poster

696. Human Motor and Sequence Learning I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 696.13/AA41

Topic: H.02. Human Cognition and Behavior

Support: NSF BCS 1558535
NSF OIA 1632849

Title: Neural evidence that reward alters visual statistical learning

Authors: *S. PARK, L. L. ROGERS, T. J. VICKERY;
Dept. of Psychological and Brain Sci., Univ. of Delaware, Newark, DE

Abstract: Humans are adept at detecting, extracting, and exploiting regularities in the visual environment—a type of learning termed visual statistical learning (VSL). Many aspects of learning from reward also resemble statistical learning in some respects, yet whether and how these two forms of learning may be related is largely unknown. In two studies, we examined how monetary reward modulates VSL and the neural basis of this interaction. Thirty subjects completed a gambling task, in which they learned the values (high or low) of fractal images through a trial-and-error binary-choice gambling task. Choices to gamble were associated with a 50% chance of no reward and a 50% chance obtaining either 2 or 10 points (low and high images, respectively). If they chose “No” to gamble, there was a 100% chance of getting 1 point. Unbeknownst to subjects, we paired images so that some images always predicted other images on the following trial. This led to four types of pairings (High-High, High-Low, Low-High, and Low-Low). In the following recognition task and reward memory task, we asked them to choose the more familiar of two pairs (a target and a foil) and to recall the value of images (high or low). We found better recognition when the first item of pair was a “High” item, with High-High pairs showing the highest recognition rate. To investigate the neural basis of this finding, we measured brain responses to visual images that were associated with both varying levels of reward and

sequential contingencies with event-related fMRI. Twenty subjects completed the same gambling task. Then, subjects passively viewed a stream of the images with pairwise relationships intact. Brain responses to images during the gambling task were affected by both value and statistical contingencies. When we compared the first image of a pair with high-value to the first image of a pair with low-value, we found the orbitofrontal cortex and right nucleus accumbens showed higher activation, suggesting that the high value of the first image led more expectation of reward processing, thus potentially enabling better memory for associated items. In addition, the lingual gyrus showed greater activation for the second image of a pair with high value than the second image of a pair with low value. Our results suggest that reward contingencies affect VSL, with relatively higher value associated with stronger behavioral and neural signals of such learning. Thus, reward may play a role similar to selective attention in VSL, or affect VSL via such a mechanism.

Disclosures: S. Park: None. **L.L. Rogers:** None. **T.J. Vickery:** None.

Poster

696. Human Motor and Sequence Learning I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 696.14/AA42

Topic: H.02. Human Cognition and Behavior

Support: NSF OIA 1632849
NSF BCS 1558535

Title: Neural and behavioral signatures of visual statistical learning are shaped by tasks and categories

Authors: *L. L. ROGERS, S. PARK, T. J. VICKERY;
Psychological and Brain Sci., Univ. of Delaware, Newark, DE

Abstract: Visual statistical learning (VSL) describes the ability to unintentionally learn temporal and spatial statistical regularities from visual information. Little is known about how VSL is modulated by different task conditions during familiarization, or how natural and artificial groupings influence VSL. To examine this question, we had subjects view sequences of face and scene images, in which were embedded image pairs that always co-occurred (i.e., image A was always followed by image B). Participants' task was to learn, through trial and error, an arbitrarily assigned response-mapping to each image (one of two buttons). Therefore, each image possessed a natural category (face or scene) and an arbitrary response mapping (A or B). In a surprise test task at the end of the experiment, participants were informed of this structure and performed a two-alternative forced choice task to decide whether they had seen a target pair or a foil pair comprised of two temporally unassociated images. Pairs of the same arbitrary response

mapping ($p < .001$) and same natural category ($p < .001$) were much better recognized compared to mixed arbitrary response mapping and mixed natural categories, respectively. In an fMRI study, we examined how such task and category differences might shape neural signatures of VSL. Before scanning, participants were exposed to a stream of face and scene images but were now required to perform one of tasks that alternated on a block-by-block basis. Both tasks used distinct sets of images with paired images that always co-occurred. The first task was the arbitrary response mapping task described above, while the second task was a 1-back task. Inside the scanner, participants passively viewed a stream of the same images in a rapid event-related design, still presented in their original paired contexts. BOLD responses were modulated by item order and training context. First items of pairs learned under response-mapping elicited higher activity in premotor compared to the first image of a pair learned during 1-back, suggesting that response prediction may play a role in the modulation of learning during categorization. Second items did not show the same modulation by task context. However, higher activity in the lateral occipital cortex was observed for the second image of a pair learned during arbitrary response mapping compared to 1-back, potentially reflecting enhanced learning during response mapping. Our findings suggest that tasks, response-mapping, and natural categories shape multiple signatures of VSL, and that understanding the consequences of training context variation is important to understand how VSL may operate in realistic environments.

Disclosures: L.L. Rogers: None. **S. Park:** None. **T.J. Vickery:** None.

Poster

696. Human Motor and Sequence Learning I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 696.15/AA43

Topic: H.02. Human Cognition and Behavior

Support: RISE GM063787

Title: Examining motor abilities and skill transfer within a virtual environment

Authors: *J. A. ARMENDARIZ[1], M. F. AWAD[2], I. J. LACHIA[4], A. X. KRAUSE[4], B. GABAY[4], R. MORALES[5], J. HINKEL-LIPSKER[4], S. A. DREW[3];
[1]California State Univ. Northridge, Northridge, CA; [2]Col. of Social and Behavioral Sci., [3]California State University, Northridge, Northridge, CA; [4]California State Univ. of Northridge, Northridge, CA; [5]California State Univ. of Northridge, Los Angeles, CA

Abstract: Virtual reality (VR) systems have become increasingly popular and offer an immersive experience to the general public. It is being used more often in a variety of fields including therapeutic rehabilitation, occupational training, and commercial gaming. Currently there is little research examining the latest generations of VR technologies and the physiological

impact that could accompany use of these new devices. This study aims to determine if there are differences in movement patterns of a newly learned skill either within or outside of a virtual environment using a three-dimensional motion capture system and an HTC Vive headset. In addition, we investigated whether learned motor skills within a virtual environment can be transferred over to the real world. Participants completed an immersive VR or real-world (RW) dart throwing task for 30 minutes. Movement and accuracy of dart throwing outside of the virtual environment were measured. Preliminary results show no significant differences between participants' joint kinematics and accuracy while throwing darts during or outside of the VR task. These results suggest that training in a virtual environment is comparable to training in the real world, thereby support the viability of VR training for motor tasks, which can lead to more cost effective, accessible, and efficient training in the future.

Disclosures: J.A. Armendariz: None. **M.F. Awad:** None. **I.J. Lachia:** None. **A.X. Krause:** None. **B. Gabay:** None. **R. Morales:** None. **J. Hinkel-lipsker:** None. **S.A. Drew:** None.

Poster

696. Human Motor and Sequence Learning I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 696.16/AA44

Topic: H.02. Human Cognition and Behavior

Support: R01AG040133-05

Title: Age-related changes in sleep-dependent procedural learning consolidation

Authors: *K. A. KAINEC[1], A. B. FITZROY[2], R. M. SPENCER[3];
[2]Psychological and Brain Sci., [1]The Univ. of Massachusetts Amherst, Amherst, MA; [3]Dept Psychology, Univ. Massachusetts, Amherst, Amherst, MA

Abstract: The benefit of sleep across taxonomic classes of memory has become increasingly apparent in recent years. Over the course of normal aging, the benefit of sleep for memory declines and has been reliably shown to decrease substantially for procedural memory in particular. Previous studies have investigated either underlying functional and structural neural correlates of procedural learning, but results remain unclear. Advances in neuroimaging analysis techniques allow for combined examination of both the structural and functional neural correlates of procedural learning consolidation. Here, we use a multimodal imaging approach in which we integrate high resolution structural and functional MRI scans, diffusion tensor imaging, and high-density polysomnography, in order to investigate age-related changes in the consolidation of motor memory traces following sleep. Older (58-75 years; N = 18) and younger (18-30 Years; N = 18) adults underwent a multi-day multi-session protocol in which a nap and wake day condition were separated by one week (order counter-balanced). On each day,

participants performed an explicit variant of the serial reaction time task (SRTT) both before and after a 2-hour nap or wake interval. During the task, participants were instructed to respond quickly and accurately by pressing buttons corresponding to boxes in spatial locations. Spatial locations changed either randomly or according to a repeating pattern, which participants were instructed to learn while reaction times and imaging data were recorded. High-density polysomnography was also recorded during both nap and wake intervals. Skill learning was operationalized as the relative decrease in reaction time for patterned stimulus presentation compared to random. Brain activation patterns in young and older adults comprised similar core sensorimotor regions, namely the cerebellum, striatum, and primary motor and sensorimotor cortices before and after a nap or wake interval. Interestingly, age-related differences in anterior cingulate and dorsal prefrontal cortex emerged where young adults indicated greater activation in these regions during task performance following a nap than older adults. Additionally, following a nap interval, an evident shift from a subcortically dominant to a cortically dominant activation pattern in both young and older adults emerged.

Disclosures: K.A. Kainec: None. **A.B. Fitzroy:** None. **R.M. Spencer:** None.

Poster

696. Human Motor and Sequence Learning I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 696.17/BB1

Topic: A.08. Development of Motor/ Sensory/ and Limbic Systems

Support: NIE

Title: Development of simultaneity detection ability following late sight onset in congenital cataract blinds

Authors: *T. K. GANDHI[1], S. GUPTA[2], P. GUPTA[3], P. SINHA[4];
[1]Electrical Engin., IIT Delhi, New Delhi, India; [2]Electrical Engin., Indian Inst. of Technol. Delhi, New Delhi, India; [3]Project Prakash Charitable Trust, New Delhi, India; [4]Brain and Cognitive Sci., MIT, Cambridge, MA

Abstract: The elemental judgment of whether two events happened together in time forms the basis for inferring relationships between them. Past work has shown that windows of simultaneity progressively narrow over the developmental timeline. But, since the youngest infants enrolled in these studies have typically been a few months old, it is unclear what the status of simultaneity judgment is at the very onset of vision. Also, it is unknown whether the narrowing of the simultaneity window is related to physiological maturation (due to factors like myelination). To address these issues, we assess simultaneity judgments in a set of longitudinal studies with congenitally blind children who were provided sight surgeries as part of Project

Prakash (www.ProjectPrakash.org), beginning immediately after sight onset. Our paradigm involves presenting two equal-duration transient stimuli; Visual (discs) and Auditory (beeps) that transpire either precisely synchronously or have a lag (with values: ±1000, ±500, ±300, ±200, ±100, ±50 ms). Conditions were blocked and subjects indicated which stimulus in a pair came first. Data from seven Prakash children were collected before and after their sight restoring surgery. The preoperative data suggests that the subjects are partially impaired in accurate judgment of simultaneity but learn this ability in short span of time. The results have two important implications. First, they indicate whether that coarse simultaneity judgments are feasible immediately upon sight onset, and hence can subserve intra- and inter-modal integration at the outset of visual experience. Second, they present a timeline for how experience refines the width of the simultaneity windows. Third, the longitudinal data reveal when the asymmetries in simultaneity judgments (e.g. differential lag sensitivities for when A leads V, versus the other way around) become evident. By following the Prakash children over extended durations (a few years), we hope to be able to determine whether they are ever able to match the simultaneity windows of their normally sighted counterparts, or if there are potentially permanent differences, pointing to sensitive periods in development for this skill.

Disclosures: **T.K. Gandhi:** None. **S. Gupta:** None. **P. Gupta:** None. **P. Sinha:** None.

Poster

696. Human Motor and Sequence Learning I

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 696.18/BB2

Topic: H.02. Human Cognition and Behavior

Support: DARPA HAPTIX Contract NC66001-15-C-4041
VA Center Award #C3819C

Title: Learning artificial sensation through long-term home use of a sensory-enabled prosthesis

Authors: I. CUBEROVIC[1,2], A. GILL[3], L. J. RESNIK[3], D. J. TYLER[1,2], ***E. L. GRACZYK**[1,2]; [1]Case Western Reserve Univ., Cleveland, OH; [2]Louis Stokes Cleveland VA Med. Ctr., Cleveland, OH; [3]Providence VA Med. Ctr., Providence, RI

Abstract: Skilled tool use in humans is acquired over time and involves neural and cognitive changes. A hand prosthesis is a specialized tool that can replace the functional capabilities of a lost hand and modify the user's perception of their body. Prior studies have shown that electrical stimulation of the residual nerves can provide sensory feedback to amputees. Extended usage of a sensory feedback prosthesis may lead to progressive changes in sensory and bodily perception, as the user learns to integrate the artificial sensory information into their sensorimotor processes and body perceptions. In this case study, a participant with unilateral upper limb loss utilized a

sensory-enabled prosthetic hand for 115 days at home. Sensory feedback was provided via electrical stimulation through implanted neural interfaces, and the sensations were controlled by three pressure sensors and one joint angle sensor embedded in a myoelectric prosthetic hand. We examined how learning over this period of home use influenced sensory perception, prosthesis function, and psychosocial outcomes. We tracked perceived sensation location, intensity, and quality at system donning and doffing each day, and found that percepts became more congruent with transduced sensor information over time. Within a day, sensation locations were more likely to shift to become aligned with the prosthesis sensor positions than misaligned for two channels ($p<0.001$). Across the 115 day study, these sensation locations also more frequently overlapped with the prosthesis sensor position at system donning ($p<0.01$), suggesting plastic changes in the cortex. Likert ratings of sensation descriptors indicate that intensity increased over the course of the study for two channels, and perceived naturalness and perceived touch increased for three channels ($p<0.01$ for all). Sensation qualities that did not correspond to transduced sensor information were either not perceived (Ex. “sharp”) or decreased over time (Ex. “vibrating,” $p<0.01$). Prosthesis function during in-lab testing was significantly better with sensation compared to without ($p<0.001$), but did not change over time. Survey scores of the perceived ability to perform daily tasks significantly improved with time (PSFS, MDC-95=1.3). Psychosocial survey scores of self-efficacy, prosthesis embodiment, and social touch with the prosthesis improved significantly within the first month of home use ($p<0.02$ for all), then plateaued. Our findings demonstrate that learning modulates the perceptual and psychological experience of a sensory-enabled prosthesis over time.

Disclosures: E.L. Graczyk: None. **I. Cuberovic:** None. **A. Gill:** None. **L.J. Resnik:** None. **D.J. Tyler:** None.

Poster

697. Human Motor and Sequence Learning II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 697.01/BB3

Topic: H.02. Human Cognition and Behavior

Title: Efficiency of declarative and procedural presentation to the hierarchical motor-sequence-learning

Authors: Y. SUGIHARA[1], *S. N. KUDOH[2];
[1]Dep. Human Syst. Interaction, Sch. of Sci. and Technol., [2]Dep. Human Syst. Interaction, Sch. of Sci. and Technology,, Kwansei Gakuin Univ., Sanda, Hyougo, Japan

Abstract: Motor-Sequence-Learning(MSL) is essential for acquisition of sports skill. Especially, it is often required for the learning of hierarchical motor sequence. Declarative or procedural presentations are able to be candidate for the instruction method of MSL. Declarative

presentations is verbal and episodic, and procedural presentation is non-verbal and symbolic, visually indicating the real movement. Thus declarative and procedural presentation induces declarative and procedural memory, respectively.In this study, we elucidated the efficiency of declarative and procedural presentation to the hierarchical MSL. The sequential patterns of the button-press-task includes 3 independent blocks of 3-buttons-sequence.In case of declarative presentation, both of inter-block-time and intra-block-time of button press slightly decreased during trials. Inter-block-time immediately after changing the order of the blocks increased, especially in the case of declarative presentation, though the order of the button press in each block was not changed. The θ-power of EEG at the forehead (F3, Fz, F4) tended to increase during the MSL. In addition, α-power of EEG at the parietal region (C3, Cz, C4) increased after changing the block order, especially in case of procedural presentation.These results suggest that re-learning of the block-sequence was performed after the changing order of the blocks in case of procedural presentation. On the contrary, if the sequence of button press was procedurally indicated, experimental participants can adapt the changing the block order more than in the case of declarative presentation.

Disclosures: **Y. Sugihara:** None. **S.N. Kudoh:** None.

Poster

697. Human Motor and Sequence Learning II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 697.02/BB4

Topic: H.02. Human Cognition and Behavior

Support: KAKENHI JP 15K16366,17K13096
Pfizer Health Research Foundation (Internal Joint Research for researchers of 39 and younger)

Title: Effect of individual modality dominance of working memory on fNIRS-based neuromodulation for the prefrontal cortex

Authors: *M. MATSUMOTO[1], T. SAKURADA[2,3], S.-I. YAMAMOTO[1];
[1]Col. of Engin. and Sci., Shibaura Inst. of Technol., Saitama, Japan; [2]Dept. of Robotics, Col. of Sci. and Engin., Ritsumeikan Univ., Shiga-ken, Japan; [3]Dept of Neurosurg., Jichi Med. Univ., Tochigi, Japan

Abstract: Neurofeedback (NF) is a useful neuromodulation approach to improve cognitive and motor functions. Although the effect of NF training widely varies among individuals, an influential factor on the NF effect is not clear. We hypothesized that individual differences in cognitive ability affect the NF training. Regarding this point, we previously revealed that bilateral dorsolateral prefrontal cortex (DLPFC) is one of the neural bases of the individual

modality dominance of working memory. Based on our previous findings, we aimed to investigate whether the individual working memory ability determines the effect of NF training for DLPFC activities. First, 40 healthy young adults performed a searching task with the right hand. The participants had to find and memorize randomly located 6-targets on a drawing tablet as quickly as possible (pre-sequential task). We prepared 2 conditions which differ in how to memorize the target locations. When the participant's hand came close to a target location, either vibration stimuli on their hand (tactile condition) or visual stimuli on a monitor which was set over the tablet (visual condition) were presented. To evaluate the individual dominance of working memory, we compared the searching costs under the visual and tactile conditions. Next, the same participants performed NF training to increase the bilateral DLPFC activities. We randomly assigned the participants into the real group (20 participants) and the sham group (20 participants). The real group was received visual feedback based on their own DLPFC activities, whereas the sham group was received visual feedback based on the pre-recorded other's DLPFC activities. Lastly, the participants performed the searching task after NF training (Post-sequential task). In the pre-sequential task, 28 participants showed lower searching cost under the visual condition (visual-dominant), and the others showed the opposite trend (tactile-dominant). After the NF training, only tactile-dominant in the real group showed a significant increase in the connectivity between right and left DLPFCs. In the post-sequential task, we found that the individual's capacity of working memory in the non-dominant modality improved. This cognitive improvement was stronger in the real group compared to the sham group. These results suggest that the individual modality dominance of working memory characterized by the bilateral DLPFC activities is one of the influence factors to determine the NF training effect. The relationship between neural modulation in the bilateral DLPFC and the improvement of motor performance can contribute to developing a new tailor-made neurorehabilitation program.

Disclosures: M. Matsumoto: None. **T. Sakurada:** None. **S. Yamamoto:** None.

Poster

697. Human Motor and Sequence Learning II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 697.03/BB5

Topic: H.02. Human Cognition and Behavior

Title: Causal interactions of medial temporal lobe and associative cortex during implicit learning

Authors: *S. LONG[1], F. CHEUNG[1], A. GUNDUZ[1,2];
[1]J. Crayton Pruitt Family Dept. of Biomed. Engin., [2]Dept. of Electrical Engin., Univ. of Florida, Gainesville, FL

Abstract: Humans have an innate ability to unconsciously recognize patterns, predict subsequent events, and adapt behaviors to interact with the surrounding environment. This ability is known

as implicit learning, and until recently was thought to rely primarily on associative cortical regions outside the medial temporal lobe (MTL). However, more recent work in animals and in human fMRI and lesion studies have pointed to the importance of the connections between MTL structures and many associative cortical regions. In this study we focus on examining functional connectivity by establishing causal relationships between intracranial stereoEEG (SEEG) local field potential (LFP) recording sites during an implicit learning task. The SEEG data was collected from subjects cleared to undergo a two-stage neurosurgery for treatment of refractory epilepsy at the Neuromedicine Hospital at the University of Florida with IRB approval. At stage one, subjects are implanted with multiple intracranial stereoEEG (sEEG) electrodes to localize the epileptic focus and at second stage the focus is resected. Subjects consented to participate in the study and performed two cognitive tasks that depend on statistical regularities and are known to induce implicit learning. The first cognitive task is an alternating serial reaction time (ASRT) task that involves an embedded probabilistic sequence of alternating sequence and random stimuli. The second task is a two-alternative forced choice (2AFC) task that involves the extraction of temporal regularities within a continuous stream of stimuli. Each run of a task lasted 8-10 minutes with periods of rest throughout the duration of the task. During each run of the cognitive tasks, multi-electrode SEEG data was collected and synchronized with the behavioral aspects of the task using a bioamplifier, custom-made hardware, and BCI2000 software. This is the first SEEG study that allows us to study the causal interactions of LFPs from MTL structures and associative cortical regions during implicit learning with high signal fidelity and temporal resolution lacking in surface EEG and fMRI studies.

Disclosures: **S. Long:** None. **F. Cheung:** None. **A. Gunduz:** None.

Poster

697. Human Motor and Sequence Learning II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 697.04/BB6

Topic: H.02. Human Cognition and Behavior

Support: I-CORE program of the Planning and Budgeting Committee (ISF Grant 51/11)
ISF Grant 526/17
United States - Israel Binational Science Foundation (BSF)

Title: Rapid motor skill learning: Behavioral and neurophysiological evidence

Authors: *J. HERSZAGE[1], H. SHARON[2,3], N. CENSOR[1];
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Abstract: Learning motor skills is assumed to be a time consuming process, requiring repeated executions to enhance the performance of the skill. However, in a different learning domain, brief reactivations of a visual perceptual task were recently reported to induce efficient learning, suggesting a novel rapid learning mechanism (Amar-Halpert et al., 2017). Here, we tested the hypothesis that motor skill learning can be achieved with rapid learning through brief reactivations, requiring significantly reduced amount of practice. Participants learned a motor skill, in which they were required to tap a sequence with their non-dominant hand as fast and accurate as possible (Karni et al., 1995), and returned to the lab for a retest following one week. Participants in the *Reactivations* and *Extensive Practice* groups performed 2 additional sessions between test and retest: Participants in the *Reactivation* group briefly reactivated the skill memory for only 30 seconds, while *Extensive Practice* participants performed standard full-length sessions in which they practiced the task for 12 minutes. Non-invasive neurophysiological measurements of changes in corticospinal excitability (CSE) were evaluated, quantifying muscle EMG activity evoked by single-pulse transcranial magnetic stimulation (TMS) over primary motor cortex (M1), prior-to and post learning. Results show that these brief reactivations were sufficient to induce learning gains, with additional practice of the task further improving learning. Furthermore, these results were supported by neurophysiological measurements, with changes in CSE between pre and post learning significantly different between groups, and correlated with the behavioral retest performance. This set of results indicates that motor skill learning can be achieved by brief reactivations, significantly shortening the required practice, pointing to plastic changes in the motor system induced by rapid learning. The results demonstrate a novel form of rapid motor skill learning, having far-reaching implications, for example in accelerated motor rehabilitation following neurological injuries.

Disclosures: J. Herszage: None. **H. Sharon:** None. **N. Censor:** None.

Poster

697. Human Motor and Sequence Learning II

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 697.05/BB7

Topic: H.02. Human Cognition and Behavior

Support: TTW15989

Title: Exploring exploration in reward-based motor learning

Authors: *N. M. VAN MASTRIGT, J. B. J. SMEETS, K. VAN DER KOOIJ;
Human Movement Sci., Vrije Univ. Amsterdam, Amsterdam, Netherlands

Abstract: Exploration is thought to be a key element in reward-based motor learning. This has been studied predominantly in reaching tasks, but not in balance tasks that are relevant for

rehabilitation practice. We hypothesize that exploration is explicit. Therefore, we examined whether performing a secondary cognitive task in a novel repetitive weight shifting task reduces exploration. Since both (sensori)motor noise and exploration result in motor variability, exploration is difficult to measure. We therefore tested whether our measure of exploration is sensitive enough to detect that exploration is higher after non-rewarded than after rewarded trials. In upright stance, subjects (N=12) repetitively shifted their weight to one leg, aiming for a fixed target with their center of pressure within 1.5 s. After a practice block with online visual feedback of their center of pressure, and a pretest block without feedback, subjects received only binary feedback in the feedback blocks. Sensorimotor noise was estimated as the endpoint variability in the pretest block; exploration in feedback blocks was defined as the endpoint variability minus this sensorimotor noise. Subjects performed two feedback blocks, in which they performed a visual 2-back task (cognitive task) or passively looked at a similar stimulus (control task) directly after each movement repetition. Each block consisted of 50 trials. To estimate exploration after (non-)rewarded trials, half of the motor trials were rewarded randomly. We found that subjects tended to explore less when performing a secondary cognitive task compared to performing the control task, but not significantly. Exploration after non-rewarded trials was significantly higher than after rewarded trials, and this effect tended to be more pronounced in the control task condition. However, also this interaction effect was not significant. We have established that we can detect the known effect of success on exploration in our new paradigm. These results allow us to estimate the sample size for a follow-up experiment to test our hypothesis that exploration is explicit.

Disclosures: **N.M. Van Mastrigt:** None. **J.B.J. Smeets:** None. **K. van der Kooij:** None.

Poster

697. Human Motor and Sequence Learning II

Location: Hall A

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Program #/Poster #: 697.06/BB8

Topic: H.02. Human Cognition and Behavior

Title: The influence of practice conditions on the emergence of habitual action selection

Authors: *Y. DU, S. LEE, A. M. HAITH;
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Abstract: We all sometimes perform particular actions without thinking. This automatic action could become habitual, which persists even sometimes being no longer appropriate, such as typing the wrong symbols on a foreign keyboard. Though this phenomenon is commonly seen in our daily life, it has proven difficult to demonstrate in human participants. We recently showed, in an arbitrary visuomotor association task, that participant's action selection becomes habitual within 4,000-trials of practice (Hardwick, Forrence, Krakauer, & Haith, 2018). In that task,

participants responded to arbitrary symbols by pressing specific keys as quickly and accurately as possible (free reaction time conditions). Two elements of the association were then switched in order to assess whether their action selection was habitual. Participants had no difficulty performing the revised mapping with little practice. When forced to respond at low preparation times, however, they reverted to the original association, revealing the habitual nature of their action selection. This effect did not occur in a control condition in which the original association was practiced only briefly (<100 trials). We are asking here if the habitual actions will emerge after moderate practice (e.g., 1000 trials). In addition, the emergence of habitual action selection may have been attributable simply to repetitions of the task. However, extensive training does not merely promote repetition. Reaction times improved substantially during practice. The emergence of habitual response following 4,000 trials of practice might also be attributable to more experience performing the association at low reaction times. The formation of habitual action selection might, therefore depend not just on the volume of practice, but on the nature of that practice. To test this hypothesis, we had three groups of participants practice an arbitrary visuomotor association for 1000 trials, either under free-reaction-time conditions or under forced-reaction-time conditions imposing either a relatively long (800ms) or very short (400ms) preparation time. Like our previous study, habitual action selection was examined in a timed-response task after they learned a revised association. We found that 1000 trials of practice were sufficient to create a habit in both the free-reaction-time and short forced-reaction-time groups.

Disclosures: Y. Du: None. **S. Lee:** None. **A.M. Haith:** None.

Poster

697. Human Motor and Sequence Learning II

Location: Hall A

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Program #/Poster #: 697.07/BB9

Topic: H.02. Human Cognition and Behavior

Title: Investigating the brain regions and circuitry that mediate visual statistical learning

Authors: *S. KUMAR[1], E. KOELE[1], L. G. UNGERLEIDER[2];
[1]Natl. Inst. of Mental Hlth., Bethesda, MD; [2]Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: Though humans and animals are known to extract statistical regularities from their environment, the neural mechanisms and the brain circuitry underlying this statistical learning are still poorly understood. In this study, we used functional magnetic resonance imaging (fMRI) and behavioral measures to look at the brain regions involved in visual statistical learning. Human participants (Experiment 1, N=17; Experiment 2, N=7) performed a categorization task, in which they were asked to view and classify stimuli as belonging to one of two predefined categories. In Experiment 1, participants classified images as either animate or inanimate and, in Experiment 2, they classified shapes as either red or blue in color. The stimuli were grouped into

different sets of either ‘patterned’ or ‘random’ images. In the ‘patterned’ set, unbeknownst to the subjects, the presentation of the images for categorization followed a pattern; that is, the images were presented in a fixed order (e.g. AABBAABB, where ‘A’s represent animate and ‘B’s inanimate images in Experiment 1). In the ‘random’ set, the images followed a random order. fMRI and behavioral (reaction times and trial accuracy) data were collected while subjects performed the categorization task while viewing the ‘patterned’ and ‘random’ sets of images in separate runs. We hypothesized that the subjects would implicitly learn the embedded pattern in the ‘patterned’ runs while performing the categorization task, resulting in faster reaction times as compared to the random runs. In Experiment 1, we found 10 out of 17 subjects learned the pattern and in Experiment 2, 6 out of 7 subjects learned. In both Experiment 1 and 2, fixed effects analysis contrasting fMRI activation during ‘random’ compared to ‘patterned’ runs of images, revealed voxels with greater activation for random runs throughout visual cortex, extending from early visual areas to the ventral temporal lobe. These results suggest that visual statistical learning of patterns follows predictive coding models in which there is an attenuation of the responses for predicted patterns in the visual cortex.

Disclosures: S. Kumar: None. **E. Koele:** None. **L.G. Ungerleider:** None.

Poster

697. Human Motor and Sequence Learning II

Location: Hall A

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Program #/Poster #: 697.08/BB10

Topic: H.02. Human Cognition and Behavior

Title: Perceptual-motor sequence learning using auditory cues

Authors: *Y. C. HAN, P. J. REBER;
Psychology, Northwestern Univ., Evanston, IL

Abstract: The ability to automatically extract and use statistical regularities from complex, acoustic, sequential patterns found in language and music is hypothesized to be an important component of learning such skills. Prior laboratory research in implicit perceptual-motor sequence learning, such as the Serial Interception Sequence Learning (SISL) task, has primarily utilized visually-cued, motor response sequences to characterize the neural basis and operating characteristics of this process (Gobel et al., 2011). In the SISL task, moving visual cues signal participants to make a precisely timed motor keypress response in a rapidly-paced, game-like task. While participants are not informed of an embedded repeating sequence, knowledge of the sequence is still exhibited through greater accuracy of the repeating sequence compared to performance on unfamiliar sequences (Sanchez et al., 2010). While this particular approach has established that perceptual-motor sequence learning occurs outside of awareness, it is unknown if the same mechanisms support this kind of learning in the auditory domain.

In the auditory SISL variant, auditory cues are used to signal one of four motor (keypress) responses based on the pitch of the tone at onset, with keys D, F, J, and K mapped to starting frequencies 440 Hz, 587 Hz, 698 Hz, or 880 Hz. To mimic cue movement analogous to the visual task, cues include a simulated glissando effect, in which pitch rises from the starting frequency to one 20% higher. Participants were instructed to time their response to the offset of the glissando. As in the visual SISL task, the sequence of cues (and responses) followed a covertly embedded repeating sequence on 80% of trials. The overall task speed was adaptively adjusted based on individual performance to maintain ~80% accuracy through training. Sequence-specific learning was measured as the difference in accuracy on the repeating sequence compared to unfamiliar sequences presented at test. Participants completed training with two 540-trial blocks (72 sequence repetitions) followed by a test block that contained the practiced sequence (180 trials) and two novel sequences (180 trials each). Participants who completed the task exhibited sequence learning that was reliably greater than chance (M=13.7%, SE=5.8%), $t(11)=2.3$, $p<0.05$. These preliminary results suggest that perceptual-motor sequence learning exhibited with auditory cues is similar to learning with visual cues. Moreover, these results suggest that the neural mechanism underlying implicit perceptual-motor sequence learning operates similarly for both visual and auditory perceptually-cued sequences.

Disclosures: **Y.C. Han:** None. **P.J. Reber:** None.

Poster

697. Human Motor and Sequence Learning II

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Title: Computational model of complex combinatorial binding: Neurobiological simulations and hypotheses

Authors: *R. M. CALMUS[1], B. WILSON[1], Y. KIKUCHI[1], Z. KOCSIS[2,1], H. KAWASAKI[2], T. D. GRIFFITHS[1], M. A. HOWARD, III[2], C. I. PETKOV[1];
[1]Inst. of Neuroscience, Newcastle Univ., Newcastle upon Tyne, United Kingdom; [2]Dept. of Neurosurg., Univ. of Iowa, Iowa City, IA

Abstract: Understanding how the brain binds complex information distributed over time is a challenging problem facing the neuroscientific community, requiring computationally and

neurobiologically informed approaches to solve. The combinatorial binding problem is particularly salient in language, whereby human syntactic knowledge supports the encoding and detection of complex regularities at multiple scales and temporal granularities. Yet nonhuman animals are also capable, to varying degrees, of detecting regularities between sensory events over time. Thus the problem is not confined to language, and addressing it is of importance for advancing both machine and animal models of human cognition. There is evidence that structured-sequence-learning tasks engage human and monkey fronto-temporal regions, including inferior frontal areas 44/45 and the frontal operculum. However, the neural mechanisms segmenting continuous sensory input and binding segregable dependencies remain unknown, as do the transformations occurring between these regions. Moreover, the role of the hippocampus, now implicated in aspects of structured sequence learning, is poorly understood within this context. We propose a vector symbolic computational model of structured-sequence-learning, integrating formally defined additive and conjunctive binding operators with a modern Spiking Neural Network implementation of neurobiologically plausible dynamics. Using defined combinatorial operators allows us to plausibly transform between internal representations, rendering these into both mathematically idealized and neurally simulated site-specific activity. The model allows binding temporally segregated dependencies in structured sequences, readily operates on multiple timescales and encodes or decodes sequences with respect to chunked items wherever dependencies occur. We show that the model can predict previous findings under structured-sequence-learning tasks that engage fronto-temporal regions, specifying mechanistic roles for areas 44/45 and the frontal operculum during interactions with temporal cortex. Moreover, the model yields principled, mechanistic predictions of oscillatory dynamic patterns of activity during the chunking of structured serial input. Finally, its predictions underscore the importance of serial position information, which requires input from “time cells” that are known to be present in the hippocampus and dorsolateral prefrontal cortex. Simulations are being tested with neurobiological data from human intracranial recordings during structured-sequence-learning tasks.

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Poster

697. Human Motor and Sequence Learning II

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Topic: H.02. Human Cognition and Behavior

Support: Fondazione Cadssa di Risparmio di Perugia
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Title: Improved motor control of upper limb movement in healthy subjects after optimized sensory stimulation

Authors: *R. PANICHI[1], S. CONTEMORI[2], A. BISCARINI[1];
[1]Exptl. Medicine, Section of Physiol. and Biochem., Univ. of Perugia, Perugia, Italy; [2]Sch. of Human Movement and Nutr. Sci., Univ. of Queensland, Brisbane, Australia

Abstract: Mounting evidence suggests that improving sensory-motor behaviors may be achieved by repetitive sensory stimulations in the absence of explicit task training as well as by intense and specific practice. It has been argued that optimized sensory stimulations might cause high activation in the targeted sensory-motor systems, leading to reorganization changes that may underlie behavioral modifications. However, how effective sensory stimulation might be in impacting the motor domain remains an open question. The modulation of proprioceptive inflow by focal muscle vibration (f-MV) is well suited to investigate the effectiveness of a mere sensory stimulation in influencing motor outcomes. Thus, the aim of this study was to verify whether optimized f-MV stimulation patterns may affect motor control of upper limb movement. To answer this question, we vibrated the slightly tonically contracted anterior deltoid (AD), posterior deltoid (PD) and pectoralis major muscles in different combinations in healthy subjects at a frequency of 100 Hz for 10 minutes in single or repetitive administrations. We evaluated the vibration effect immediately after f-MV application on upper limb targeted movements tasks and 1 week later. We assessed target accuracy, movement mean and peak speed and normalized Jerk using a 3D optoelectronic motion capture system and we evaluated AD and PD activity during the tasks using wireless electromyography. We found that f-MV may induce increases in movement accuracy, mean speed and smoothness and changes in electromyographic activity. The main effects of f-MV were detected over time after repetitive vibration of AD and PD muscles. These effects were comparable to those that occur over the course of motor practice. Thus, in healthy subjects optimized f-MV stimulation patterns might over time affect the motor control of upper limb movement. Our finding implies that f-MV may improve the individual's ability to produce expected motor outcomes and may promote learning-like phenomena in the absence of explicit task training. We believe that processes underlying our observations operate through mechanisms that rely on cellular plasticity and reorganization of the circuitry controlling motor behavior. Finally, our results offer interesting insights into the possibility of developing novel strategies to enhance the efficacy of acquisition of motor skills and/or to support functional recovery in sensory-motor disorders.

Disclosures: R. Panichi: None. **S. Contemori:** None. **A. Biscarini:** None.

Poster

697. Human Motor and Sequence Learning II

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Title: Does chronic low back pain affect locomotor learning or retention and is cognition a factor?

Authors: *J. E. GALGIANI[1,2], G. E. HICKS[1,2], S. M. MORTON[1,2];
[1]Physical Therapy, [2]Biomechanics and Movement Sci., Univ. of Delaware, Newark, DE

Abstract: Recent work in our lab has demonstrated that acute pain experienced during motor learning of a new walking symmetry pattern can reduce retention of learning. Therefore, individuals with chronic pain might also have impairments in motor learning or retention, however this hypothesis has not been systematically tested. Critically, chronic painful conditions, such as chronic low back pain, are associated with structural and functional changes throughout the brain, including somatosensory and multisensory association areas, affective, cognitive, and even motor areas, including the primary motor cortex, which could provide a mechanism for deficits in motor learning or retention. Likewise, cognitive changes associated with some chronic pain conditions also could negatively impact motor learning or retention. This might compromise rehabilitation for individuals with chronic pain because motor learning-based interventions are commonly used in this population. Therefore, we examined the learning and 24-hour retention of a new locomotor pattern in men and women with chronic low back pain (n=16) compared to matched controls. On Day 1, participants learned an asymmetric gait pattern while walking on a treadmill using real-time visual feedback of their step lengths. This was presented as a dynamic bar graph with two bars, one for each leg, the vertical height of which represented each leg's step length. A target line for each leg was also displayed. To teach asymmetric walking, participants were instructed to make the height of the bars match the height of the target line, however, we distorted the feedback to make it appear that one leg was taking a shorter step than it really was, and that the other leg was taking a longer step. Thus, to make the bars match the target lines, participants had to learn to change their baseline step length and adopt a novel asymmetric gait pattern. On Day 2, participants were tested for retention. They also completed a short neurocognitive battery, in order to determine whether cognitive performance was related to motor learning or retention. We measured learning and retention in terms of the accuracy of each step relative to the target step length. Learning the new stepping pattern appears to be similar between control and chronic low back pain groups, but 24-hour retention appears to be reduced in people with chronic low back pain. Further, specific cognitive measures may be correlated with measures of locomotor learning and retention. This indicates that chronic pain conditions may interfere with the consolidation of new motor memories, and that changes in cognition associated with chronic pain may be predictive of these motor learning deficits.

Disclosures: J.E. Galgiani: None. **G.E. Hicks:** None. **S.M. Morton:** None.

Poster

697. Human Motor and Sequence Learning II

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Topic: H.02. Human Cognition and Behavior

Support: Wyss Center for Bio and Neuroengineering (Geneva, Switzerland)
Defitech Foundation (Morges, Switzerland)

Title: Cerebellar transcranial alternating current stimulation in the gamma range applied during the acquisition of a novel motor skill

Authors: *M. J. WESSEL[1], L. R. DRAAISMA[1], T. MORISHITA[1], P. J. KOCH[1], P. MACEIRA-ELVIRA[2], M. DURAND-RUEL[1], A. DE BOER[1], C.-H. PARK[1], F. C. HUMMEL[1]; [1]Defitech Chair of Clin. Neuroengineering, Ctr. for Neuroprosthetics and Brain Mind Inst., EPFL, Geneva, Switzerland; [2]Defitech Chair of Clin. Neuroengineering, Ctr. for Neuroprosthetics and Brain Mind Inst., EPFL Valais, Sion, Switzerland

Abstract: Introduction: The large burden imposed by neuropsychiatric disorders emphasizes the development of novel, neurotechnology-based interventions. A promising approach is the combination of non-invasive brain stimulation with targeted behavioral training. A current limitation of this approach is the high inter-individual variability of the conventional protocols. Novel stimulation modalities and stratified protocols may optimize effect sizes in future. Here, we aimed to test the effect of (i) a novel non-invasive oscillatory cerebellar stimulation protocol on motor skill learning and (ii) evaluated the predictive potential of system-neuroscience-based biomarkers for behavioral success.
Methods: Fifteen heathy, young subjects were recruited for the study. 50 Hz transcranial alternating current stimulation (tACS) was applied to the left cerebellum in a double-blind, sham-controlled, cross-over design, while the subjects performed a motor training of a sequential grip force modulation task (SGFMT). Retention was assessed at a ~24 h and ~10 days follow-up. The training was embedded in a multi-modal systems neuroscience assessment including behavioral testing, double-pulse transcranial magnetic stimulation (dpTMS), and MRI-based neuroimaging (diffusion-weighted imaging, resting-state fMRI, task-related fMRI). The dpTMS protocol included an assessment of short intracortical GABA-ergic inhibition (SICI) during rest and in the premovement phase.
Results: The participants improved their performance in the SGFMT significantly during the training phase with an average improvement of ~16%. There was no significant effect of STIMULATION nor a significant STIMULATION x BLOCK interaction. With multiple linear regression modeling, we were able to explain ~34% of the variance in training gain. The modulation of the premovement SICI slope during training was the most influential regressor

followed by SICI rest at baseline, baseline task performance, and a composite motor performance score.
Conclusions: Gamma-range tACS applied to the cerebellum did not enhance learning of a sequential motor skill. GABA-ergic inhibition-based biomarkers were capable of predicting learning gains and may serve as a stratifier for future behavioral interventions.

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Poster

697. Human Motor and Sequence Learning II

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Program #/Poster #: 697.13/BB15

Topic: H.02. Human Cognition and Behavior

Support: Wellcome Trust 213686/Z/18/Z

Title: Tonic pupil diameter is modulated by predictability of rapid sound sequences

Authors: *A. E. MILNE, C. TAMPAKAKI, S. ZHAO, M. CHAIT;
UCL, London, United Kingdom

Abstract: The brain is highly sensitive to auditory regularities. Listeners exploit the predictable order of sounds in many scenarios, from parsing complex auditory scenes to the acquisition of language. However, objective measures of auditory sequence learning are lacking. Pupillometry can be used across populations (e.g. infants and adults) and species (e.g. human and non-human primates); therefore, offering a potential technique to implicitly study sequence processing across different subject groups. However, it remains unclear exactly how sequence processing will be reflected in the pupil response.
Previous work using slow stimulus presentation, and where participants were required to make decisions about sequence predictability, has demonstrated a correlation between tonic increases in pupil size and predictability. The response is hypothesized to reflect release of acetylcholine linked to learning processes. Here we assess if the predictability of a rapid stream of auditory tone pips modulates tonic pupil diameter.
We manipulated predictability in two ways: 1) by presenting either regular (deterministic; 'REG') or random ('RAND') sequences of tones and 2) by systematically varying the number of different tone frequencies in the sequence alphabet (5,10 or 15), e.g. random sequences created from a tone pool of 5 ('RAND5') are more predictable than those from a tone pool of 15 ('RAND15'). This created six conditions: RAND5, REG5, RAND10, REG10, RAND15, REG15. Tone frequencies were matched across the REG and RAND sequences to isolate the

effect of predictability from other acoustic factors.
We tracked pupil diameter over nine second trials while subjects completed an auditory task unrelated to the sequence structure. We found that predictability modulated tonic pupil diameter. For all alphabet sizes random sequences produced a significantly larger response than their corresponding regular sequence. Our findings demonstrate that predictability of an auditory sequence modulates tonic changes in pupil diameter and establish the potential of this technique for implicitly studying auditory regularities across cognition. It paves the way for future work to probe the underlying neurochemical drivers and cognitive processes implicated in sequence processing.

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Poster

697. Human Motor and Sequence Learning II

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Topic: H.02. Human Cognition and Behavior

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BrainsCAN

Title: Motor plasticity revealed by changes in sequence-specific fMRI activity patterns across weeks of training

Authors: *E. BERLOT, N. J. POPP, J. DIEDRICHSEN;
Brain and Mind Inst., Western Univ., London, ON, Canada

Abstract: An important aspect of many motor skills is the ability to produce complex sequences of movement. While behavioural improvements in sequence learning tasks are easily observable, the underlying neural processes remain elusive. Numerous fMRI studies have set out to illuminate these brain-related changes, but there is very little agreement about the neural changes that occur during sequence learning. The overall aim of this study was a) to reinvestigate a number of reported fMRI findings in a longitudinal motor learning study, and b) to test a set of new hypotheses regarding multivariate pattern changes. The design and predictions were pre-registered on the Open Science Framework (https://osf.io/ueswg/). We trained 26 participants over a period of 5 weeks to perform six 9-digit sequences on a piano-like device. To examine changes in brain representation with learning, participants underwent MRI scanning four times - in weeks 1, 2, and two sessions in week 5. Per session, participants performed both the 6 trained and 6 control sequences. To control for motor output, participants performed all sequences at a fixed speed in sessions 1-3. Because the paced speed was substantially slower than speed of

performance during training, we reasoned that pacing may obscure part of the skill representation. Therefore, participants produced the sequences as fast as possible in session 4. We observed an overall decrease in activation for the same speed of execution in premotor and parietal areas, while primary motor and somatosensory areas showed constant activation across scans. Additional to these decreases in mean activation, the mean activity pattern for trained and untrained sequences became more dissimilar with learning. Next we examined whether sequence-specific activation patterns change with learning. We predicted that the specific patterns of activity for each of the trained sequences change substantially early in learning, but stabilize later on. This effect was indeed observed in premotor and parietal areas and was specific to trained sequences. Patterns were significantly correlated also between scans 3 and 4 (during performance at a paced or maximal speed), indicating that even a slower execution is able to activate the neural representations of that skill. However, the faster speed revealed more clearly that the sequence-specific patterns for trained sequences became more distinct from each other than for the control sequences. In summary, our results reveal a novel fMRI indicator of motor plasticity. The session-by-session change of movement-specific activity patterns turned out to be a sensitive measure of the underlying learning related changes.

Disclosures: E. Berlot: None. **N.J. Popp:** None. **J. Diedrichsen:** None.

Poster

697. Human Motor and Sequence Learning II

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Title: The use of sensory feedback during the production of fast motor sequences

Authors: *N. J. POPP, P. L. GRIBBLE, J. DIEDRICHSEN;
Brain and Mind Inst., Western Univ., London, ON, Canada

Abstract: Current models of motor sequence production emphasize the importance of an internal sequence representation, but conceptualize the skill as being performed in a feedforward manner. While the role of feedback in speech production has been clearly demonstrated, it has been less studied in motor sequences. Here, we investigate the role of sensory feedback on the execution of sequences of fast finger presses. Specifically, we ask to what degree are humans sensitive to a

delay in feedback from an individual finger press and how this sensitivity changes with learning. While delays have been shown to negatively impact performance early in learning, it is possible that accurate feedback might be less important for highly trained individuals, for which performance may be driven by feedforward processes. We investigated this question by introducing small feedback delays during motor sequence production and examined whether they affected subsequent key presses. Participants were trained on sequences of 11 finger presses on a keyboard-like device and were asked to execute them as fast as possible while keeping the error rate low. We trained participants either with visual, auditory, or haptic feedback. On each training day on about a third of the trials we delayed the feedback of one of the finger presses by 100ms. We then measured the effect of this delay by comparing the time interval between the delayed press and the following press to a trial of the same sequence without delay. The delay in feedback resulted in a ~40ms lag of the following press, without a substantial change of this sensitivity between training days. Our findings suggest that sensory feedback remains important for adequate performance even with extensive sequence training.

Disclosures: **N.J. Popp:** None. **P.L. Gribble:** None. **J. Diedrichsen:** None.

Poster

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Topic: H.02. Human Cognition and Behavior

Support: UGC INDIA

Title: Associate learning results in acquiring skill: An fMRI study

Authors: *C. G. N. NAVANEEDHAN, T. KAMALANABHAN;
Mgmt. Studies, Indian Inst. of Technol., Chennai, India

Abstract: Associate learning results when an individual exposed to a given information process it by comparing it with the existing information stored in the long term memory which results in a specific changes neuronal network bringing the desirable learning outcome reflected in certain regions of the brain. The question is whether associate learning helps in acquiring skill, in this particular context it means achieving outcome of learning through a series of internal learning mechanism. In order to understand the internal learning mechanism, the experiment is carried out using fMRI technique. The sample constitutes teachers N= 20 in the age group 30 to 50 years. The subjects are visually exposed to associative learning information from a particular concept in the subject Chemistry at 9^{th} grade level in the scanner to determine the effectiveness with which every teacher associates the visual clips based on individual's thinking ability is recorded as the BOLD signals. The BOLD signals are measured for each individual teacher is analyzed using

SPM12 supported by MATLAB version 16 B. The connectivity analysis reveals the regions of the brain supporting associative learning eventually playing an important role in acquiring desirable skill.

Disclosures: C.G.N. Navaneedhan: None. **T. Kamalanabhan:** None.

Poster

698. Human Long-Term Memory: Encoding and Retrieval IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 698.01/BB19

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant NS107357

Title: Hippocampal oscillations distinguish recollected from recognized memory items in associative recognition memory

Authors: *S. KOTA[1], M. D. RUGG[2], L. ROBINSON[1], B. C. LEGA[1];
[1]Neurosurg., UT Southwestern Med. Ctr., Dallas, TX; [2]Ctr. for Vital Longevity, Univ. of Texas at Dallas Ctr. for Vital Longevity, Dallas, TX

Abstract: Dual process theory holds that distinct physiological mechanisms underlie the mnemonic functions of recognition and recollection, with the latter constituting a hippocampal-dependent process incorporating associations between items, spatial context, temporal context, or some other memory feature. But it remains an unanswered question as to which specific oscillatory patterns in the hippocampus or within wider episodic memory networks support this recognition/recollection distinction. In the fMRI literature, the associative recognition (AR) paradigm has been used to operationalize this distinction, and it reliably elicits significant hippocampal BOLD signal increases during item retrieval for recollected items. This observation supports the idea of an anatomical division in activity underlying the dual process model, with hippocampus specifically supporting recollection. The goal of investigating hippocampal oscillatory patterns to test predictions of dual process theory motivated us to apply the AR paradigm to intracranial EEG patients with depth electrodes inserted into both cerebral hemispheres, including both the anterior and posterior hippocampus simultaneously. Twenty-nine subjects performed AR paradigm. We compared oscillatory activity in the hippocampus between item pairs correctly assessed as intact (successful associative memory, recollection) versus those incorrectly called rearranged but recognized as old (failed associative memory but successful recognition). We observed a power increase in the slow-theta frequency (2-5 Hz) and gamma frequency (70-110 Hz) range that was strongest in the hippocampus during memory retrieval, consistent with previous observations in episodic memory using the free recall paradigm ($p < 0.05$ for one continuous cycle of oscillation, FDR corrected). As expected based

upon fMRI investigations, theta and gamma power increases were greatest during successful recollection. Our results describe the first application of the AR paradigm to intracranial EEG recordings from both the anterior and posterior hippocampus (in both hemispheres). Our findings provide direct electrophysiological evidence that hippocampal theta and gamma specifically may support recollection but not recognition processes in human memory circuits.

Disclosures: S. Kota: None. **M.D. Rugg:** None. **L. Robinson:** None. **B.C. Lega:** None.

Poster

698. Human Long-Term Memory: Encoding and Retrieval IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 698.02/BB20

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant NS095094

Title: Gamma oscillations during episodic memory encoding and retrieval reveal reversal of information flow between the hippocampus and prefrontal cortex

Authors: *S. E. SEGER[1], B. C. LEGA[2];
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Abstract: A critical and emerging question in human episodic memory is how the hippocampus interacts with the prefrontal cortex during encoding and retrieval of items and their context. The biased competition model, synthesized using rodent models, postulates that during memory encoding, the hippocampus transmits contextual information to the prefrontal cortex, but during retrieval, this information is transmitted back to the hippocampus to govern selection of an appropriate memory trace. This “reversal of information flow” concept has been tested directly in rodents by examining theta oscillations. However, commensurate human data have not been uncovered. With the goal of specifically testing predictions of the biased competition model, we analyzed a data set of 76 individuals who performed an episodic memory paradigm with intracranial electrodes simultaneously inserted into the hippocampus and multiple prefrontal locations. Simultaneous recording allowed us to quantify the precise onset times of gamma band activation for the cortex relative to the hippocampus. Across all subjects (without any filtering of electrodes based upon their functional properties), we observed the left anterior VLPFC exhibited the following set of properties: the mean lag activation value during encoding was 13.4 msec (FDR corrected $p = 2.401 \times 10^{-5}$, t-test of activation times compared to hippocampus), while during retrieval it was -10.4 msec (FDR corrected $p = 0.0033$). For this region, the encoding versus retrieval lag distributions were significantly different (FDR corrected $p = 2.146 \times 10^{-7}$). Finally, we compared the lag distributions during successful versus unsuccessful encoding, looking for evidence of a subsequent memory effect in this measurement. For the left

aVLPFC, this was also significant (FDR corrected p = 0.0034). Taken together, these findings indicate that the lag values in the gamma activation peak in the left aVLPFC provide a signal that is sensitive to memory encoding success (exhibiting an SME), with a pattern that fits a putative model of the transfer of contextual information to the frontal cortex during encoding (significant positive lag relative to the hippocampal activation) with evidence of reversal during retrieval (significant negative lag relative to the hippocampus). Our results provide direct human evidence to support the biased competition model. We discuss how our observations fit with a wider picture of brain activity during memory encoding.

Disclosures: S.E. Seger: None. **B.C. Lega:** None.

Poster

698. Human Long-Term Memory: Encoding and Retrieval IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 698.03/BB21

Topic: H.02. Human Cognition and Behavior

Support: DARPA N66001-14-C-4016

Title: Decoding memory: Patient specific models for decoding memory categories from hippocampal spiking activities in epilepsy patients

Authors: *X. SHE[1], D. SONG[1], B. MOORE[1], B. M. ROEDER[3], B. LEE[2], S. J. SHAW[4], A. NGUYEN[4], C. N. HECK[2], C. Y. LIU[2], S. A. DEADWYLER[3], R. E. HAMPSON[3], T. W. BERGER[1];
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Abstract: A Multi-Resolution, Multi-Trial (MRMT) sparse classification model is developed to understand how visual memories are encoded in hippocampal spiking activities in human. This model can successfully decode hippocampal spatio-temporal patterns of spikes into memory labels and thus termed Memory Decoding (MD) model. We recorded hippocampal CA1 and CA3 neural spikes from epilepsy patients when she/he was performing a Delayed Match-to-Sample (DMS) memory task. Hippocampal spikes (model inputs) are projected to a set of B-Spline basis functions to form features vector for classification. Model outputs are five mutually exclusive memory labels (i.e., Animal, Building, Plant, Tool, and Vehicle) describing categories of sample images presented in the 'Sample' phases of the DMS task. A sparse logistic regression classifier is used to map spike patterns to memory labels. Bagging method is applied to mitigate overfitting. Model performances are measured with Matthews Correlation Coefficients (MCCs). Classification are performed under three conditions with the last two conditions serve as negative controls. In the first condition, spike patterns around the 'Sample Response' events, when visual

memories are formed, are used as model inputs. In the second condition, memory labels are randomly shuffled to disrupt any possible correlation between spike patterns and memory labels. In the third condition, time windows of spike patterns are shifted to be before the 'Sample Presentation' events so that the spike patterns contain no memory information about the sample images. Results show that multiple memory labels can be predicted by memory decoding models with significantly above-zero MCCs in all 31 patients. Memory decoding *control* models show zero prediction with randomly shuffled memory labels and near-zero prediction with spike trains recorded before 'Sample Presentation'. These results indicate that (1) sparse classification models effectively avoid overfitting despite the high-dimensional feature space and the small sample size, and (2) visual memories are encoded in hippocampal spiking activities in human. This finding is consistent with previous results in nonhuman primates and further suggests that the hippocampus encodes sensory information with respect to specific categories and features.

Disclosures: **X. She:** None. **D. Song:** None. **B. Moore:** None. **B.M. Roeder:** None. **B. Lee:** None. **S.J. Shaw:** None. **A. Nguyen:** None. **C.N. Heck:** None. **C.Y. Liu:** None. **S.A. Deadwyler:** None. **R.E. Hampson:** None. **T.W. Berger:** None.

Poster

698. Human Long-Term Memory: Encoding and Retrieval IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 698.04/BB22

Topic: H.02. Human Cognition and Behavior

Support: DARPA N66001-14-C-4016
WFBMC Dept. of Neurosurgery
NIBIB

Title: Decoding memory - Memory facilitation of category information for up to 75 minutes using hippocampal stimulation via a memory decoding model

Authors: *R. E. HAMPSON[1], B. M. ROEDER[2], A. S. DAKOS[3], X. SHE[4], B. MOORE[5], D. SONG[4], T. W. BERGER[4], S. A. DEADWYLER[3];
[1]Wake Forest Sch. of Med., Winston-Salem, NC; [2]Neurosci., [3]Wake Forest Sch. of Med., Winston Salem, NC; [4]Biomed. Engin., [5]USC, Los Angeles, CA

Abstract: Development of a neural prosthetic for human memory requires an understanding of how mnemonic information is categorized and encoded for storage. Our recent report (Hampson et al. J. Neural Eng, 2018, 15:036014) showed that human memory could be successfully facilitated by delivery of patterned electrical stimulation to CA1 electrode sites in human hippocampus. Recently we have developed a Memory Decoding Model (MDM) of human hippocampal ensemble activity during performance of a memory task. Patterns were derived for

five image content categories, and patterns of neural activity positively and negatively correlated with the category were used to develop patterns for facilitatory stimulation. Patterned category stimulation was tested within a Delayed-Match-to-Sample+Delayed Recognition (DMS+DR) task, to determine whether MDM-based stimulation facilitated memory for category content of DMS+DR visual stimuli.
In human patients undergoing Phase II invasive monitoring for intractable epilepsy, recordings from an initial DMS (training) session were employed to determine neuron firing patterns for five categories of images; animal, building, plant, tool, and vehicle. Calculation of category specific stimulation patterns prior to the stimulation session allowed for identification of both CA1 and CA3 neurons as stimulation targets. During a second (stim test) session, subjects received micro-electrical stimulation on approximately 50% of trials during the sample phase of the DMS portion of the DMS+DR task. Stimulation trials were a combination of positive stim (stim pattern positively correlated with category) and negative stimulation (stim pattern negatively correlated with category) and were intermixed with non-stimulated control trials. Positive stimulation based on a patient's own hippocampal neural ensemble encoding resulted in facilitated performance and reduction of errors in all five categories. Memory for the image category was facilitated for up to 75 minutes in the Delayed Recognition phase. Facilitation was 10% over all categories, with single categories exhibiting up to 20% improvement. An additional test using a model derived across patients yielded mixed results with respect to positive vs. negative stimulation yielding facilitation in some categories. These results thus provide an important foundation for further design considerations for the current neural prosthetic to restore human memory damaged by injury or disease.

Disclosures: **R.E. Hampson:** None. **B.M. Roeder:** None. **A.S. Dakos:** None. **X. She:** None. **B. Moore:** None. **D. Song:** None. **T.W. Berger:** None. **S.A. Deadwyler:** None.

Poster

698. Human Long-Term Memory: Encoding and Retrieval IV

Location: Hall A

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Program #/Poster #: 698.05/BB23

Topic: H.02. Human Cognition and Behavior

Support: DARPA N66001-14-C-4016
WFBMC Dept. of Neurosurgery
NIBIB

Title: Decoding memory - "Write-in" of category information on ambiguous trials via human hippocampal memory decoding model

Authors: ***S. A. DEADWYLER**[1], B. M. ROEDER[2], A. S. DAKOS[3], X. SHE[4], B. MOORE[5], D. SONG[4], T. W. BERGER[4], R. E. HAMPSON[3];

[1]Wake Forest Sch. of Med., Winston-Salem, NC; [2]Neurosci., [3]Wake Forest Sch. of Med., Winston Salem, NC; [4]Biomed. Engin., [5]USC, Los Angeles, CA

Abstract: To determine the effectiveness of a model neural prosthetic for human memory (see Hampson et al., this session) we have tested facilitation of memory retention in a combination Delayed-Match-to-Sample+Delayed Recognition (DMS+DR) task. Within this task, subjects are presented with clip-art and photographic images which are later tested for memory retention and recognition. Memory Decoding Model-based stimulation during the encoding (Sample) phase of the DMS portion of the task results in up to 34% improvement in later recognition during the DR portion. However, it is unknown whether this facilitation results from strengthening an already existing mnemonic code, or the effects of "writing-in" a code other than that produced by the patient's own memory function. The ability to write-in new codes was tested using MDM stimulation accompanying ambiguous "Sample" images in the DMS task.

MDM models and DMS-DR sessions were configured the same as in previous studies detailed in Hampson et al. (adjacent poster, this session, and J. Neural Eng. 2018). Approximately 10-15% of Sample images were replaced by a solid gray square (instead of clip-art or photographic image). Subjects were instructed to choose any image during the subsequent Match phase to measure personal preferences. Subjects were not informed that stimulation would occur during these trials; however, each "Ambiguous Sample" trial was stimulated with an MDM-based pattern derived either from the patient's individual model, or a shared model computed from other patients.

For at least three of five possible image-content categories derived by the Memory Decoding Model, stimulation with that MDM-derived pattern resulted in greater-then-chance selection of a Match-phase image appropriate to the category. Interestingly, shared model stimulation appeared more effective than individualized model stimulation. This suggests that codes derived from a patient's own model serve to reinforce existing content. When no content is present, an individual patient's "reinforcing" codes are less effective, but shared codes may contain sufficient information to serve as a cue on their own. These results thus provide an important information to the composition of memory codes necessary for a truly adaptable neural prosthetic for human memory.

Disclosures: S.A. Deadwyler: None. **B.M. Roeder:** None. **A.S. Dakos:** None. **X. She:** None. **B. Moore:** None. **D. Song:** None. **T.W. Berger:** None. **R.E. Hampson:** None.

Poster

698. Human Long-Term Memory: Encoding and Retrieval IV

Location: Hall A

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Program #/Poster #: 698.06/BB24

Topic: H.02. Human Cognition and Behavior

Support: DARPA N66001-14-C-4016

Title: Decoding memory - towards building patient common memory decoding model using a transfer learning approach

Authors: *D. SONG[1], X. SHE[1], B. MOORE[1], B. M. ROEDER[2], G. NUNE[1], B. LEE[1], C. N. HECK[1], C. Y. LIU[1], S. A. DEADWYLER[2], R. E. HAMPSON[2], T. W. BERGER[1];
[1]USC, Los Angeles, CA; [2]Neurosci., Wake Forest Sch. of Med., Winston Salem, NC

Abstract: We previously built memory decoding models using hippocampal spiking activities recorded from epilepsy patients. These models are patient specific in the sense that each model is estimated using input-output data recorded from one patient and thus can be predictive only in each specific patient. In this study, we seek to build a patient common memory decoding model that can be generalized to decode memory categories for multiple patients. This is a particularly difficult task, since on top of all the challenges already existing in building patient specific models, there is an additional need for defining a common coordinate system that allows combining heterogeneous dataset recorded from different patients into a single dataset. We explore two transfer learning approaches for creating the coordinate system and further building patient common models. In the first approach, neurons are grouped based on anatomical locations, i.e., anterior/posterior, CA3/CA1, and left/right regions of the hippocampus. Spike patterns of neurons from the same anatomic location are summed to form ensemble patterns. Ensemble patterns and memory labels from different patients then are concatenated to form the input-output data for the ensemble classification, which is performed using a sparse B-spline logistic regression classifier. In the second approach, neurons are grouped with respect to their firing patterns during Sample Response (SR) events, when memories are formed, in the delayed match-to-sample (DMS) task. First, principal component analysis is performed to SR patterns of spikes of all neurons from all patients to extract the principal components of spike patterns during SR. Second, each neuron's SR spike pattern is projected to the principal component space to position the neuron in an "activity space". Third, neurons are grouped within the activity space and summed to form ensemble patterns. Fourth, ensemble patterns and memory labels from different patients are concatenated to form the ensemble data. Finally, ensemble classification is performed as in the first approach. Spikes of 1594 neurons recorded during 3333 DMS trials from 28 patients are included to build two patient common models. Results show insignificant classification performance in all 5 memory categories with the first approach, and significant classifications in 3 out of 5 memory labels with the second approach. These results suggest that (1) it is possible to build patient common models for decoding memory categories from hippocampal spiking activities, and (2) there exist common features in the hippocampal spiking patterns across different patients in encoding memory information.

Disclosures: D. Song: None. **X. She:** None. **B. Moore:** None. **B.M. Roeder:** None. **G. Nune:** None. **B. Lee:** None. **C.N. Heck:** None. **C.Y. Liu:** None. **S.A. Deadwyler:** None. **R.E. Hampson:** None. **T.W. Berger:** None.

Poster

698. Human Long-Term Memory: Encoding and Retrieval IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 698.07/BB25

Topic: H.02. Human Cognition and Behavior

Support: DARPA N66001-14-C-4016
WFBMC Dept. of Neurosurgery
NIBIB

Title: Decoding memory - 24 hour memory facilitation of category information via a memory decoding model of hippocampus

Authors: *B. M. ROEDER[1], A. S. DAKOS[2], X. SHE[3], B. MOORE[4], D. SONG[3], T. W. BERGER[3], S. A. DEADWYLER[2], R. E. HAMPSON[2];
[1]Wake Forest Sch. of Med., Winston-Salem, NC; [2]Wake Forest Sch. of Med., Winston Salem, NC; [3]Biomed. Engin., [4]USC, Los Angeles, CA

Abstract: In prior demonstrations of a model neural prosthetic for human memory (see Hampson et al., this session) we tested memory retention in a combination Delayed-Match-to-Sample+Delayed Recognition (DMS+DR) task. As in prior reports using a model constructed from the patients' own hippocampal neural ensemble encoding (Hampson et al. J. Neural Eng, 2018, 15:036014), we determined that model-based stimulation was highly effective in facilitating memory up to 75 minutes after stimulation (simultaneous with image presentation). In the current study, we tested retention of the same image and category information via an additional Delayed Recognition (DR24) assessment between 20 and 24 hours after the original presentation and stimulation.
Human patients undergoing Phase II invasive monitoring for intractable epilepsy were studied as detailed in Hampson et al. (adjacent poster, this session, and J. Neural Eng. 2018). MDM models were computed for each patient and used to determine CA3 and CA1 stimulation patterns during the encoding (DMS) phase of the task. Trials that were correctly recognized in the DR phase up to 75 min after presentation (including Stim and NoStim trials) were utilized to construct a set of DR trials to be tested the next day. All procedures for DMS-DR testing were identical on the day of stimulation (see Hampson et al.), with only the additional DR24 assessment conducted 20-24 hours after the original DMS trials.
All trials tested in the DR24 assessment were correctly recalled (i.e. 100% correct) in the DR phase on the day of stimulation. Both stimulated and nonstimulated trials showed a decrease in recall up to 24 hours later (mean 60-70% correct recognition); however, MDM-stimulated trials exhibited in less decline in recognition overall (10% improvement) as well as 20-40% improvement in at least three of five categories (compared to NoStim trials) indicating that

MDM stimulation resulted in improved mnemonic retention over the same time period compared to unstimulated trials. Effectiveness of individualized MDM model vs. a model computed across patients is also underway. These results indicate this implementation of a neural prosthetic has the potential for long-lasting efficacy with respect to restoring human memory function in individuals with memory deficits due to disease or injury.

Disclosures: B.M. Roeder: None. **A.S. Dakos:** None. **X. She:** None. **B. Moore:** None. **D. Song:** None. **T.W. Berger:** None. **S.A. Deadwyler:** None. **R.E. Hampson:** None.

Poster

698. Human Long-Term Memory: Encoding and Retrieval IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 698.08/BB26

Topic: H.02. Human Cognition and Behavior

Support: DARPA RAM Project N66001-14-2-4032
NIH UH2/UH3 - NS95495
First Team Programme of the Foundation for Polish Science co-financed by the European Union under the European Regional Development Fund
Biomedical Engineering and Physiology Graduate Program supported by Mayo Clinic Graduate School of Biomedical Sciences

Title: Human intracranial EEG reveals neural correlates of verbal memory processing across the large-scale of brain dynamics

Authors: *V. S. MARKS[1], K. SABOO[2], Ç. TOPÇU[3,4], G. A. WORRELL[4,5], M. T. KUCEWICZ[3,4,5];
[1]Biomed. Engin. and Physiol., Mayo Clin. Grad. Sch. of Biomed. Sci., Rochester, MN; [2]Electrical and Computer Engin., Univ. of Illinois, Urbana-Champaign, IL; [3]Multimedia Systems Dept., Gdansk Univ. of Technol. Fac. of Electronics, Telecommunications and Informatics, Gdansk, Poland; [4]Neurol., [5]Physiol. and Biomed. Engin., Mayo Clin., Rochester, MN

Abstract: Brain processes underlying encoding, storage, and recall of verbal memory can be probed in intracranial EEG (iEEG) recordings during the presentation of words in a free recall task. The purpose of this study was to investigate the broad spectral, spatial, and temporal properties of brain activity underlying human verbal memory encoding. Recordings were obtained during the encoding of words from 139 patients implanted with intracranial electrodes for surgical evaluation of drug-resistant epilepsy. Participants were asked to study lists of words presented on a computer screen for a delayed test of free recall. Lists were composed of 12 nouns from a pool of common English nouns. After a distractor task, participants were asked to recall as many of the words as possible. For each electrode, we determined the average spectral power

density at each time point across all word presentation epochs and found the overall induced power during word presentation. Electrodes were then classified into active and inactive clusters. Analysis of recordings from active electrodes revealed consistent and robust differences in the low theta (2-4 Hz), high theta (5-9 Hz), alpha (10-15 Hz), beta (16-25 Hz), low gamma (25-55 Hz), and high gamma (65-115 Hz) frequency bands. Brodmann areas within the occipital lobe had the highest percentage of active electrodes in all bands (Fig. 1). Analysis of the induced power change showed that verbal memory processes are present in all frequency bands. The induced power of an electrode was found to have statistically significant dependence (ANOVA, $p<0.001$) on the frequency band analyzed, Brodmann area, and hemisphere. Post-hoc group analysis (Tukey-Kramer, $p<0.05$) showed that the total induced power gradually decreased from low to high frequency bands and was higher in right hemisphere. We also observed distinct temporal patterns of the induced power change in the frequency bands studied. The spectral, spatial, and temporal patterns identified in human iEEG recordings suggest large-scale distributed dynamics of verbal memory encoding.

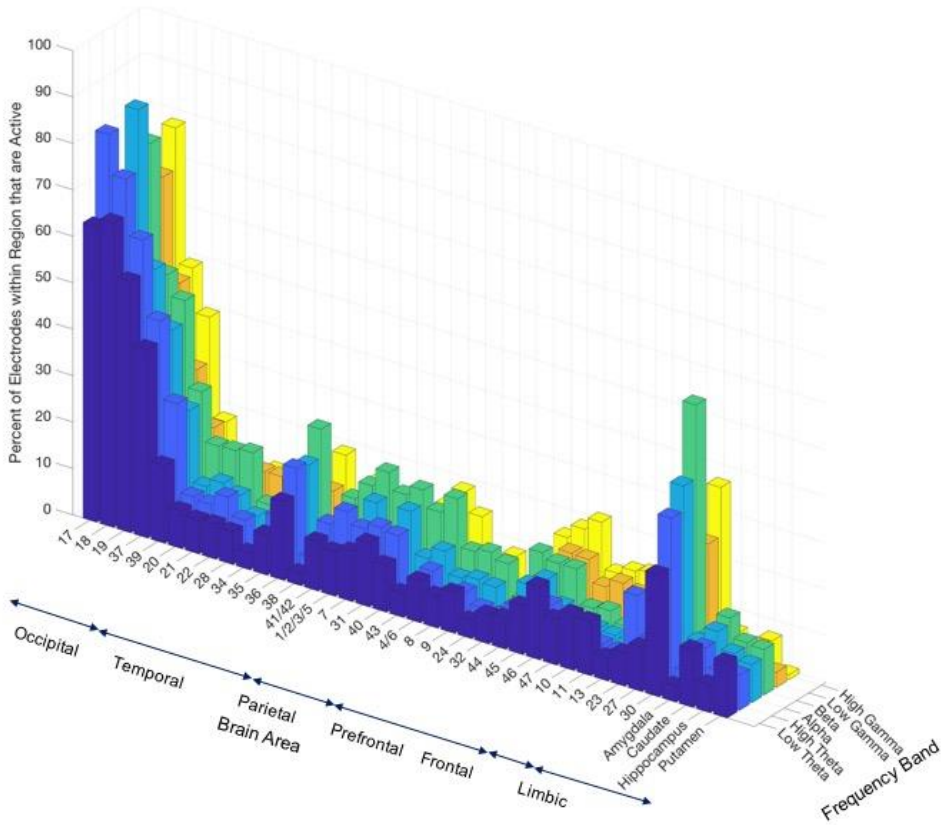

Figure 1. **Distribution of active electrodes across brain regions and frequency bands.** Proportions of active electrodes in each Brodmann area was normalized by the total number of electrodes implanted in that area. Brain areas with the highest percentage of electrodes were identified within the occipital lobe, and the frequency band with the highest percentages of electrodes was the beta band (16-25 Hz).

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Poster

698. Human Long-Term Memory: Encoding and Retrieval IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 698.09/BB27

Topic: H.02. Human Cognition and Behavior

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NIH UH2/UH3 - NS95495

Title: Human verbal memory encoding is distributed across a broad range of electrophysiological activities and brain regions

Authors: *Ç. TOPÇU[1,2], K. SABOO[3], V. S. MARKS[4], G. A. WORRELL[2,5], M. T. KUCEWICZ[1,2,5];
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Abstract: Understanding where and how verbal memory is processed in the human brain remains a challenging question that can be addressed using intracranial electroencephalography (iEEG) signals sampled from electrodes implanted across the cortical brain regions. In this work we investigated engagement of specific regions and oscillatory activities in encoding words. iEEG signals were recorded from 84 drug-resistant epilepsy patients performing a verbal short-term memory task, in which lists of 12 common nouns were presented for subsequent free recall. Memory processing was quantified by averaging the element-wise difference between the iEEG spectral power estimates during encoding of words that were subsequently recalled and that were forgotten, independently in six frequency bands: low theta (3-8 Hz), high theta (6-10 Hz), alpha (8-15 Hz), beta (15-25 Hz), low gamma (25-55 Hz), and high gamma (65-115 Hz). We used this power difference, the subsequent memory effect (SME), as a biomarker of the magnitude of memory encoding in a wide range of different Brodmann areas. We assessed the effect of the Brodmann area and the hemisphere localization on the population SME values using analysis of variance separately in all six frequency bands studied. Brodmann area had a significant effect

(ANOVA, $p<0.001$) in all six frequency bands. Hemisphere had a significant effect on the SME values (ANOVA, $p<0.01$) in both theta, alpha, and high gamma, but not in the beta and low gamma frequency bands. Post-hoc group comparisons (Tukey-Kramer, $p<0.05$) showed that the mean SME values gradually decreased from low to high frequency bands and they were significantly higher in left hemisphere. The highest mean SME values across all frequency bands were found in Brodmann area 31 (parietal lobe), in Brodmann area 8 (frontal lobe), and in the amygdala (mesial temporal lobe). The SME values were also found to have significant dependence (ANOVA, $p<0.05$) on the cortical lobe in all but the low gamma frequency band. Our results suggest that memory encoding is widely distributed across multiple brain regions and engages a broad spectrum of oscillatory activities in the low and high frequency bands. Human verbal memory is proposed to be supported by large-scale distributed processing of the remembered words.

Disclosures: Ç. Topçu: None. **K. Saboo:** None. **V.S. Marks:** None. **G.A. Worrell:** None. **M.T. Kucewicz:** None.

Poster

698. Human Long-Term Memory: Encoding and Retrieval IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 698.10/BB28

Topic: H.02. Human Cognition and Behavior

Support: NIH Brain Initiative U01NS103792

Title: Event boundaries shape memory formation: Evidence from single unit recordings in humans

Authors: *J. ZHENG[1], A. GÓMEZ PALACIO SCHJETNAN[2], V. A. TAUFIK[2], A. N. MAMELAK[3], J. M. CHUNG[3], U. RUTISHAUSER[3], G. KREIMAN[4];
[1]Boston Children's Hosp., Boston, MA; [2]Krembil Res. Inst., Toronto, ON, Canada; [3]Cedars-Sinai Med. Ctr., Los Angeles, CA; [4]Harvard Med. Sch., Boston, MA

Abstract: Although our daily life unfolds as continuous experiences, the memories of these past experiences are carved and organized as discrete events (“episodes”). The ability to segment continuous experiences is highly adaptive: it can help update brain states for salient environmental changes and support the flexible recombination of these memory segments for future use. However, the neural mechanisms underlying event segmentation and how they influence later memory recall remain unclear. To investigate segmentation during memory formation, we tested subjects’ memory of clips with and without event boundaries (i.e. transition between clips from different movies) while recording single neuron activity from 13 drug-resistant epilepsy patients (6 female, age 41.1 ± 14.3) at two sites (Cedars-Sinai and Toronto).

Subjects' memory was evaluated in two subsequent sessions: a scene recognition task where they were asked to identify frames from watched clips as 'old' and novel frames as 'new'; and a temporal discrimination task where they need to identify which of two frames happened first in the presented clip. The presence of event boundaries did not affect performance in the scene recognition task ($F(2, 36) = 0.05$, $P = 0.948$). However, during the temporal discrimination task, subjects showed impaired performance ($F(2, 36) = 18.71$, $P = 2.7 \times 10^{-6}$), longer reaction times ($F(2, 36) = 22.93$, $P = 3.8 \times 10^{-7}$) and a lower confidence level ($F(2, 36) = 15.88$, $P = 1.1 \times 10^{-5}$) when retrieving the temporal order of frames across an event boundary. Such behavior outcomes confirmed the influence of event segmentation on memory formation, highlighting the loose temporal associations between experiences across event boundaries. Evidence of event segmentation was also observed at the neuronal level. Specifically, during encoding, we found neurons (33/468, mostly from the hippocampus: 42.4%) that showed increased firing rates closely following the presence of event boundaries. Moreover, during memory retrieval, these neurons increased their firing rates only when subjects successfully identified the temporal relationship of frames across event boundaries, with no change of firing rates when temporal discriminating frames from the same event, or when performing the scene recognition task. These findings provide initial steps towards elucidating the neural circuit mechanisms for boundary detection at the single cell level and suggest a putative role of these boundary responsive neurons in subsequent memory retrieval, potentially bridging separate memory segments together when needed.

Disclosures: **J. Zheng:** None. **A. Gómez Palacio Schjetnan:** None. **V.A. Taufik:** None. **A.N. Mamelak:** None. **J.M. Chung:** None. **U. Rutishauser:** None. **G. Kreiman:** None.

Poster

698. Human Long-Term Memory: Encoding and Retrieval IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 698.11/BB29

Topic: H.02. Human Cognition and Behavior

Support: NIH-Brain Initiative Grant U01NS103792

Title: Persistent single-neuron activity during working memory predicts strength of long-term memory in humans

Authors: *J. KAMINSKI[1], N. CHANDRAVADIA[1], A. G. P. SCHJETNAN[3], Y. SALIMPOUR[4], I. M. REUCROFT[5], C. REED[2], J. M. CHUNG[2], S. KALIA[3], W. ANDERSON[4], T. A. VALIANTE[3], A. N. MAMELAK[1], U. RUTISHAUSER[1];
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Abstract: Close interactions between Working memory (WM) and Long-Term Memory (LTM) have been known for a long time. For instance, holding an item in WM strengthens LTM for that item. Despite strong behavioral evidence of this relationship, the neuronal basis of this interaction between WM and declarative memories remains poorly understood. We performed single-neuron recordings in the Medial Temporal Lobe and the Medial Frontal Lobe in neurosurgical patients undergoing depth electrode implantation for localization of epileptic seizures. We formed a consortium between three institutions (Cedars-Sinai Medical Center, Toronto Western Hospital, and John's Hopkins Hospital) as part of the NIH BRAIN initiative to enable large-scale data collection at the single-neuron level with standardized surgical and experimental procedures. Patients performed a WM task followed by a new/old LTM recognition memory task. In the WM task we asked subjects to maintain novel images in memory for a few seconds, followed by a probe. Recognition of these images was then subsequently tested in the LTM task. We analyze 41 sessions; behavioral accuracy was 89% and 69% for the WM and LTM task, respectively. In the Medial Temporal Lobe, we identified category selective neurons during the WM task (16% of MTL neurons were category neurons). A subset of these neurons exhibited selective persistent activity during the maintenance period of WM task when a stimulus of their preferred category was held in mind. Critically, we found that the strength of this persistent activity in a given WM trial, in load 1, predicted whether an item was subsequently remembered or forgotten in the LTM recognition task. Z-scored persistent activity was 0.74 and 0.32 for remembered and forgotten trials respectively (permuted t-test t[27]=25.03, p=0.02). These results not only show a direct link between the activity of neurons in MTL and the subsequent strength of declarative memories but also demonstrates that persistent neuronal activity acts as a common neural substrate for both WM maintenance and LTM formation.

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Poster

698. Human Long-Term Memory: Encoding and Retrieval IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 698.12/BB30

Topic: H.02. Human Cognition and Behavior

Support: CV Starr Foundation

Title: March madness: An fMRI study of continuously updated surprise and suspense during basketball-watching

Authors: *J. W. ANTONY[1], S. D. MCDOUGLE[2], U. HASSON[1], K. A. NORMAN[1];
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Abstract: In domains where humans observe events unfold in time, such as listening to narratives or watching sports games, probabilistic beliefs in particular outcomes are continuously updated. In these domains, one important variable, surprise, increases when there is a large discrepancy between previous and current beliefs. Another key variable, suspense, increases when upcoming events have the potential to dramatically alter the current belief (i.e., when the perceived variance in upcoming beliefs is high). Both variables are important for understanding how events are structured and remembered. Here, we set out to characterize dissociable neural correlates of surprise and suspense in event cognition. We used fMRI to measure the neural activity of human subjects as they viewed and recalled the final five minutes of high-stakes NCAA basketball games. We operationalized momentary beliefs (i.e., which team would win) using a "win probability" metric derived from an expert basketball analyst (https://kenpom.com/). These belief values were updated every time the possession of the ball changed. We approximated surprise using the derivative of the belief time course, which often changed after a score or change in possession. We hypothesized that highly surprising events would enhance memory for those events, drive responses in the ventral striatum, and delineate neural event boundaries in multimodal association cortices, as measured by representational similarity analysis. Moreover, we also predicted that cumulative surprise would correlate with game enjoyment. We operationalized suspense by 1) finding instances in a large set of games with a particular game state (amount of time remaining and difference in win probability between the teams) and 2) calculating, for each state, the variability in the change in belief produced by the following state. We predicted that increased suspense would be associated with increased inter-subject correlations in visual and auditory cortices and multimodal association areas. Results pertaining to these predictions will be discussed. More broadly, we hope to demonstrate that sports games (which are both engaging and rich in quantifiable outcomes) are a promising way to explore the neural mechanisms underlying event segmentation and memory.

Disclosures: J.W. Antony: None. **S.D. McDougle:** None. **U. Hasson:** None. **K.A. Norman:** None.

Poster

698. Human Long-Term Memory: Encoding and Retrieval IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 698.13/BB31

Topic: H.02. Human Cognition and Behavior

Support: NSERC Discovery Grant RGPIN-2017-06753
NSERC Discovery Grant RGPIN-2018-04933

Title: Hippocampal white matter microstructure predicts rapid category learning

Authors: *M. GUMUS, T. ZHU, M. L. SCHLICHTING, M. L. MACK;
Univ. of Toronto, Toronto, ON, Canada

Abstract: People rapidly acquire new knowledge in light of their previous experiences. Emerging empirical evidence suggests such learning relies on complementary functions of the hippocampus (HPC). These findings are consistent with neurobiological memory theories positing that during learning, HPC comparator processes evaluate the overlap between new information and current knowledge. The result of this process is thought to trigger either pattern separation, wherein new information is represented distinctly from existing knowledge, or pattern integration, wherein new information is incorporated into existing memories. The extent that these HPC functions impact learning depends on the engagement of anatomically and functionally distinct HPC subfields that are interconnected through two main pathways: the trisynaptic pathway (TSP), which loops from the entorhinal cortex (EC) through dentate gyrus (DG) and cornu ammonis 3 (CA3) en route to CA1; and the monosynaptic pathway (MSP), which projects directly from EC to CA1. Whereas the slower learning rates of MSP projections are thought to be important for forming unitized representations of features over many repetitions, TSP is thought to support rapid flexible encoding via DG- and CA3-mediated functions of pattern completion and relational binding. Despite the theorized significance of intra-HPC circuitry for behaviour, providing an empirical characterization of how information flows within HPC to support learning remains a challenge in humans. Here, we combine anatomically defined hippocampal subfields with high-resolution diffusion-weighted imaging (DTI) to quantify white matter connections underlying the TSP and MSP and link their integrity to category learning behaviour. Participants learned to categorize complex visual objects composed of multiple features based on a multidimensional rule linking features to categories. Rapid learning performance was quantified by participants' ability to successfully categorize rarely-seen category members. Participant-specific structural connectomes of HPC subfields were constructed according to the relative number of interconnecting streamlines as defined by probabilistic anatomically-constrained tractography. A mixed-effects regression relating learning performance to the relative strength of TSP (CA3-CA1 connections) and MSP (ERC-CA1 connections) showed that better learning was uniquely associated with greater TSP tract integrity. By linking sophisticated DTI measures with individual differences in learning ability, these findings shed light on how information flow within HPC supports rapid category learning.

Disclosures: M. Gumus: None. **M.L. Mack:** None. **M.L. Schlichting:** None. **T. Zhu:** None.

Poster

698. Human Long-Term Memory: Encoding and Retrieval IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 698.14/BB32

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant R01 EY028746

Title: Shaping visual memories with real-time fMRI neurofeedback

Authors: *E. S. LORENC, E. F. OBLAK, J. S. SULZER, J. A. LEWIS-PEACOCK;
Univ. of Texas at Austin, Austin, TX

Abstract: Mounting evidence suggests that item representations that linger in a moderately active state in working memory (WM) are susceptible to degradation from competitive processes, subsequently impairing long-term retention. Here, we examined whether real-time fMRI neurofeedback can be used to endogenously manipulate levels of competition in WM, thereby shaping the likelihood of long-term forgetting.

On an initial fMRI scan day, 3 participants completed a perceptual category localizer task, used to train multivoxel pattern classifiers in ventral temporal cortex (VTC) to distinguish between faces, scenes, objects, and periods of rest. This was followed by five runs of a WM task, in which a face and a scene image were presented on each trial, and a retrospective cue indicated which image would be probed after a delay. Pattern classifiers tracked the representational states of the two items, and confirmed that on average, the cued item showed higher delay-period activation than the un-cued item.

In a subsequent fMRI scan day, participants completed another eight runs of the WM task. Participants were instructed to complete the WM task as before, and also to maximize a visual feedback signal related to their delay-period brain activity, presented at the end of each trial. Unbeknownst to them, the feedback was based on the activation level of the un-cued item, decoded from VTC. This allowed us to manipulate the competition between WM items in two ways: in the 'isolate' condition, feedback was designed to *reduce* competition by rewarding low levels of activation for un-cued items. In contrast, in the 'compete' condition, feedback was intended to *increase* competition by rewarding higher levels of activation for un-cued items. Across participants, we found that this neurofeedback procedure successfully modulated WM activations, with more similar activation (greater competition) for items in the 'compete' condition compared to the 'isolate' condition ($p = .047$).

A final fMRI session included two reminder neurofeedback runs, and then three 'transfer' runs per condition without feedback. Participants struggled to maintain the condition-specific modulations in the absence of feedback, with no significant difference in WM competition between conditions. However, we found preliminary evidence that the neurofeedback-induced WM competition had the predicted impact on long-term memory: participants showed more forgetting of un-cued items from 'compete' runs (where they were trained to activate these items *more*) than from 'isolate' runs ($p = .026$). These data provide promising evidence that fMRI neurofeedback can be used to covertly manipulate the fate of visual memories.

Disclosures: **E.S. Lorenc:** None. **E.F. Oblak:** None. **J.S. Sulzer:** None. **J.A. Lewis-Peacock:** None.

Poster

698. Human Long-Term Memory: Encoding and Retrieval IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 698.15/BB33

Topic: H.02. Human Cognition and Behavior

Support: Defense Advanced Research Projects Agency (DARPA)

Title: Transcutaneous vagus nerve stimulation strengthens semantic encoding during novel tone word learning: Evidence from event-related potentials

Authors: *I. PHILLIPS, V. P. KARUZIS, N. B. PANDŽA, P. O'ROURKE, S. E. KUCHINSKY;
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Abstract: Learning a tone language, in which pitch changes word meaning, is difficult for adult speakers of non-tone languages. Learners must rapidly discern pitch contour and height differences and link these cues to word meaning. Research shows that both speech perception training and musical experience improve tone language learning, yet interventions that more directly target neurocognitive processes are understudied. Clinical studies of vagus nerve stimulation (VNS) via implanted electrodes show improvements in associative memory, but it is unclear if non-invasive transcutaneous VNS (tVNS) has a similar effect. To test whether receiving tVNS during tone word training improves learning outcomes, we conducted a double-blind study with native English speakers learning Mandarin pseudowords, using similar methods as a recent study that found faster tone word learning for professional musicians (Dittinger, et al., 2016). We analyzed accuracy and response time (RT) to establish tVNS efficacy and the N400 event-related potential (ERP) component to determine whether learning improvements coincided with enhanced lexico-semantic word representations, as Dittinger et al. found. 43 healthy native English speakers (11 male, ages 18-34) received active or sham tVNS via electrodes placed on the left outer ear canal (21 active, 22 sham, groups balanced on self-rated musicianship, pitch aptitude, working memory) while they learned 9 tone words, made by pairing 3 syllables (/ba/, /bi/, /pi/) with 3 Mandarin tones (flat, rising, falling) over 2 days. Both days involved a passive word learning task in which subjects saw an English word on screen and then heard the tonal translation, and a matching task in which subjects saw an English word, heard a tonal word, and then pressed a button to indicate if the words were correct translations or not. Before each task, the active group received 10 minutes of continuous tVNS priming below perceptual threshold. No differences in accuracy were found for the matching task, but the active group had faster RTs for correct answers than sham. These RT improvements aligned with differences in N400 distribution and amplitude in both tasks, similar to Dittinger et al.'s findings. N400s were observed for both groups, but had a larger amplitude and a more posterior distribution for the

active group in both word learning and matching tasks, suggesting tVNS recipients developed stronger lexico-semantic representations for the trained tone words faster than the sham group. These findings largely parallel those reported for professional musicians, and suggest short periods of tVNS may confer similar benefits as musical training to tone language learners.

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Poster

698. Human Long-Term Memory: Encoding and Retrieval IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 698.16/BB34

Topic: H.02. Human Cognition and Behavior

Support: NSERC Discovery Grant RGPIN-2017-06753

Title: Early learning hippocampal engagement supports flexible category learning

Authors: *Z. CHENG, T. LIU, M. L. MACK;
Univ. of Toronto, Toronto, ON, Canada

Abstract: Emerging evidence points to the hippocampus (HPC) as a key brain structure in learning flexible knowledge that extends beyond memories for individual episodes. These findings lend support to neurobiological memory theories that formalize how HPC functions of pattern completion, separation, and integration contribute to building memory structures that highlight goal-relevant information. Although recent human and animal work has identified goal-specific coding in HPC at the end of learning, it remains unknown how the interplay of neural mechanisms early in learning support the formation of such flexible knowledge. Here, we combine human neuroimaging with SUSTAIN, a computational model that formalizes how newly-encountered information is encoded in light of prior learning, to characterize how early learning processes are reflected in neural function. During fMRI scanning, participants learned to categorize visual objects composed of multiple features based on a multidimensional rule linking object features to category labels. Category prototypes were shown more frequently than non-prototype stimuli resulting in high learning performance for prototypes across all participants at the end of the task, but large individual differences in learning non-prototypes. Whereas some participants fully learned non-prototypes, others perseverated on simple rules that miscategorized non-prototypes; as such, non-prototype performance served as a behavioural index of flexible learning. We interrogated neural function during initial learning finding that univariate activation in anterior HPC not only discriminated prototypes from non-prototypes, but the degree of this effect predicted individual differences in flexible learning. Similar effects were seen in bilateral frontal pole and superior parietal cortex. SUSTAIN was fit to participants' behaviour to derive

trial-by-trial predictions of information gain, a measure reflecting the degree of knowledge updating resulting from any one trial. Across all trial types during initial learning, information gain was reflected in the engagement of the caudate, consistent with its role in prediction error and reward processing. Posterior HPC activation also correlated with information gain but did so differently for prototype and non-prototypes. Importantly, this relationship between HPC engagement and model-based information gain predicted individual differences in non-prototype learning. These findings suggest that HPC engagement to informative experiences during initial learning supports the formation of flexible knowledge that generalizes to similar experiences.

Disclosures: Z. Cheng: None. **T. Liu:** None. **M.L. Mack:** None.

Poster

698. Human Long-Term Memory: Encoding and Retrieval IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 698.17/BB35

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant 2T32MH067564

Title: Theta entrainment after learning enhances episodic memory

Authors: *N. WHITMORE, K. A. PALLER;
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Abstract: Converging evidence from computational, animal, and human approaches suggests that theta-band EEG oscillations (3-7 Hz) play a role in memory functions, but their precise role remains mysterious. Sensory entrainment paradigms allow researchers to induce theta waves and potentially link theta to specific memory mechanisms. Although this method has been used to probe the role of theta during encoding, theta's role in consolidation is less well understood. To address this issue, we investigated theta entrainment during a post-learning period when active rehearsal was discouraged. In an exploratory study, participants (N=22, 13 female, age 18-31 yrs, mean age=21.5 yrs) first viewed pictures of 30 common objects and were instructed to remember the objects. Immediately afterwards, they took free recall and recognition tests. Then they performed a continuous performance test (CPT) for 25 minutes (responding whenever "X" appeared), followed by the same two memory tests. During the CPT, we produced entrainment by flickering the brightness of the screen. Each participant performed this procedure two times using different sets of pictures and different delay-period stimulation, at either an individualized theta frequency or at a control frequency. Order of theta and control entrainment was counterbalanced. Theta rhythms were entrained, in general, but not to the same extent in all individuals. Regression revealed that the memory effects of theta stimulation depended on the strength of EEG entrainment, quantified by the degree to which EEG theta power increased with

stimulation versus stimulation-off baseline periods. Stronger EEG entrainment was associated with increased benefit from theta stimulation in recognition and recall ($p < 0.001$ for both). Participants with the strongest EEG entrainment (n=10) recognized 3% more objects and recalled 6% more objects after theta stimulation than after control stimulation. These results suggest that theta oscillations facilitate offline consolidation. Theta may improve memory by modulating plasticity and network connectivity, or alternatively by enhancing binding when memories are spontaneously reactivated. These results link theta with memory improvement, but the extent to which theta was associated with memory reactivation is unclear, given that the theta entrainment occurred during the CPT. Therefore, we conducted a follow-up study in which theta entrainment occurs during memory retrieval. Comparing results between the two studies may shed additional light on the neurocognitive mechanisms through which post-learning theta is associated with memory improvement.

Disclosures: **N. Whitmore:** None. **K.A. Paller:** None.

Poster

698. Human Long-Term Memory: Encoding and Retrieval IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 698.18/BB36

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant MH096698
NSF Grant #SMA-1041755
#NSF-REU DBI #1560061

Title: Levels-of-processing during memory encoding: An explanation for the other-race effect in face memory

Authors: *G. HERZMANN[1], T. CURRAN[2];
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Abstract: People are better at memorizing own-race than other-race faces. Previous research suggests that own-race faces are automatically memorized at a deep level (e.g., holistic), whereas other-race faces are memorized on a shallow level (e.g., less holistic or part-based). In the present study, we tested if instructions to encode own-race and other-race faces either deep or shallow modulated the other-race effect in face memory performance and ERPs related to memory encoding. In Experiment 1, Caucasian participants performed deep (Would you recognize this face in a crowded airport?) and shallow (Does this face have a small nose?) encoding tasks while studying Caucasian and African-American faces for later recognition. Experiment 2 included two groups of Caucasians: One group replicated Experiment 1, and the other group studied Caucasian and African-American faces without encoding instructions to

obtain measures of natural memory encoding. Shallow encoding reduced the other-race effect in face memory by making performance for own-race faces more similar to that of other-race faces, which did not differ from natural encoding. ERPs during memory encoding for shallowly encoded own-race faces matched that of natural as well as shallowly encoded other-race faces. This suggests that an encoding task that focuses on facial features mimics memory encoding naturally seen for other-race faces. Our hypothesis of naturally occurring deep encoding for own-race faces was not confirmed. Deeply encoded own-race faces showed better performance than naturally encoded own-race faces. ERPs during memory encoding showed a stronger involvement of frontal brain regions in the deep encoding of own-race faces, which was significantly different from natural encoding conditions. The current results suggest that the main contribution to the other-race effects is the naturally occurring shallow memory encoding of other-race faces. It also shows that memory for own-race faces can be increased with encoding instructions that emphasize holistic processing.

Disclosures: G. Herzmann: None. **T. Curran:** None.

Poster

698. Human Long-Term Memory: Encoding and Retrieval IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 698.19/BB37

Topic: H.02. Human Cognition and Behavior

Support: Fyssen Fellowship
Cortex Labex (NR-11-LABX-0042)
French ANR-11-IDEX-0007

Title: Neural oscillations in olfactory and memory regions predict episodic odor memory richness: Unraveling the Proust phenomenon

Authors: *A.-L. SAIVE[1], T. THIERY[2], E. COMBRISSON[3], J.-P. ROYET[4], S. GARCIA[4], S. RHEIMS[5], J. ISNARD[5], J. PLAILLY[4], N. RAVEL[4], K. JERBI[2];
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Abstract: Odors benefit from a unique access to memory, leading to particularly specific and detailed - *i.e.*, rich - memories. However, whether our ability to remember rich episodic odor memory depends on specific patterns of neural oscillations induced during the encoding and/or the retrieval has so far remained unknown. Here, using the unmatched spatiotemporal resolution of iEEG recordings and an objective graded memory richness score, we found that the richness of odor memory is primarily based on encoding rather than retrieval processing. At encoding,

single-trial increases in broad-band gamma [30-120 Hz] activity in frontal regions alongside decreases of theta [3-7 Hz] and alpha [8-13 Hz] activity in the olfactory regions and the hippocampus (HC) predicted subsequent odor memory performance. Moreover, theta and alpha decreases linearly predicted odor memory richness and significantly correlated with retrieval speed. In addition, temporal pattern similarity analyses revealed that the reinstatement of encoding neural patterns in the hippocampus at retrieval benefited the richness of episodic odor retrieval. In sum, our results provide critical evidence for an oscillatory neural code of episodic odor memory in which HC and olfactory regions can form rich multisensory associations at encoding that would be later reinstated via the HC.

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Poster

698. Human Long-Term Memory: Encoding and Retrieval IV

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 698.20/BB38

Topic: H.02. Human Cognition and Behavior

Support: Alfred P. Sloan Research Fellow in Neuroscience

Title: The intrinsic neonatal hippocampal network: rsfMRI findings

Authors: ***A. L. HOWELL**[1], D. E. OSHER[2], J. LI[2], Z. M. SAYGIN[3];
[1]Neurosci., [2]Psychology, [3]The Ohio State Univ., Columbus, OH

Abstract: The development of the hippocampal network likely plays a significant part in the emergence of the ability to form long-lasting memories. Many adults cannot voluntarily recall memories before the ages of 3-5, a phenomenon referred to as “infantile amnesia”, possibly due to an immature hippocampus/hippocampal network. An understanding of the hippocampal network at birth and its development may elucidate the brain mechanisms behind infantile amnesia. We studied resting-state hippocampal connectivity to 7 networks across the brain in neonates scanned within one week of birth (Developmental Human Connectome Project) and adults (Human Connectome Project). In adults, our results show the greatest hippocampal connectivity to the limbic and then default networks followed by the somatosensory, visual and dorsal attention networks and an anti-correlated (i.e. negative connectivity) pattern in both the ventral attention and frontoparietal areas; these findings are similar to that previously reported. The neonates, however, lacked a clear hierarchal pattern of connectivity to the seven networks. Moreover, there were no anti-correlated networks within the neonatal hippocampus. Next, we split the hippocampus into anterior and posterior portions to assess the long axis gradient of the

hippocampus. We found greater anterior (vs posterior) connectivity to the limbic, default and somatomotor networks and greater posterior connectivity to the dorsal attention, frontoparietal and ventral attention regions, again consistent with previous work. Neonates, however, showed no significant differences in the connectivity of the anterior vs. posterior hippocampus to the networks. Together, these results indicate that the neonatal hippocampal network and the long-axis specialization of the hippocampus are not mature at birth and the development of this connectivity may have implications for memory formation and infantile amnesia.

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Poster

699. Attention and Cognition

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 699.01/BB39

Topic: H.02. Human Cognition and Behavior

Support: ANR-15-CE37-0014-01
ANR-14-CE130005-01
Inserm
CNRS
Lyon 1 University

Title: Effects of the presence of a familiar peer on eye movements and attention

Authors: ***L. TRICOCHE**, J. FERRAND-VERDEJO, D. PÉLISSON, M. MEUNIER; CRNL Inserm CNRS UCBL, Lyon, France

Abstract: "Social facilitation or impairment" (SFI) refers to the enhancement or impairment of performance engendered by the mere presence of others. It has been shown for a diversity of behaviors. This study assessed whether SFI also affects attention and eye movements, and if so, which decision-making mechanisms are involved. Adult volunteers (19-35 years, n=79, 47 females) were tested using 3 tasks assessing eye movements (saccades), spatial attention (visual search), and sustained attention (continuous performance). Subjects were tested alone (n=39) or in the presence of a familiar peer (n=40). In the saccades task, subjects performed two separate blocks of pro- and anti-saccades (simple condition) or a single block of randomly-mixed pro- and anti-saccades (complex condition). In the visual search task, subjects pressed one of two keyboard keys to signal the presence or absence of a target among distractors presented simultaneously. In the continuous performance task, stimuli appeared one at a time mixing rare targets requiring a Go response with frequent distractors requiring a NoGo response. We measured either reaction times (RTs), percent errors (%Err), accuracy, duration, and peak velocity of saccades, or RTs and %Err of manual responses. The LATER model was used to

assess two decision making mechanisms in the saccadic and continuous performance tasks: threshold and rate of rise. The saccades task showed that SFI: 1) exists for eye movements (affecting mainly RTs); 2) is modulated by task difficulty (a majority of socially tested subjects were facilitated in the simple saccade condition and inhibited in the complex one). The two attentional tasks failed to show a significant group effect. However, the individual-level analysis suggests a social effect in most subjects but with an equal proportion of facilitated and inhibited subjects. The LATER model showed a change of both the threshold and the rate of rise in subjects affected by social presence. These findings demonstrate that SFI affects eye movements, and possibly attention, in a task complexity-dependent manner, by affecting two decision making mechanisms. They also stress the need for a better understanding of SFI individual variability to better predict the impact of social presence at school or work.

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Poster

699. Attention and Cognition

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 699.02/BB40

Topic: H.02. Human Cognition and Behavior

Title: Examining visual selection in children across levels of attentional ability

Authors: *J. KLEIN[1], A. COOK[1], H. ALLEN[2], J. CLIBBENS[1], E. MAVRITSAKI[1]; [1]Birmingham City Univ., Birmingham, United Kingdom; [2]Univ. of Nottingham, Nottingham, United Kingdom

Abstract: Successful goal-directed behaviour is contingent upon selectively processing relevant information at the expense of the irrelevant - a process commonly referred to as attention. Within the spectrum of human behaviour, there exists a wide range of attentional ability. This range includes impairment, such as typically seen in disorders like attention-deficit hyperactivity disorder (ADHD). The classic profile of ADHD is associated with alterations in the prefrontal cortex (PFC) as well as suboptimal functioning of the powerful neuromodulators dopamine (DA) and norepinephrine (NE). These alterations have previously been linked to problems in visual selection and orienting (Brennan & Arnsten, 2008). Previous work has shown that children with ADHD have difficulty allocating attention not only to specific locations in space (Mullane & Klein, 2008), but also to moments in time (Mason, Humphreys, & Kent, 2003). The present study compared three age and IQ-matched groups based on ADHD probability on performance in four visual search tasks. In single-feature search, targets differed from distractors by one feature (shape), while in conjunction search, targets were defined by a combination of two features (colour and shape) relative to distractors. In standard preview search, one set of

distractors appears 750 ms before the onset of a second set. Finally, in preview gap search, a 250 ms temporal gap is introduced between the two distractor sets after the initial 750 ms interval. Participants were grouped based on informant responses obtained from the Conners' 3 Parent Questionnaire (Conners, 2008) which determined whether they had a low (11-39%), borderline (40-60%) or high (61-99%) probability of ADHD. This allowed for an in-depth analysis of performance, where search efficiency is measured by reaction times and accuracy, as it relates to severity of symptoms. We discuss the implications for understanding differing profiles of impairment, calling attention to the need for more comprehensive measures in identification and aid for individuals with attention difficulties. References: Brennan, A. & Arnsten, A. (2008). Neuronal mechanisms underlying Attention Deficit Hyperactivity Disorder. Annals of the New York Academy of Sciences, 1129(1), 236-245. Conners, C. K. (2008). Conners 3rd Edition. Toronto: Multi-Health Systems, Inc. Mason, D., Humphreys, G., & Kent, L. (2003). Exploring selective attention in ADHD: visual search through space and time. Journal of Child Psychology and Psychiatry, 44(8), 1158-1176. Mullane, J., & Klein, R. (2008). Literature review: Visual search by children with and without ADHD. Journal of Attention Disorders, 12(1), 44-53.

Disclosures: J. Klein: None. **A. Cook:** None. **H. Allen:** None. **J. Clibbens:** None. **E. Mavritsaki:** None.

Poster

699. Attention and Cognition

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 699.03/BB41

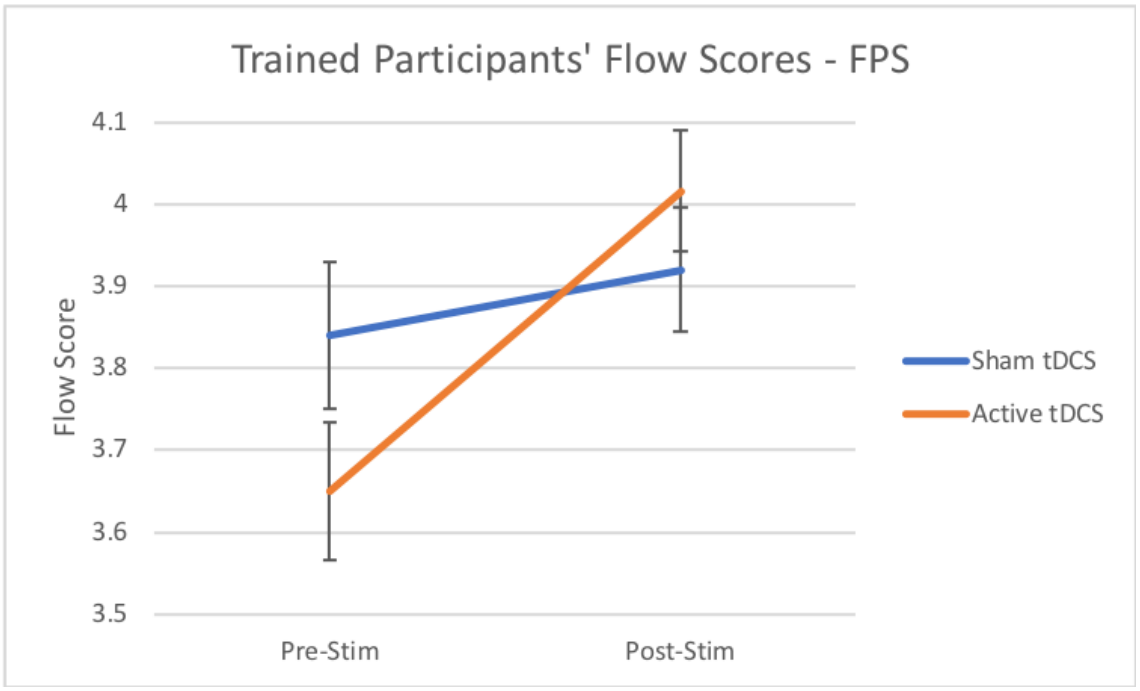
Topic: H.02. Human Cognition and Behavior

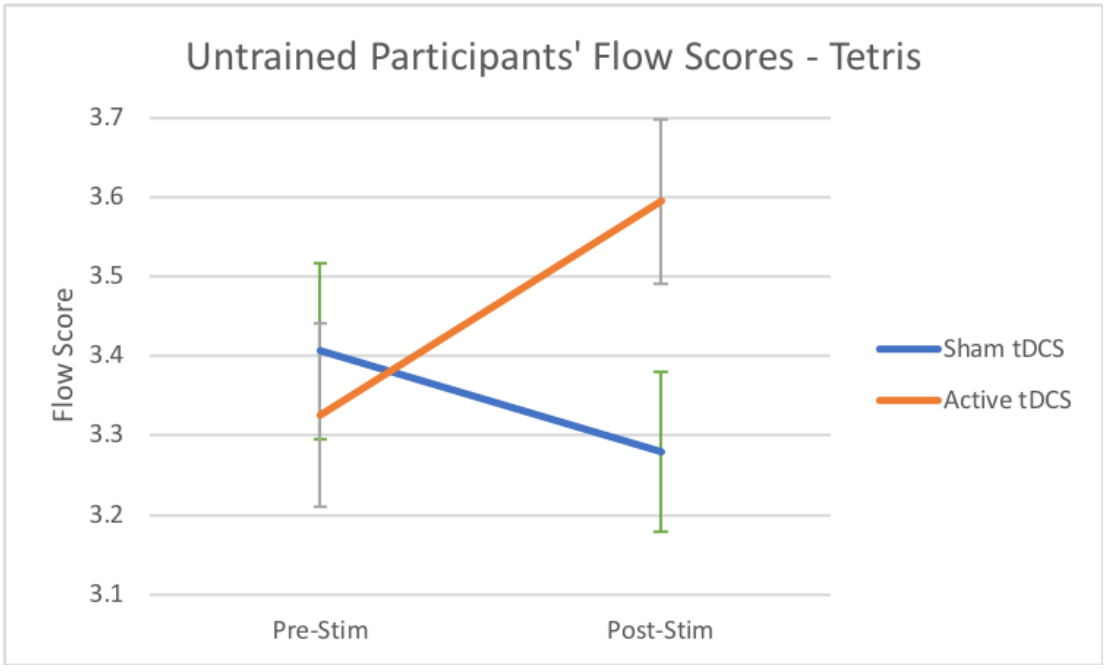
Title: A transcranial stimulation intervention to support flow state induction

Authors: *J. M. GOLD, J. CIORCIARI;
Swinburne Univ. of Technol., Melbourne, Australia

Abstract: Background: Flow states are considered a positive, subjective experience during an optimal balance between skills and task demands. Previously, experimentally induced flow experiences have relied solely on adaptive tasks. Objective: To investigate whether cathodal transcranial direct current stimulation (tDCS) over the left dorsolateral prefrontal cortex (DLPFC) area and anodal tDCS over the right parietal cortex area during video game play will promote an increased experience of flow states. Methods: Two studies had participants play Tetris or first-person shooter (FPS) video games while receiving either real tDCS or sham stimulation. Tetris recruited twenty-one untrained players who infrequently played video games while the ten FPS participants played FPS frequently. Flow experience was assessed before and after stimulation. Results: Compared to sham stimulation, real stimulation increased flow experience for both untrained Tetris and trained FPS players. No ceiling effects were noticed

between trained and untrained groups. Conclusion: Cathodal and anodal tDCS over the left DLPFC and right parietal areas respectively may encourage flow experiences in complex real-life motor tasks that occur during sports, games and everyday life.





Disclosures: **J.M. Gold:** None. **J. Ciorciari:** None.

Poster

699. Attention and Cognition

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 699.04/BB42

Topic: H.02. Human Cognition and Behavior

Title: Changes in resting state functional connectivity induced by one session mindfulness meditation

Authors: *Y. HOSHINO[1], N. YAMAYA[2], S. IKEDA[2], Y. HAMAMOTO[2], A. KOBAYASHI[2], R. KAWASHIMA[2];
[1]Fac. of Medicine, Tohoku University, Sendai, Japan, Sendai, Japan; [2]Inst. of Development, Aging and Cancer, Tohoku University, Sendai, Japan, Sendai, Japan

Abstract: One-session mindfulness meditation decreases mind wandering, which often occurs at rest and is associated with negative feelings. The effect of one-session meditation has been seen even in meditation novices. However, it remains unclear how functional brain activity during rest changes immediately after meditation in novices. We assumed that one-session meditation changes resting-state functional connectivity (RSFC) among brain regions. To test the hypothesis, we recruited 28 meditation novices. All subjects were randomly divided into a meditation group (n = 13) and a sham meditation group (n = 15). In the meditation group, subjects were instructed to focus on and count their breaths (i.e., Su-soku meditation) for 10 minutes. In the sham meditation group, subjects were instructed to relax and lie still in the scanner for 10 minutes (i.e., mind wandering). The subjects underwent resting-state fMRI immediately before and after the Su-soku/sham. In addition, we collected behavioral measures of mood, sleepiness (three time points: immediately before 1st fMRI scan, and immediately before and after meditation), and effort to meditation. The fMRI images were preprocessed using the CONN toolbox. RSFC between each pair of regions of interest was
assessed using the pre- and post-meditation fMRI data. RSFC changes were calculated by subtracting the pre- from the post-meditation RSFC. The RSFC changes were then statistically compared between the So-soku and sham groups using false discovery rate (q = 0.05). As a result, the Su-soku group showed increased functional connectivity within the cerebellar regions, between the cerebellum and the fusiform gyrus, between the supramarginal gyrus and fronto-parietal network and so on. Our findings may be supported by some previous studies. The cerebellum has been known to be associated with sustained attention, which represents the ability to maintain focus on a task and is enhanced by meditation. In addition, meditation induces structural changes in the fusiform gyrus. Therefore, the increased RSFC of the cerebellum and the fusiform gyrus may be supported by the previous findings. On the other hand, the supramarginal gyrus (a part of salience network) and fronto-parietal network play a key role in mediating internally and externally directed cognition. The increased RSFC between the

supramarginal gyrus and fronto-parietal network suggests that Su-soku facilitates a function of dynamically switching between internal and external attention according to task demands.

Disclosures: **Y. Hoshino:** None. **N. Yamaya:** None. **S. Ikeda:** None. **Y. Hamamoto:** None. **A. Kobayashi:** None. **R. Kawashima:** None.

Poster

699. Attention and Cognition

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 699.05/BB43

Topic: H.02. Human Cognition and Behavior

Title: Temporal changes in the state effect of meditation on executive function

Authors: *N. YAMAYA[1], S. IKEDA[1], Y. HOSHINO[2], H. TAKEUCHI[1], R. KAWASHIMA[1]; [1]Inst. of Development, Aging and Cancer (IDAC),Tohoku Univ., Sendai, Japan; [2]Sch. of Medicine, Tohoku Univ., Sendai, Japan

Abstract: One-session mindfulness meditation has been reported to temporarily enhance executive function, which is referred to as state effect. However, it remains unclear how the state effect changes over time immediately after a meditation session. Based on previous findings, we hypothesized that the state effect lasts for at least 20 minutes and decreases with time. To test the hypothesis, we focused on the state effects of two meditations: Su-soku and sham meditations (i.e., mind-wandering). The Su-soku meditation was performed by focusing on and silently counting one's breaths. The sham meditation was performed by relaxing and keeping still. We recruited 39 healthy right-handed participants; 11 participants were excluded from the analysis for failing to complete the entire experiment. The participants were instructed to perform each meditation for ten minutes in the meditation session. To evaluate the temporal changes in the state effect on executive function, the participants performed the Stroop task at the following five time points: immediately before and after each mediation, 20, 40, and 60 minutes after each meditation. The Stroop interference (i.e., the response time of incongruent minus neutral) was used to evaluate executive function. In addition, the participants were asked to answer subjective assessments: mood scale (all the time points), effort to each meditation, and sleepiness (immediately before and after each meditation). The Stroop interference and the mood scale were analyzed across two within-subjects factors (1st factor: Su-soku/sham, 2nd factor: all the time points), using two-way repeated-measures analysis of variance. The effort and sleepiness were compared between Su-soku and sham using the Wilcoxon signed-rank test. In the Stroop interference, we observed a statitstically significant interaction effect as expected [$F(4, 108) = 2.921$, $p = 0.02$]. As a post-hoc test, we examined differences between Su-soku and sham at each timepoint using the Wilcoxon signed-rank test. Contrary to our expectations, Su-soku showed better Stroop interference than sham only at 60 minutes after the meditation ($Z = -2.437$,

p = 0.015, medium effect size r = -0.46). On the other hand, we observed no significant interaction effect in the mood and no significant differences in the effort and the sleepiness. Therefore, the significant differences of task performance between Su-soku and sham cannot be explained by effects of the mood, effort, and sleepiness. Although the obtained results were inconsistent with our hypothesis, the results suggest that Su-soku showed stable task performance even 60 minutes after the meditation compared to sham.

Disclosures: **N. Yamaya:** None. **S. Ikeda:** None. **Y. Hoshino:** None. **H. Takeuchi:** None. **R. Kawashima:** None.

Poster

699. Attention and Cognition

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 699.06/BB44

Topic: H.02. Human Cognition and Behavior

Title: Resting state functional connectivity of the amygdala and bed nucleus stria terminalis (BNST) in response to threat bias

Authors: *S. K. JENKS[1], C.-S. R. LI[2], S. HU[1];
[1]Dept. of Psychology, SUNY Oswego, Oswego, NY; [2]Dept. of Psychiatry, Yale Univ. Sch. of Med., New Haven, CT

Abstract: This study investigated the resting state functional connectivity (rsFC) of the amygdala and bed nucleus stria terminalis (BNST) in healthy controls (HC) and patients with anxiety-related disorders (PAD, ICD-9) performing a Dot-Probe task. Resting state functional magnetic resonance imaging (fMRI) data and behavioral data were obtained from the Nathan Kline Institute (NKI) - Rockland Sample. Eighty-three HC and 30 PAD performed a Dot-Probe task in which two faces appeared (neutral, threatening, or happy) on each side of the screen. A subsequent dot appeared on either side replacing the face, instructing a button press to the corresponding location. Threat bias was computed as the difference in reaction time (RT) of the response to the dot replacing neutral faces and that replacing threatening faces (i.e., RT in neutral - RT in threat). A positive threat bias indicates faster response to the dot replacing threatening faces, a frequent observation in patients with anxiety disorders. We first compared whole brain rsFC of amygdala and BNST between the two groups. Compared to PAD, HC showed greater positive amygdala rsFC to the posterior cingulate cortex (PCC) and cerebellum, and greater positive BNST rsFC to the PCC; PAD did not show greater connectivity than HC at the same threshold. We then performed regressions between threat bias and rsFC of amygdala and BNST, respectively, in each group, with age as a covariate. HC showed amygdala-thalamus rsFC in positive correlation with threat bias, and PAD showed BNST-caudate rsFC in positive correlation with threat bias. On the other hand, HC did not show significant BNST rsFC and

PAD did not show significant amygdala rsFC in correlation with threat bias. Region of interest (ROI) analysis confirmed that the correlations between threat bias and amygdala-thalamus rsFC and between threat bias and BNST-caudate rsFC were significantly different between the two groups. These results suggest that the amygdala and BNST connectivities may represent important neural markers of anxiety disorders.

Disclosures: **S.K. Jenks:** None. **C.R. Li:** None. **S. Hu:** None.

Poster

699. Attention and Cognition

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 699.07/BB45

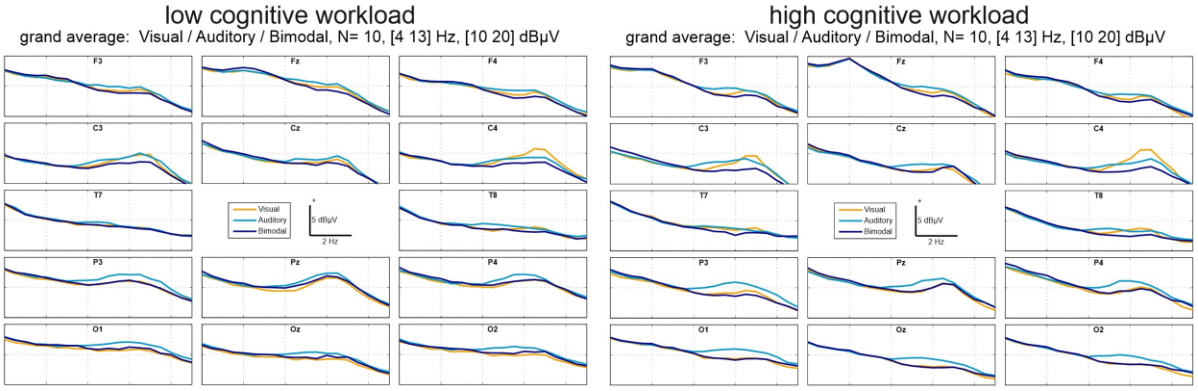
Topic: H.02. Human Cognition and Behavior

Title: Alpha and theta oscillations as a measure for cognitive workload - Why do they fail in certain settings and what do they really mean?

Authors: *D. MIKLODY, L. VAUTH, B. BLANKERTZ;
Technische Univ. Berlin, Berlin, Germany

Abstract: Using electroencephalography (EEG), higher cognitive workload is commonly linked to decreasing parieto-occipital alpha and increasing frontal theta oscillations also relevant in visual attention and working memory. In a series of studies, we investigated this connection in realistic scenarios. One study with a complex maneuvering task in a tug-boat simulator did not show a systematic alpha/theta effect. The alpha effect was also absent in an auditory n-back task during easy ship navigation, indicating that it is not a general measure of cognitive workload.
In the present study, we used the workload-inducing n-back task in a laboratory setting (N=10, ages 23 to 37, 6 female) in different modalities (auditory/visual/bimodal) while evaluating the effect on alpha and theta in EEG (32 channels) comparing the power spectral densities. We expected a modality-dependent effect on alpha.
We found a higher level of frontal theta for high rather than low workload for all conditions. Between the conditions, the only difference was in low workload a higher theta in bimodal than in auditory.
The alpha decreased with increasing workload for all conditions in parieto-occipital electrodes. Alpha was highest for auditory, followed by bimodal and lowest for visual-only conditions. Close to auditory processing areas, we observed a change in alpha with certain characteristics limited to auditory and bimodal. The effect was stronger in bimodal with lateralization at the peak (9Hz) more to the right while to the left for auditory. Differences are significant ($p<=0.05$).
In summary, the parieto-occipital alpha level commonly used for workload shows a weaker effect in the tasks involving auditory attention. Auditory attention has additional effects including decreased characteristic frequency.

This leads us to the conclusion that alpha and theta levels do not measure cognitive workload, but the processes of attention/suppression and working memory which are modulated by cognitive workload. With high workload, the differences between conditions decrease as attention/suppression is generally high.



Disclosures: D. Miklody: None. **L. Vauth:** None. **B. Blankertz:** None.

Poster

699. Attention and Cognition

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 699.08/BB46

Topic: H.02. Human Cognition and Behavior

Support: NCATS CTSA ULT1TR001436

Title: Population motor attention fields in human parietal cortex: Variation in pAFs predicts individual variation in behavior

Authors: *W. E. HUDDLESTON[1], A. S. GREENBERG[2], E. A. DEYOE[3];
[1]Kinesiology: Integrative Hlth. Care & Performance, Univ. of Wisconsin - Milwaukee, Milwaukee, WI; [2]Dept. of Psychology, Univ. of Wisconsin-Milwaukee, Milwaukee, WI; [3]Dept. of Radiology, Med. Col. of Wisconsin, Milwaukee, WI

Abstract: Attention shapes perception and action by modulating a network of hierarchical brain maps in specific topographic patterns (cortical “population attention fields”; pAF) that can provide predictive models of behavior if quantified at the individual level. Yet, we lack a comprehensive, quantitative account of attention-related brain mechanisms responsible for variable behaviors across individuals and modalities. We **hypothesize** that variations in motor pAF size would account for *individual differences* in the crowding limit across saccadic motor tasks in healthy individuals. We predicted that individuals with relatively narrow pAFs would

demonstrate more precise saccades than individuals with broad pAFs. Nine participants completed a delayed saccade task during fMRI at 7 Tesla (GE, Inc) while in-scanner eye movements were quantified. Our Attentional Drift Design (ADD) required participants to selectively attend to a centrally presented RSVP stream surrounded by a thin circular outline (radius 10°) representing clock positions on a circle. Every 4 seconds, a digit appearing in the RSVP stream cued the participant to prepare an accurate saccade to the indicated 'clock' location (e.g., 3 = 3:00). However, participants delayed saccade execution until a rarely presented 'X' appeared in the RSVP stream (approx. 5 times per run). The cued locations were incremented sequentially through 24 locations around the circle, creating a focus of motor attention (i.e., saccade intention) drifting through a saccade target map modulating the successive locations representing the intended saccade trajectories. Absolute errors in both the horizontal and vertical directions of initial saccade endpoints relative to the cued target location were correlated with motor pAF sizes in saccade-related maps. fMRI data from the ADD task were used to constrain a model of the size and shape of the focus of attention, the voxel's motor pAF. Preliminary data demonstrate a trajectory-specific relationship between parietal motor pAF diameter and saccade accuracy across participants, suggesting that parietal cortex is critical for the observed behavioral limitations. Establishing a firm, predictive link between brain mechanisms and behavior will ultimately lead to a more "evidence-based" framework for diagnosing, managing, and even ameliorating attention-related deficits such as hemispatial neglect or Alzheimer's Disease.

Disclosures: W.E. Huddleston: None. **A.S. Greenberg:** None. **E.A. DeYoe:** None.

Poster

699. Attention and Cognition

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 699.09/BB47

Topic: H.02. Human Cognition and Behavior

Support: RO1 MH112737
R21 DA042271
R21 AG056958
R21 MH113018

Title: Deep learning applied to spectral ERP data for ADHD discrimination

Authors: *L. DUBREUIL-VALL[1,2], G. RUFFINI[2], J. A. CAMPRODON[1];
[1]Massachusetts Gen. Hospital, Harvard Med. Sch., Boston, MA; [2]Neuroelectrics, Cambridge, MA

Abstract: Background: Attention deficit hyperactivity disorder (ADHD) is a heterogeneous neurodevelopmental disorder that affects 5% of the pediatric and adult population worldwide.

The diagnosis remains essentially clinical, based on history and exam, with no available biomarkers. On the other hand, machine and deep learning systems have been increasingly used in clinical applications with promising results in prognosis and diagnosis applications. **Methods:** In this paper, we describe a deep convolutional neural network (DCNN) for ADHD classification derived from the time-frequency decomposition of electroencephalography data (EEG), particularly of event-related potentials (ERP) collected from 20 ADHD adult patients and 20 healthy controls (HC) while they performed the Eriksen-Flanker task. For comparison purposes, we trained another DCNN with a dataset of spontaneous EEG data recorded while the same subjects and ADHD patients were at resting state with eyes closed. **Results:** The DCNN model reaches a classification accuracy of 88%, superior to other deep learning approaches and superior to resting state EEG spectrograms, with the key advantage of avoiding the need for manual selection of EEG spectral or channel features. Through the use of feature visualization techniques, we show that the main features exciting the DCNN nodes are a decreased power in the alpha band and an increased power in the delta band around 100ms for ADHD patients compared to HC, suggestive of attentional and inhibition deficits, which has been previously suggested as a neurophyisiological signature of ADHD. **Discussion:** In this study we present a viable deep learning model for effective discrimination of patients with ADHD, providing a new tool for the analysis of EEG dynamics in ADHD and supporting the potential of deep learning strategies for biomarker development in neuropsychiatry. While confirmation with larger clinical samples is necessary, these results highlight the potential of this methodology to develop CNS biomarkers of practical clinical utility.

Disclosures: L. Dubreuil-Vall: A. Employment/Salary (full or part-time):; Neuroelectrics Corporation. **G. Ruffini:** A. Employment/Salary (full or part-time):; Neuroelectrics Corporation. **J.A. Camprodon:** F. Consulting Fees (e.g., advisory boards); Apex Neuroscience.

Poster

699. Attention and Cognition

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 699.10/BB48

Topic: H.02. Human Cognition and Behavior

Title: Neural processing of unattended spatial locations predicts the detection of attended visual targets

Authors: *C. LUO, N. DING;
Zhejiang Univ., Hangzhou, China

Abstract: Individuals vary in their ability to detect visual targets in a complex visual scene. Here, we use EEG to investigate potential neural correlates of individual performance during a visual target detection task. In the experiment, colored circles are presented in a circular

grayscale background. The background is either simple, i.e., a gray screen, or complex, i.e., a grayscale cartoon movie and is divided into a central region and a peripheral region, which fluctuate with distinct time signatures. The circles are either purple or yellow, presented at random times in the random position of the central region and peripheral region. The participants are requested to press a button as soon as possible when a target circle (yellow circle) appears in the central region of the background. We analyze the event-related potentials (ERP) evoked by the colored circles and by the fluctuations of the central/peripheral regions of the visual background. It is found that when the background is complex, the detection accuracy is lower, the reaction time is longer, and the P300 response evoked by the visual target is weaker. In the complex background condition, both the P300 amplitude and the ERP evoked by peripheral fluctuations in the visual background can predict individual detection performance (both the detection accuracy and the reaction time). Importantly, the P300 and the peripheral ERP response capture different neurophysiological processes in the detection task so that jointly considering these two factors can better predict individual performance. These results suggest that the individual ability to detect visual targets in a complex visual scene is modulated by visual processing in both the attended visual region and the unattended visual region.

Disclosures: C. Luo: None. **N. Ding:** None.

Poster

699. Attention and Cognition

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 699.11/BB49

Topic: H.02. Human Cognition and Behavior

Support: The Landis-Berkman Family Fund

Title: Qigong movement meditation impacts neural correlates of attention and sensorimotor function in a population with cancer-related fatigue: A pilot clinical trial

Authors: *S. TEMEREANCA[1], C. S. ZIMMERMAN[2], D. DANIELS[1], B. CULLEN[2], H. HUGHES[3], T. CANNONIER[1], C. E. KERR[2], S. R. JONES[1];
[1]Dept. of Neurosci., Brown Univ., Providence, RI; [2]Warren Alpert Med. Sch. of Brown Univ., Providence, RI; [3]Fordham Univ., Bronx, NY

Abstract: Movement meditation training has been associated with health benefits, yet little is understood about the underlying brain-body mechanisms. Qigong, a form of movement meditation, combines low-impact body movements with meditation, training the mind to focus and engage those movements. In this pilot randomized controlled clinical trial, we test whether ten-weeks of Qigong training is not inferior to an exercise-nutrition control program in reducing fatigue (via the FACIT-Fatigue Questionnaire) in 48 female cancer survivors with cancer-related

fatigue (CRF). The study employs multi-modal physiological measures of brain, cardiorespiratory, muscle dynamics, as well as inflammatory immune markers as secondary outcomes. Here we focus on treatment effects on sensorimotor function assessed using simultaneous electroencephalography (EEG) and electromyography (EMG) during a tactile discrimination task and a precision grip task. We found that Qigong is not inferior to the exercise-nutrition program in improving fatigue in cancer survivors, with both interventions significantly reducing fatigue. Consistent with previous research, in both groups, cued-attention modulated beta (15-29 Hz) power measured from EEG electrodes over the sensorimotor cortex, showing decreased power 400-1000 ms after attention was cued to the contralateral hand and increased power after attention was cued to the ipsilateral hand. Further, while both therapies impacted attentional modulation of beta power, these changes occurred in opposite directions, with larger post-treatment attentional modulation of beta in one group and smaller in the other. No consistent attentional modulation of alpha (7-14 Hz) power occurred at the population level before or after treatments, albeit changes in alpha activity were measured in several individual subjects. Ongoing analysis examines the impact of treatment on the EMG activity as well as EEG-EMG beta corticomuscular coherence. This study helps identify potential EEG biomarkers of physiological effects of movement therapy on sensorimotor function and attention. Effect size estimates derived here will be used for sample size determination in subsequent clinical trials.

Disclosures: S. Temereanca: None. **C.S. Zimmerman:** None. **D. Daniels:** None. **B. Cullen:** None. **H. Hughes:** None. **T. Cannonier:** None. **C.E. Kerr:** None. **S.R. Jones:** None.

Poster

699. Attention and Cognition

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 699.12/BB50

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant 1F31AT010299-01

Title: The effect of mindfulness-based cognitive therapy on event-related potential markers of attentional bias in anxiety

Authors: *R. S. GUPTA[1], D. M. FRESCO[2], A. BERNSTEIN[3], H. KANG[4], E. M. MOHR[4], P. L. A. SCHOENBERG[4], D. R. VAGO[5];
[1]Vanderbilt Univ., Nashville, TN; [2]Kent State Univ., Kent, OH; [3]Univ. of Haifa, Haifa, Israel; [5]Physical Med. & Rehabilitation; Psychiatry & Behavioral Sci., [4]Vanderbilt Univ. Med. Ctr., Nashville, TN

Abstract: Anxiety disorders are associated with attentional bias to threat, which refers to differential attentional allocation towards threatening stimuli relative to neutral stimuli. Anxious

individuals direct their attention toward threat during early, automatic stages of processing, whereas during later, more strategic stages of processing, they tend to direct their attention away from threat. Attentional bias may prolong anxiety states by placing inordinate priority on potential threats in the environment, thus intensifying anxious mood states. Using a dot-probe (DP) paradigm, Mueller and colleagues (2009) observed that individuals with social anxiety disorder display enhanced P1 event-related potential (ERP) component amplitudes to angry–neutral versus happy–neutral face pairs, suggesting early hypervigilance to angry faces, and decreased P1 amplitudes to probes replacing emotional (angry and happy) versus neutral faces, suggesting reduced visual processing of emotionally salient locations at later stages of information processing—potentially a manifestation of attentional avoidance. In their mindfulness model, Vago and Silbersweig (2012) propose that meditation improves the control of attention by improving efficiency of engagement and disengagement processes, thereby reducing bias of attention. This study investigates the effects of Mindfulness-Based Cognitive Therapy (MBCT) on P1 ERPs time-locked to angry-neutral and happy-neutral face pair cues and probes in a DP task with anxious populations. Individuals with moderate to high levels of trait anxiety (n=42) will be recruited. Before and after MBCT, P1 amplitudes and latencies to cues and probes will be monitored. In our preliminary pre-MBCT data, we observed (1) longer P1-cue latencies to angry-neutral and happy-neutral face pairs, (2) larger P1-cue amplitudes for angry-neutral versus happy-neutral face pairs, (3) larger P1 amplitudes to probes replacing angry versus neutral faces, and (4) larger P1 amplitudes to probes replacing happy versus neutral faces. However, in our preliminary post-MBCT data, we observed (1) shorter P1-cue latencies to angry-neutral and happy-neutral face pairs, (2) larger P1 amplitudes for happy-neutral versus angry-neutral face pairs, (3) larger P1 amplitudes to probes replacing neutral versus angry faces, and (4) larger P1 amplitudes to probes replacing happy versus neutral faces. These preliminary results suggest that mindfulness targets and decreases threat-related attentional bias, leading to faster processing of emotional faces and more attentional allocation to non-threatening faces.

Disclosures: **R.S. Gupta:** A. Employment/Salary (full or part-time):; Osher Center for Integrative Medicine. **D.M. Fresco:** None. **A. Bernstein:** None. **H. Kang:** None. **E.M. Mohr:** A. Employment/Salary (full or part-time):; Osher Center for Integrative Medicine. **P.L.A. Schoenberg:** A. Employment/Salary (full or part-time):; Osher Center for Integrative Medicine. **D.R. Vago:** A. Employment/Salary (full or part-time):; Osher Center for Integrative Medicine.

Poster

699. Attention and Cognition

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 699.13/BB51

Topic: H.02. Human Cognition and Behavior

Support: Swedish Research Council

Title: Leftward bias in visuospatial attention during a non-conscious working memory task

Authors: *T. PEDALE[1], A. FONTAN[1], F. GRILL[1], F. BERGSTRÖM[2], J. ERIKSSON[1]; [1]Dept. of Integrative Med. Biol., Umeå Univ., Umeå, Sweden; [2]Coimbra Univ., Coimbra, Portugal

Abstract: A critical feature of working memory is the ability to retain task-relevant information while discarding task-irrelevant information. Previous research has demonstrated that also non-conscious information can be maintained and affect subsequent behavior. However, little is known about the possibility to prioritize and maintain non-conscious task-relevant stimuli and the neural correlates supporting this process. Here, during fMRI, we used continuous flash suppression to present stimuli non-consciously while participants performed a delayed match-to-sample task in which the task relevance of the stimuli was manipulated. An unexpected finding was that the behavioral performance was significantly better than chance when the non-conscious task-relevant targets were presented in the left visual field. This asymmetry was also supported at the neural level; multivariate pattern analyses of the BOLD signal in the occipital cortex were better at classifying the presence versus absence of the non-conscious stimuli when the targets were presented in the left than in the right visual field. Such behavioral and neural asymmetries are in agreement with the pseudo-neglect phenomenon in healthy subjects, consisting of a leftward bias in visuospatial attention. The asymmetry could be explained by different contributions of right and left parietal regions during attentional tasks. We hypothesize that the leftward bias could be evident specifically for non-consciously presented information, due to a reduction in crosstalk between hemispheres during non-conscious processing. Further fMRI analyses may help us to clarify the neural mechanisms supporting such attentional asymmetry during non-conscious working-memory tasks and possibly confirm the different contributions of the right and left parietal attentional regions during the prioritization of non-consciously perceived information.

Disclosures: T. Pedale: None. **A. Fontan:** None. **F. Grill:** None. **F. Bergström:** None. **J. Eriksson:** None.

Poster

699. Attention and Cognition

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 699.14/BB52

Topic: H.02. Human Cognition and Behavior

Support: MOST 107-2622-8-002-009-TA

Title: Are you concentrating or mind-wandering? Electroencephalogram signals reveal differences in attentional states

Authors: *H.-H. LEE[1], C.-Y. SHIH[2], Z.-L. CHEN[3], A.-Y. WU[2], S.-L. YEH[1];
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Abstract: When performing tasks, sustained attention is necessary for us to focus on the ongoing task and ignore irrelevant thoughts during information processing. However, technological advancement nowadays leads to the current era of distraction that people spend nearly half of the time mind-wandering. This might cause devastating effects while operating machines or jeopardize the efficiency of learning. Attentional training to regain sustained attention for longer time is thus imperative. The first step, then, is to detect the current attentional state. Participants were recruited to conduct the sustained attention to response task (SART) while their brain waves were recorded by 32-channels electroencephalogram (EEG). They were instructed to press the button as quickly as possible when they saw a letter (randomly selected from A to Z) except for the letter "C" that required them to withhold the response (stop trials). A probe question was presented at the end of each run, asking participants to rate how concentrated they were just now with a 7-point Likert scale. By analyzing the 10-second time window of FP1, FP2, and Fz channels in alpha, beta, theta, and gamma band powers prior to the target C and the probe question, we found different frequency powers in self-rated focused and non-focused state: higher powers in alpha, beta, and theta band for the self-rated focused state compared to the non-focused state. However, no such difference was found in the powers between the successful stop and fail-to-stop trials. This study suggested that EEG signals could be served as a predictor for states of sustained attention and could be further utilized in educational occasions such as distance learning to monitor students' attentional state instantly. The different patterns of brain responses found for subjective and objective measures of sustained attention indicate different underlying mechanisms of sustained attention with or without awareness.

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Poster

699. Attention and Cognition

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 699.15/BB53

Topic: H.02. Human Cognition and Behavior

Title: Dynamics of posterior hemispheric activity related to variable vs static cue-target interval

Authors: *A. DREW[1], K. GRAY[1], A. T. KARST[2];
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Abstract: The N2pc ERP component has been labeled as a marker of visual attentional selectivity because it is elicited when a participant attends to a stimulus in a lateral portion of the

visual field (Eimer, 1996). However, researchers debate what specific aspect of visual selectivity is driving the hemispheric differences in neural activity underlying the N2pc. One perspective holds that the localization of relevant information triggers these hemispheric differences (Drew & Karst, 2019; Tan & Wyble, 2015). The current work investigates static and variable intervals between a spatial cue and a target, with regard to subsequent N2pc observations. Two experiments asked participants to identify numbers amid letters presented in a dual rapid serial visual presentation paradigm. In Experiment 1, a spatial cue occurred immediately prior to the number target, and indicated the location of an upcoming target. In Experiment 2, a spatial cue occurred either immediately prior to the number target, or 700ms prior to the target. Experiment 1 showed that N2pc activity was present for cues presented in isolation, and cues that preceded targets, whereas targets presented after a cue did not elicit N2pc activity. This result supports the notion that spatial processing is driving activity giving rise to the N2pc. Experiment 2 demonstrated that when cue-target intervals are uncertain, the N2pc elicited by cue stimuli is altered. Specifically, when cues immediately precede targets, the N2pc is extended in latency such that mean amplitudes for both target and cue epochs represent an observed N2pc component. When cues are presented in isolation, or preceding targets by 700ms, an N2pc is observed with a more standard latency. These results comply with episodic models of visual attention which posit flexibly-gated selection mechanisms that operate on a time-course consistent with observations from the present studies (Wyble, Bowman, & Nieuwenstein, 2009).

Disclosures: **A. Drew:** None. **K. Gray:** None. **A.T. Karst:** None.

Poster

699. Attention and Cognition

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Program #/Poster #: 699.16/BB54

Topic: H.02. Human Cognition and Behavior

Support: EPSRC-Jaguar Land Rover TASCC project grant

Title: The effect of perceptual load on neural oscillations in multi-target visual search with free eye-movements

Authors: *A. M. HARRIS[1], J. O. EAYRS[1], O. JENSEN[2], N. LAVIE[1];
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Abstract: Visual attention has been linked to neural oscillations in multiple frequency bands, in particular, modulations of ~10 Hz alpha amplitude and the phase of ~5 Hz theta oscillations. Alpha amplitude reflects the degree of cortical inhibition, with attention-related changes linked to neural gain modulation (e.g., Iemi et al., 2017) and gating of neural information flow (Jensen

& Mazaheri, 2010). Theta phase has also been strongly linked to attention, with recent work proposing theta oscillations reflect cyclic changes in neural signal enhancement (Fiebelkorn & Kastner, 2018). The relationship between these signals and attention has typically been ascertained as a comparison between attended and unattended conditions, however, attentional allocation is not all or none. Prior work has demonstrated that the degree of attentional engagement varies with the perceptual load of a task (Lavie & Cox, 1997). When perceptual load is low (e.g., during simple feature search) attention is engaged to some extent, however, when perceptual load is high (e.g., during conjunction search) attention is engaged more strongly. Here we asked how the amplitude and phase of neural oscillations were modulated by the degree of attentional engagement required to perform a multi-target visual search with free eye-movements. Participants searched for targets defined by either a shape feature (low load) or conjunctions of shape and colour (high load). Level of attentional engagement was confirmed by comparing performance on an auditory detection task performed during the visual search. Tone detection was significantly impaired under high (vs. low) load, confirming the manipulation of attentional engagement. EEG responses co-registered to the onset of nontarget fixations revealed that high load search was associated with significantly lower tonic alpha power and significantly higher fixation-locked theta phase alignment than low load search. These results demonstrate that different attentional requirements recruit alpha-amplitude- and theta-phase-mediated attentional processes to different extents, consistent with their role in an attentional system that is engaged to differing degrees depending on task requirements.

Disclosures: **A.M. Harris:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Jaguar Land Rover. **J.O. Eayrs:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Jaguar Land Rover. **O. Jensen:** None. **N. Lavie:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Jaguar Land Rover.

Poster

699. Attention and Cognition

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 699.17/BB55

Topic: H.02. Human Cognition and Behavior

Title: Augmenting phasic norepinephrine activity with an irrelevant loud noise produces correlated increases in the amplitude of the P3 event-related potential, and the pattern of sparing and deficit observed in the attentional blink paradigm

Authors: *C. M. WARREN[1], A. S. HANCOCK[2], A. W. SNOWDEN[2], K.-D. TONA[3];
[2]Neurosci., [1]Utah State Univ., Logan, UT; [3]Psychology, Leiden Univ., Leiden, Netherlands

Abstract: Phasic norepinephrine (NE) release from the locus coeruleus (LC) transiently improves the signal-to-noise ratio of neural processing. NE has been linked to the accessory stimulus effect, whereby including an irrelevant tone simultaneously with a target stimulus typically improves performance through augmented phasic NE release (Tona, Murphy, Brown, & Nieuwenhuis, 2016). After a phasic release of NE, the LC undergoes a refractory-like period due to auto inhibition. This refractory-like period is a potential cause of a transient deficit in attention known as the attentional blink. The attentional blink refers to the phenomenon that when participants try to identify two targets embedded within a rapid serial presentation of distracter characters they exhibit a deficit for reporting the second target (T2) only within a very specific time-window relative to the first target (T1). If T2 falls less than 200 ms after T1, accuracy is high (termed "sparing"). If T2 falls >600 ms after T1, accuracy is normal. Only between 200 ms and 600 ms after T1, does T2 processing summer. This temporal profile shows a striking similarity to the temporal profile of phasic NE release, whereby processing benefits from a flood of NE within 200 ms, and then may suffer for a half second during the period of LC auto inhibition. We introduced an accessory stimulus consisting of an irrelevant loud tone to the attentional blink paradigm, to test if augmenting phasic NE release would affect the AB in a manner consistent with NE effects. The theory that the attentional blink is due to auto inhibition of the LC predicts that including an accessory stimulus simultaneously with T1 will (1) improve performance of T1, (2) improve performance of T2 when T2 is presented very close in time to T1, and (3) decrease accuracy for T2 if T2 is presented during LC auto inhibition. In addition, we recorded the electroencephalograph to examine a component of the event-related brain potential called the P3, which may be an electrophysiological manifestation of phasic NE. Analysis of data from 34 participants indicates that including a loud tone with T1 improved T1 performance, and improved T2 performance within 160 ms of tone onset, and this benefit to T2 switched to a deficit by 480 ms after tone onset. In addition, including the accessory stimulus increased the amplitude of the P3 component. Most importantly, the effect of the accessory stimulus on the attentional blink was correlated with the effect of the accessory stimulus on P3 amplitude. This experiment provides strong convergent evidence that phasic NE activity underlies the P3, the attentional blink, and the accessory stimulus effect.

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Poster

699. Attention and Cognition

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Support: CSIR fellowship (File No:09/821(0044)/2017-EMR-I)
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Ramalingaswami fellowship (BT/RLF/Re-entry/31/2011)

Title: Moving vs stationary: Do we attend to a 'pop-out' stimulus equally in both cases?

Authors: *P. GHOSH, D. ROY, A. BANERJEE;
Natl. Brain Res. Centre, Manesar, GURGAON, India

Abstract: The ability to detect and orient attention toward salient, significant changes around us is critical for survival. While we need focussed attention for any goal-directed behavior, the temporal component of attention becomes very important in conditions that demand rapid shift of attention like applying brakes during driving upon seeing a pedestrian suddenly crossing the road. This brings forth two concepts: top-down attention that is critical for any goal driven activity and bottom-up attention that involves a reorientation of attention toward an unexpected (salient) stimulus. In the latter, it is the 'pop-out' feature of the stimulus that demands a shift in attention from the ongoing task. But do the underlying neural signatures involved in this attentional shift remain same when we look at a static versus a dynamic stimulus?
Using a custom-designed behavioral paradigm and simultaneous high-density EEG, we investigated the effect of saliency during two different kinds of visual search: 1) where both the task and salient stimulus were static/stationary and 2) where both the task and salient stimulus were dynamic/moving. Data were collected from 22 right-handed healthy human volunteers (21-29 years, 11 females) who signed informed consent forms, approved by the Institutional Human Ethics Committee of NBRC, India.
We observed that along with a slower reaction time in trials with saliency, the spectral power in the alpha frequency band was also significantly higher as compared to the trials without saliency for both static and dynamic tasks. The increase in alpha power was very similar in both the task conditions. Although the deployment of attention for a static task is very different from that of a dynamic task, their spectral energy enhancement was similar upon the occurrence of saliency. The underlying sources of these enhanced alpha power were also similar. We observed that the anterior insula (part of salience network) and the ventral frontal cortex (part of ventral attention network) showed an increased activation in both dynamic and static tasks. Additionally, for the dynamic task there was activation in the right temporo-parietal junction (part of ventral attention network), which is activated in response to a behaviorally relevant stimulus. The salient stimulus used in the dynamic task, was behaviorally relevant to the task whereas in the static task it was not, suggesting that the sources contributing to the enhanced alpha power change with the type of salient stimuli associated but not with the task condition *per se*. Further studies on other sensory modalities can bring forth a more general role of alpha power in the brain beyond simple visual processing tasks.

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Poster

699. Attention and Cognition

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Program #/Poster #: 699.19/BB57

Topic: H.02. Human Cognition and Behavior

Support: FWF W1233

Title: Pre-stimulus alpha oscillations reflect eye dominance and bias object perception

Authors: *E. EL RASSI[1], D. ENGEMANN[2], N. WEISZ[3], V. VAN WASSENHOVE[4]; [1]Universirty of Salzburg, Salzburg, Austria; [2]INRIA, Paris, France; [3]Ctr. for Cognitive Neurosci., Univ. of Salzburg, Salzburg, Austria; [4]CEA.DSV.I2BM.Neurospin, Gif Sur Yvette, France

Abstract: Ongoing fluctuations in neural activity interact with perceptual processes. For example, the phase of pre-stimulus alpha oscillations influence whether a near-threshold target will be detected or not, and in perceptually ambiguous settings, changes in the power of alpha oscillations have been shown to counter-act individual priors or biases. Recent findings have suggested that serial order is one such individual bias such that people might be naturally biased towards perceiving an auditory or visual stimulus first. Consistent with this, it has been suggested that alpha power may regulate the timing of sensory inputs such that higher alpha power inhibits the structural prior/bias. In the present study we asked whether alpha dynamics could inform on a basic structural bias (eye dominance) and thereby predict subsequent perceptual outcomes. Specifically, at the onset of binocular rivalry, people are biased towards perceiving (first) the content shown to the dominant eye and then the content of the non-dominant eye. In this magnetoencephalography study, we presented human participants with an ambiguous image, briefly, and repeatedly. The image consisted of 2 gabor patches: each was either red or blue, and either right- or left-oriented. Participants wore red/blue glasses, looked at the image, and indicated its perceived orientation each time. Before the experiment, we determined each participant's dominant eye. We then could label MEG trials as a function of whether they were perceived with the dominant or non-dominant eye. We found evidence that higher pre-stimulus visual alpha power was needed to suppress the dominant eye compared to the non-dominant one.

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Poster

699. Attention and Cognition

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Program #/Poster #: 699.20/BB58

Topic: H.02. Human Cognition and Behavior

Support: Roberta K. Courtman Revocable Trust
NIH T32 GM007356

Title: Mobile brain/body imaging (MoBI) during systematic changes in cognitive load

Authors: *D. P. RICHARDSON[1], K. A. MAZUREK[2], N. ABRAHAM[2], S. HOFFMAN[2], S. MIZOBUCHI[2], J. J. FOXE[2], E. G. FREEDMAN[2];
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Abstract: Background Cognitive motor interference is thought to emerge as cognitive load exceeds an individual's ability to divide attention between coincident cognitive and motor tasks. This competition for limited neural resources erodes performance of either or both tasks, and is prominently demonstrated in individuals with executive function deficits. Task switching paradigms are sensitive interrogators of executive function. Task-set reconfiguration has been proposed as a mechanism for switching between the relevant tasks, though this transition exacts a toll in the form of a behavioral switch-cost. These costs manifest as increases in response times evident even in healthy young adults. Our group has previously described differential electrophysiological responses related to whether a trial was a task repetition, preceded a switch, or was a task switch. Utilizing electroencephalography (EEG) based Mobile Brain/Body Imaging, we studied cue-based task switching in healthy young adults while sitting and walking. We examined the effect of increasing cognitive load through the addition of a physical task upon the electrophysiological response to task switching. **Methods** 19 healthy young adults (18-22 years old) participated in a cue-based task switching experiment with pseudorandom task sequences while sitting or walking on a treadmill. Trials were composed of cues followed by a stimulus of gabor pairs differing in spatial frequency and rotation projected on a screen in front of the participant. Magnitudes of differences in spatial frequency and rotation between gabor pairs varied. Cues instructed subjects to identify either the gabor with higher spatial frequency, or the gabor rotated further clockwise. 64-Channel EEG, whole body motion capture, and behavioral performance were synchronously recorded. **Results** Electrophysiological alterations related to trial type (task repetitions, trials preceding a switch, or task switch trials) or physical state (sitting or walking) were identified in the cue-target interval. Moreover, alterations related to both trial type and physical state were identified in the cue-target interval. When task repetition trials containing correct responses were stratified by trial difficulty based upon group

performance, EEG alterations related to both trial difficulty and physical state were identified. These findings suggest altered cognitive processing of sensory information and decision making dependent upon the degree and modal quality of cognitive load. We will next explore the expression of cognitive motor interactions in task switching in healthy older adults, and older adults with cognitive impairments.

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Poster

699. Attention and Cognition

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 699.21/BB59

Topic: H.02. Human Cognition and Behavior

Title: The effect of musical engagement on auditory selective attention

Authors: *R. H. DYE, Jr, S. E. DARNELL, M. A. IZQUIERDO, D. VELASQUEZ, M. O. BONDI, A. M. SHELDON;
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Abstract: Musicianship has been found to enhance many cognitive abilities, including executive function, auditory memory, language processing, and selective attention. Most studies have compared groups of musicians and non-musicians, but musical engagement is a multidimensional construct consisting of at least music listening, musical instrument playing, and musical training. The goal of the current study was to identify which aspect of musical engagement was most associated with enhanced auditory selective attention. Participants (N=93) completed the Musical Use (MUSE) Survey (Chin and Rickard, 2012) to assess music listening, musical instrument playing, and musical training along with various styles of musical engagement. Auditory selective attention was assessed with a task in which listeners judged the direction of a level change of one of three concurrent components that were separated by 2 octaves (253, 1012, and 4048 Hz). Each component served as the target in different 200-trial blocks. The to-be-judged target component was presented alone in interval one, followed by all three components in intervals two and three. All three intervals were 300-ms in duration. Mean levels of each component in the second interval were set to 57 dB SPL, but each level was varied independently on each trial by adding a DL chosen from a Gaussian distribution with a mean of 0 and a standard deviation of 4 dB. The signs of the DLs were reversed in the third interval. Listeners reported whether the target component went up or down in level across intervals two and three, ignoring the levels of the other (distractor) components. A correlational analysis (Lutfi, 1995) was used to assess the relative weights given to each of the three components, the proportion of responses predicted from the weights, and proportion correct. The average target

weight (across the three target frequencies) was used as the metric of auditory selective attention. It was found that only index of musical instrument playing was significantly correlated with mean target weight (R=0.297). Passive listening and even musical training were not significantly correlated with mean target weight. Only actively playing a musical instrument enhances auditory selective attention.

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Poster

699. Attention and Cognition

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Program #/Poster #: 699.22/BB60

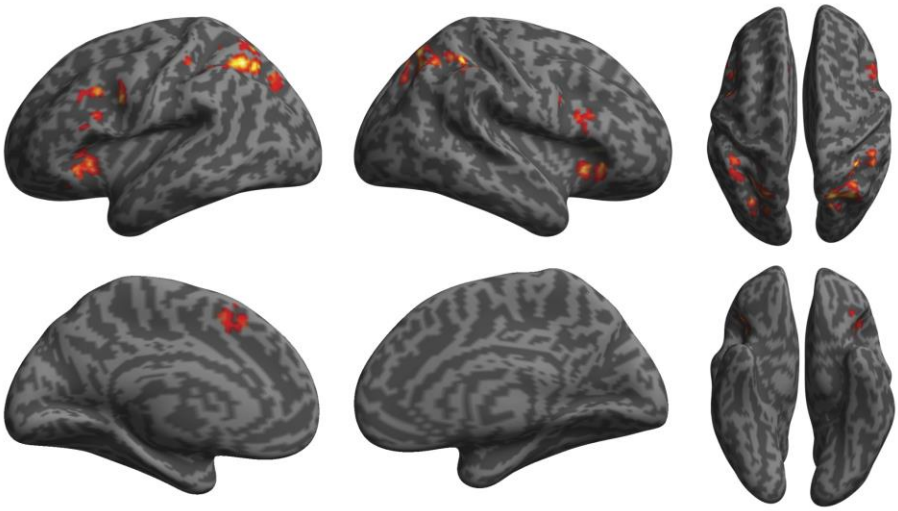
Topic: H.02. Human Cognition and Behavior

Title: Unveiling the mathematical brain: A meta-analysis of brain regions supporting complex arithmetic operations

Authors: *E. WEST[1], U. OFOEZIE[2], A. SPAGNA[2];
[1]Dept. of Psychology, Barnard College, Columbia Univ., New York, NY; [2]Dept. of Psychology, Columbia Univ., New York, NY

Abstract: Performing arithmetic operations is a fundamental aspect of human cognition, and math ability is a predictor of academic as well as professional success. Although the quest for the "mathematical brain" has persisted since the advent of non-invasive neuroimaging techniques, it has not yet revealed a clear map of the brain regions and networks underlying this basic cognitive function. To fill gaps in prior literature and determine the cognitive processes involved in varied mathematic operations, we conducted a large-scale meta-analysis of peer-reviewed publications which investigated the neural substrate of arithmetic using an activation likelihood estimation method (Ginger-ALE v2.3.6). This method calculates the overlap of activation across prior studies by modeling the activation foci as 3D Gaussian distributions centered at the reported coordinates. It estimates the variability of the spatial location of activation foci across different studies by accounting for the number of participants included in each study. Five-thousand permutations were conducted to generate the null distribution of the ALE scores as the random spatial overlap across studies, and the ALE map computed from the real activation coordinates was then tested against this null distribution, resulting in a statistical map representing the *p*-values of the ALE scores. The *p*-value threshold was defined as cluster-level corrected $p < 0.001$, with FDR corrected $p < 0.001$. Results showed a domain-general network of brain regions was activated when performing a variety of mathematical operations (addition, subtraction, multiplication, division, and comparison) and included regions commonly associated with cognitive control. Specifically, significant activation was found in six clusters, including the

superior parietal lobe bilaterally, the anterior insular cortex bilaterally, and the inferior frontal gyrus bilaterally. Results suggest that complex mathematical operations might rely on the activation of the cognitive control network, supporting a cognitive control model of human intelligence.



Disclosures: **E. West:** None. **A. Spagna:** None.

Poster

699. Attention and Cognition

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Topic: H.02. Human Cognition and Behavior

Support: NIH Grant U01AG062371

Title: Distraction hangover: Cognitive effects of distraction during simulated driving

Authors: *J. SNIDER[1], L. CHUKOSKIE[2], A.-M. ENGLER[4], S. HACKER[4], L. HILL[4], J. TOWNSEND[3];
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Abstract: That texting and driving is a dangerous combination comes as no surprise. Distracting a driver's attention from the road for even a few seconds is an accident waiting to happen, with more than 3000 deaths directly attributed to distracted driving in the US in 2017 (National Highway Traffic Safety Administration, 2018). Audio, hands-free communication may be a safer way to communicate with our devices than active texting, but it is unclear how distracting hands-free devices are.

The Center for Human Urban Mobility at UC San Diego augmented a driving simulator to test behavior with controlled levels of distraction. The simulator consists of an intuitive combination of a steering wheel, pedals, and screen-based simulation. In addition, we mounted a smart phone next to the simulator's steering wheel and programmed it to periodically ring or popup a text at preset locations in the simulated drive. For a hands-free call, participants accepted the call by touching the smartphone and responding vocally to a recorded question. During a text, an audio text sound alerted participants to read a short text message and respond to yes/no questions. We probed driving performance with a peripheral response task followed by a tailgating task, where participants maintained a constant distance to a lead car with a variable speed. Both tasks started with a baseline drive, without any phone distraction.

The primary behavioral outcome measures are percent correct in responding to the peripheral cue and speed coherence with the lead car during tailgating. In an initial cohort of 38 participants, we observed a significant drop in accuracy during distraction from 98.4(6)% to 88.3(6)% (mean(se), $F(1,37)=220$, $p<1e-10$) and a coherence drop from a respectable 0.50(3) to an abysmal 0.061(8) where some drivers even collided with the lead car ($F(1,37)=102$, $p<1e-10$). These are the expected distraction effects on driving, but interestingly hands-free and texting distraction modalities showed no significant difference in either main effect ($F(1,37)<0.2$, $p>0.65$) or interaction ($F(1,37)<0.5$, $p>0.48$). This is evidence that the distraction from a hands-free device is just as strong as reading a text.

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Poster

699. Attention and Cognition

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Topic: H.02. Human Cognition and Behavior

Support: NSF EPSCoR Award Number 1632738

Title: Volitional attention selectively enhances recognition memory

Authors: *K. ZIMAN, M. R. LEE, A. R. MARTINEZ, J. R. MANNING;
Dept. of Brain and Psychological Sci., Dartmouth Col., Hanover, NH

Abstract: Our attentional systems selectively filter aspects of ongoing experiences to optimize our behaviors. This filtering can also affect how we remember those experiences later: we may remember different aspects of the same perceptual experience depending on what we attended to. Here we used two novel variants of a Posner cueing task to study the effects of volitional attention on memory. In each trial, participants viewed two images (on the left and right of the screen, respectively) while fixating a central cross (verified using eyetracking data). Each image comprised a grayscale composite of a photograph of a face and an outdoor scene. In different blocks (Experiment 1) or individual trails (Experiment 2), participants were instructed to shift the focus of their attention, without moving their eyes, to either the face or scene component of either the left or right image. In this way, the participants' perceptual experiences were held (largely) constant throughout the experiment, but their volitional attention varied. We then asked all participants to perform a recognition memory task, where they rated a set of images according to how "familiar" they were (a proxy for how much the participants "remembered" each image). Half of the rated images were novel, and the remaining half of the images were drawn equally from the images we showed participants. Across both experiments, we found that attended images received a memory "boost" (i.e. higher familiarity). The opposite-category image from the attended-side image received a (smaller) memory boost. The category-matched image from the unattended side also received a (still smaller) memory boost. The unattended image on the unattended side was slightly suppressed relative to novel images (Experiment 1) or was indistinguishable from novel images (Experiment 2). Taken together, our results indicate that aspects of our experience that we attend to (or that share features or locations of attended aspects) are better remembered than unattended aspects of our experiences. In ongoing work, we are collecting neuroimaging data to study the neural basis of these phenomena. In particular, we are studying how the changing focus of volitional attention modulates the flow of information from primary sensory to memory areas.

Disclosures: K. Ziman: None. **M.R. Lee:** None. **A.R. Martinez:** None. **J.R. Manning:** None.

Poster

699. Attention and Cognition

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 699.25/BB63

Topic: H.02. Human Cognition and Behavior

Support: NIH-RO1-MH113855-01A1

Title: Pattern similarity in middle frontal gyrus reflects the target template during visual search

Authors: *X. YU, J. J. GENG;
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Abstract: Theories of attention commonly refer to the collection of target features in working or long-term memory as the "target template" (or "attentional template"). It is often assumed that the contents of the attentional template are veridical, but recent studies have found that it is adjusted to increase the target-to-distractor distinctiveness when distractors are similar to the target. However, it remains unclear where the biased target template is encoded in the brain (Scolari, Byers, and Serences, 2012). We investigated this problem using representational similarity analysis (RSA) of 20 healthy young adults' fMRI data. Subjects were asked to engage in a visual search "training" task, in which they searched for a target defined by color (e.g., blue-greenish), among three distractors with colors selected from one side of the target (e.g., greener). The target representation was measured on separate template "probe" trials, in which subjects reported if a single colored circle (e.g., ranging from blue to green) was target color or not. The behavioral results replicate previous findings that the target representation was shifted away from distractor color values, and sharpened to better exclude distractors (Yu and Geng, 2019). Subjects were also more accurate in the visual search when their templates were more distinct from distractors. A whole brain RSA searchlight was conducted using the pattern of probe trial responses as the behavioral representational dissimilarity matrix. The results identified bilateral middle frontal gyrus (MFG) and motor cortex as encoding an activation pattern correlated with the behavioral matrix. The same regions were activated during visual search, suggesting that MFG encodes the target template, which is shaped by the visual search context and reciprocally defines the relevant features for target selection.
Scolari M., Byers A., and Serences J. T. (2012). Optimal deployment of attentional gain during fine discriminations. *Journal of Neuroscience, 32*(22), 7723-7733.
Yu, X., and Geng, J. J. (2019). The Attentional Template is Shifted and Asymmetrically Sharpened by Distractor Context. *J Exp Psychol Hum Percept Perform, 45*(3), 336-353.

Disclosures: X. Yu: None. **J.J. Geng:** None.

Poster

699. Attention and Cognition

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 699.26/BB64

Topic: H.02. Human Cognition and Behavior

Support: Mission for Interdisciplinarity of the CNRS (Infiniti program "BrainTime")
Uruguay Agency of Research of innovation (ANII)
PharmaCog IMI

Title: Slowing-down of resting state dynamic functional connectivity as a marker of cognitive dysfunction induced by sleep deprivation

Authors: D. LOMBARDO, C. CASSE-PERROT, O. BLIN, *D. BATTAGLIA, M. DIDIC; INS, Univ. Aix-Marseille, Marseille, France

Abstract: A substantial evidence suggests that dynamic Functional Connectivity (dFC) during both rest and task conditions is an indicator of performing cognitive processing.The shift to a dynamic chronnectome perspective is however hampered by the lack of a consensus on which are the best approaches to estimate not-artefactual dFC. We have recently introduced the notion of dFC speed, quantifying in a time-resolved manner the rate at which brain-wide FC networks are changing from one time-window to the next. We thus describe dFC as a smooth flow across continually morphing connectivity configurations, rather than as a non-stationary sequence of sharp inter-state transitions. Here we probe the hypothesis that differences in resting state dFC speed correlate with differences in cognitive performance, at the whole-brain level but also selectively within specific functional subnetworks.

In particular, we concentrate on Sleep Deprivation (SD) as a reversible model of cognitive dysfunction, which has also been proposed as a cognitive challenge model of cognitive impairments arising in amnesic Mild Cognitive Impairment and Alzheimer's disease. We then study how 24 hs of sleep deprivation affect our novel dFC speed markers, in relation to cognitive performance.

We observe that the speed of reconfiguration of resting state whole-brain FC networks (global dFC speed) is significantly slowed-down by SD. However, the reduction in this global dFC speed only poorly correlate with cognitive performance variations. On the contrary, we show strong correlations between performance variations in various tasks, including a Rapid Visual Processing (RVP, which probe the capacity for sustained visual attention and its executive control) and dFC speed defined now at the level of specific functional sub-networks. Unlike global dFC speed analyses -in which information about where network changes are happening is lost, because the rate of change is averaged over the whole brain-, modular dFC speed allows quantifying a different speed of dFC reconfiguration independently for each different sub-network of interest. In particular, we find that performance in the RVP attentional task correlates with the modular dFC speed of a characteristic fronto-parietal functional module but not with global dFC speed.

Therefore our findings suggest that analyses of dFC speed variations are well able to detect the temporal reorganization of resting state FC fluctuations after SD. Furthermore, beyond mere changes in reaction time or vigilance, our quantifications of dFC variations robustly track the magnitude of the cognitive performance impairments induced by SD within each specific subject.

Disclosures: D. Lombardo: None. **C. Casse-Perrot:** None. **O. Blin:** None. **D. Battaglia:** None. **M. Didic:** None.

Poster

699. Attention and Cognition

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 699.27/BB65

Topic: H.02. Human Cognition and Behavior

Support: CONACYT grant No. 786315

Title: Neuropsychological profiles of a sample of Mexican pregnant women with and without LES

Authors: *D. CHINCHILLA[1], O. GALICIA-CASTILLO[1], C. CHAO[3], M. BUENROSTRO-JAUREGUI[2];
[1]Univ. Iberoamericana, Ciudad de México, Mexico; [2]Univ. Iberoamericana, Mexico, Mexico; [3]Universiad Iberoamericana, Ciudad de México, Mexico

Abstract: Introduction: Alterations in cognitive function are neuropsychiatric manifestations of systemic lupus erythematosus (SLE); they have been reported more frequently in women than in men. 81% of the healthy women that have been pregnant reported cognitive changes. **Objective:** Describe differences in cognitive function between healthy pregnant women and pregnant women with SLE. **Method:** A case-control study was carried out, including 50 participants, 29 women diagnosed with SLE and 21 healthy pregnant women. Neuropsychological and neurophysiological assessments were carried out between week 28-35 of gestation. **Results:** Pregnant patients with SLE presented mild to severe alterations in a 17.84% on the NEUROPSI scale; in MoCA test 40.47% presented scores below the cut-off point (≤ 26) with an average score of 23.57 ± 5.76. The P300 evoked potential reported averages of 297.3 ± 63.3ms and 3.89 ± 2.89mv in latency and amplitude respectively. Healthy pregnant women presented moderate to severe alterations in 20% of the NEUROPSI scale. 41.67% presented scores below the cut-off point with an average score of 23.28 ± 10.05 in the MoCA. In P300 evoked potential, the means in latency and amplitude were 294.4 ± 57.14ms and 5 ± 2.57mv. When we compared groups, we found statistically significant differences in the language sub-scale in the MoCA evaluation (t = 0.026). **Conclusion:** Both healthy pregnant women and with SLE presented alterations in cognitive function. The alterations found in pregnant women with SLE are similar to women with non-pregnant SLE previously reported. The language was the only cognitive function with alterations that showed statistically significant differences between the groups.

Disclosures: D. Chinchilla: None. **O. Galicia-Castillo:** None. **C. Chao:** None. **M. Buenrostro-Jauregui:** None.

Poster

699. Attention and Cognition

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 699.28/BB66

Topic: H.02. Human Cognition and Behavior

Support: R01 MH069456

Title: Attentional engagement of frontoparietal cortex in infant fMRI

Authors: *C. T. ELLIS, L. J. SKALABAN, T. S. YATES, N. B. TURK-BROWNE;
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Abstract: Goal-directed and stimulus-driven modes of attention remain difficult to disentangle because they interact contingently in natural settings. For instance, a typical task for investigating stimulus-driven attention requires responding as quickly as possible to event onsets; yet, in order to do this, a participant must maintain and execute task instructions. Often overlooked is the opportunity to use early development as a model system for distinguishing cognitive processes with different trajectories. In this case, infants are thought to lack adult-like goal-directed attention but have robust stimulus-driven attention, allowing us to isolate the neural underpinnings of stimulus-driven attention. In particular, reorienting spatial attention to new or unexpected stimuli engages the frontoparietal network in adults, but this same network is also involved in goal pursuit. Here we investigate whether the frontoparietal attention network is involved in stimulus-driven attention in infants even with diminished goal-directed attention. We used event-related fMRI with awake, behaving infants while they performed a child-friendly Posner cuing task. Peripheral cues were presented briefly to infants before a peripheral target appeared in the same (valid) or opposite location (invalid), as well as trials where cues appeared bilaterally (neutral). Eye-tracking was used to measure reaction time (RT), namely the time taken to saccade to the target. We found evidence of behavioral facilitation in two small samples of younger (4-7 months) and older infants (18-24 months), with faster RTs to valid vs. invalid targets. Initial fMRI analyses suggest that when attention is directed to the wrong location (invalid trials) there is greater activation throughout frontoparietal cortex, compared to valid and neutral trials. This suggests that the frontoparietal network can be engaged in stimulus-driven reorienting of attention even in infants. This also tentatively suggests that even young infants can rely on frontal brain regions to allocate attention. More generally, the field of infant cognition relies heavily on looking time measures, and this work starts to provide a mechanistic account of the behavior to help inform ongoing debates in that field.

Disclosures: C.T. Ellis: None. **T.S. Yates:** None. **L.J. Skalaban:** None. **N.B. Turk-Browne:** None.

Poster

699. Attention and Cognition

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 699.29/BB67

Topic: H.02. Human Cognition and Behavior

Support: NWO Vidi
NWO Vici

Title: Neural features associated with mind wandering: A simultaneous fMRI, EEG, and pupillometry study

Authors: *J. M. GROOT[1,2], N. M. BOAYUE[1], G. CSIFCSÁK[1], W. BOEKEL[3], R. HUSTER[4], B. U. FORSTMANN[2], M. MITTNER[1];
[1]UiT - The Arctic Univ. of Norway, Tromsø, Norway; [2]Univ. of Amsterdam, Amsterdam, Netherlands; [3]Erasmus Univ., Rotterdam, Netherlands; [4]Univ. of Oslo, Oslo, Norway

Abstract: Humans pervasively engage in shifting attentional focus from external demands toward internal processing of self-generated thoughts and feelings, irrespective of risking a loss of reward or causing crucial performance errors (Smallwood & Schooler, 2015). The brain network most strongly associated with mind wandering is the default mode network (DMN), showing increased activity during episodes of task-unrelated thoughts (TUT's; Fox et al., 2015). Additionally, the locus coeruleus/norepinephrine (LC/NE) system has been studied in relation to mind wandering, as it is thought to adaptively modulate neural gain of cortical neurons through tonic and phasic modes of operation (Aston-Jones & Cohen, 2005). However, the exact neural systems underlying task-related and task-unrelated attentional states and the mechanisms driving transitions between these states, as well as their temporal dynamics, remain largely unknown. Therefore, the purpose of this study was to resolve the spatio-temporal dynamics of TUT's in an attempt to explain how the interplay of neural systems gives rise to the subjective experience of mind wandering. Self-reported, probe-caught mind wandering was collected for 28 healthy adults during performance of the sustained attention to response task (SART) and simultaneous fMRI-EEG. Pupil diameter was recorded as a derivative for LC/NE tonic and phasic activity (Gilzenrat et al., 2010). Features of interest were extracted for each modality based on previous literature, including: activation in and connectivity between regions of the DMN and anti-correlated network (ACN); prestimulus alpha, beta, theta, and delta oscillations; event-related N1, P1, and P300 components; and baseline and evoked pupil dilation. This yielded a total of 87 features that were collectively fed into a support vector machine (SVM). Thought probe responses were used as target labels to train the SVM to help classify individual trials as either on- or off-task cognitive states, allowing subsequent analyses of neural signatures at the single-trial level. Preliminary results of classification performance show above chance level accuracy in

predicting episodes of TUT's. Unique contributions of each modality furthermore suggest that combining measures superior in conveying either temporal or spatial information improves predictive power. This indicates that multimodal classification enabling single-trial analyses may provide new and powerful means to gain mechanistic insights into the neural basis of attentional fluctuations.

Disclosures: **J.M. Groot:** None. **N.M. Boayue:** None. **G. Csifcsák:** None. **W. Boekel:** None. **R. Huster:** None. **B.U. Forstmann:** None. **M. Mittner:** None.

Poster

699. Attention and Cognition

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 699.30/BB68

Topic: D.07. Vision

Support: Stanford Neurosciences Institute

Title: Steady-state visual evoked potentials reveal parietal contributions to abstract numerosity

Authors: ***P. J. KOHLER**[1,2], B. D. MCCANDLISS[3], E. BARZEGARAN[2], A. M. NORCIA[2]; [1]Dept. of Psychology and Ctr. for Vision Res., York Univ., Toronto, ON, Canada; [2]Dept. of Psychology, [3]Grad. Sch. of Educ., Stanford Univ., Stanford, CA

Abstract: Steady-state visual evoked potentials (SSVEPs) are an EEG measure that can provide portable, high-signal-to-noise assays of cortical tuning to specific representations, and thus have high potential value for educational neuroscience. Fast periodic oddball stimulation is useful for isolating SSVEPs related to processing of complex stimuli such as faces, words, and objects (Norcia et al., 2015). When applied towards measuring cortical responses to abstract numerosity, the oddball technique has until now identified responses originating in early visual cortex (Park, 2018; Guillaume et al., 2018) rather than in parietal areas as indicated by functional MRI studies. Here, we address this discrepancy by exploring novel conditions, such as using equiluminent discs as stimuli, slower stimulation rates, and smaller quantities. In Experiment 1, arrays of 5 discs were presented, updating at a "carrier" frequency of 3, 3.75, or 6 Hz, with size, area, or density changing on each update. On half the trials, changes in numerosity (arrays of 8 dots) were introduced at a slower "oddball" frequency, ~1/6 of the carrier frequency (1 Hz, 0.75 Hz, or 0.5 Hz). After each trial (5 stimulus cycles), participants were asked if a number change had occurred. SSVEPs generated by the carrier frequency were centered over occipital cortex, consistent with visual responses to the array updates. By contrast, the oddball frequency produced parietal SSVEPs associated with changes in numerosity, evident as early as 200 ms after oddball onset. Slower frequencies produced the most reliable oddball responses, so we used the 3 Hz (carrier) and 0.5 Hz (oddball) frequency in additional experiments. In Experiment 2, we

compared number change events that were above the behavioral threshold for detecting a number change (i.e. carrier = 8 dots, oddball = 5 dots) or below threshold (carrier = 8 dots, oddball = 9 dots). Only the supra-threshold conditions produced parietal oddball responses, reflecting a "distance effect". Experiment 3 replicated the parietal oddball SSVEP effect across four distinct supra-threshold carrier-oddball pairings. Finally, we passed our stimuli through a two-stage model of early visual cortex responses (Kay et al., 2013), and found that although our disc arrays were well-matched on non-number dimensions, the model produced some evidence of dissociable responses to number-oddball arrays. These findings support the use of oddball SSVEPs for measuring parietal computations of number, but highlight that care must be taken to rule out the contribution of generic visual processing. A model-based approach to stimulus generation would be a helpful step in this direction.

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Poster

700. Attention Networks

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 700.01/BB69

Topic: H.02. Human Cognition and Behavior

Support: JSPS KAKENHI JP15K01391

Title: Prism adaptation changes resting state functional connectivity in the dorsal stream of visual attention networks in healthy adults

Authors: *K. TSUJIMOTO;
Univ. of Tokyo Hosp., Tokyo, Japan

Abstract: Unilateral spatial neglect (USN) can be defined as a failure to orient to contra-lesional stimuli in the absence of either sensory or motor defects. Although the behavioral and clinical effects of prism adaptation (PA) are widely accepted, its underlying mechanisms are still controversial. However, recent neuroimaging and neurophysiological studies support the idea that PA affects the visual attention and sensorimotor networks including in the parietal cortex and cerebellum. We investigate the effect of PA on functional connectivity (FC) in attention and sensorimotor networks, evaluating changes of resting-state FC before and after PA in healthy individuals using functional magnetic resonance imaging (fMRI). A total of 19 healthy participants (mean age 28.5 ± 5.5; 8 men and 11 women) took part in the study. The pointing tasks were performed four times throughout the entire session (baseline phase, prism adaptation phase, post prism adaptation phase (Post1), and 1 h after the post prism adaptation phase (Post2). The visual stimuli were displayed on a 25-inch monitor with a touch panel display. An optical

prism inducing a rightward shift with a 20-diopter was used for both eyes. The baseline phase was six pointing movements, without the prism. The prism adaptation phase consisted of 90 pointing movements with the prism. The Post1 and Post2 phases were both six pointing movements, without the prism. MR sessions were conducted before PA, after PA (Post1), and 1 h after PA (Post2). Functional images were acquired on a 1.5-T MR scanner. A seed-based correlation analysis was performed to investigate the FC in the attention network. We investigated the difference of FC in a Dorsal Attention Network (DAN) and Ventral Attention Network in the three phases. In addition, FEF and ACC are commonly coactivated for cognitive saccade tasks. During prism exposure, there was a significant pointing error in the first trial (3.03 ± 0.19 cm) to the right (that is in the direction for the displacement). In the Post1 phase, there was a significant pointing error (-2.08 ± 0.16 cm) to the left, which decreased in the Post2 phase (-1.08 ± 0.11 cm). The FC between the right frontal eye (FEF) field and the right intraparietal sulcus was significantly decreased at Post1 and that between the right FEF and the right anterior cingulate cortex was significantly increased after PA and recovered within 1 h. This is the first study to demonstrate transient changes of resting-state FC in the right DAN by PA in healthy adults using fMRI. These results will contribute to the elucidation of the underling mechanism of PA therapy and to devising new therapies for USN and/or other higher cortical dysfunctions.

Disclosures: K. Tsujimoto: None.

Poster

700. Attention Networks

Location: Hall A

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Program #/Poster #: 700.02/BB70

Topic: H.02. Human Cognition and Behavior

Support: NSF Grant BCS-1439188
NIH Grant MH117991

Title: Decoding visual spatial attention control

Authors: *S. MEYYAPPAN[1], A. RAJAN[1], J. J. BENGSON[2], G. R. MANGUN[3], M. DING[1]; [1]J Crayton Pruitt Family Dept. of Biomed. Engin., Univ. of Florida, Gainesville, FL; [2]Sonoma State Univ., Rohnert Park, CA; [3]Ctr. for Mind and Brain, Univ. of California Davis, Davis, CA

Abstract: Deploying anticipatory visual spatial attention in advance of stimulus onset enhances the processing of task-relevant stimuli and suppresses distraction. In this study, we investigated the neural representations of attention control signals in visual cortex by analyzing two fMRI datasets, one recorded at University of Florida (n=13) and the other at University of California, Davis (n=18), using machine learning techniques. In both datasets, the participants performed a cued visual spatial attention task, in which each trial began with a visual cue at fixation that

instructed the subject to either attend the left or the right visual hemifield. After a random delay, a grating (Gabor patch) was presented in one of the two hemifields, and the subject was asked to discriminate the spatial frequency of the grating in the attended hemifield and ignore the grating if appearing in the un-attended hemifield. We estimated cue-evoked fMRI responses and applied multi-voxel pattern analysis (MVPA) to multiple ROIs within the visual cortex. We found that: (1) Accuracy of decoding attend-left versus attend-right was significantly above chance in all the ROIs within the visual cortex (average accuracy=65%), (2) The decoding accuracy was highly correlated across different visual ROIs, with 80% of the variance explained by the first principal component, and (3) Subjects with higher decoding accuracy performed better on the task as indexed by lower inverse efficiency measures (response time/response accuracy). These results, consistent across the two datasets, suggest that (1) attention control signals are present in both high order (e.g., intra-parietal sulcus) as well as low order visual areas (e.g., primary visual cortex) and (2) the distinctness of the neural representations of attention control in visual cortex is a trait that explains individual differences in task performance.

Disclosures: **S. Meyyappan:** None. **A. Rajan:** None. **J.J. Bengson:** None. **G.R. Mangun:** None. **M. Ding:** None.

Poster

700. Attention Networks

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Topic: H.02. Human Cognition and Behavior

Support: The National Key Research and Development Program of China (2017YFB1002502)
Natural Science Foundation of China (Grant Nos. 81471368, 31571003, U1636121, and 81871398)
Hundred-Talent Program of CAS (for S.Y.).

Title: Application of granger causality in decoding covert selective attention with human EEG

Authors: *W. NIU[1], Y. JIANG[1], Y. ZHANG[1], X. ZHANG[1], T. JIANG[2], S. YU[2];
[1]Brainnetome Ctr., Inst. of Automation,Chinese Acad. of Sci., Beijing, China; [2]Brainnetome Ctr., Inst. of Automation, Chinese Acad. of Sci., Beijing, China

Abstract: Electroencephalography (EEG)-based Brain-Computer Interfaces (BCI)s have experienced significant growth in recent years, especially the passive BCIs with a wide application in the detection of cognitive and emotional states. But it is still unclear whether more subtle states, e.g., covert selective attention can be decoded with EEG signals. To examine this issue, we used a behavioral paradigm to introduce the shift of selective attention between the

visual and auditory domain, while keeping the sensory inputs to the brain exactly the same. With scalp EEG signals recorded from eight healthy human subjects, we extracted activity features based on the Grange Causality (GC) and successfully decoded the attentional shift through a support vector machine (SVM) based classifier. The decoding accuracy was significantly above the chance level for all subjects tested. The features extracted with the GC were further analyzed with tree-based feature importance analysis and recursive feature elimination (RFE) method to search for the optimal features for classification. Visualizing these highly informative features revealed the common pattern in EEG that can reflect different information flows across the brain network during visual and auditory attention. Our results demonstrate that patterns of EEG activities extracted by the GC can be used to decode subtle state changes of the brain related to cross-modal selective attention, which opens a new possibility of using passive BCIs in sophisticated perceptual and cognitive tasks.

Disclosures: W. Niu: None. **Y. Jiang:** None. **Y. Zhang:** None. **X. Zhang:** None. **T. Jiang:** None. **S. Yu:** None.

Poster

700. Attention Networks

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Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 700.04/BB72

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant HD086011

Title: The relationship between socioeconomic status and reading abilities in children with dyslexia and typical readers

Authors: *P. B. GREENWOOD[1], E. SCOTT[2], J. DUDLEY[2], J. S. HUTTON[2], J. VANNEST[3], T. HOROWITZ-KRAUS[4];
[1]Col. of Med., Univ. of Cincinnati, Cincinnati, OH; [2]Reading and Literacy Discovery Ctr., [3]Dept. of Neurol., Cincinnati Children's Hosp. Med. Ctr., Cincinnati, OH; [4]Educational Neuroimaging Ctr., Technion-Israel Inst. of Technol., Haifa, Israel

Abstract: 5 to 12% of school age children have reading difficulties, defined by deficits in phonological processing, fluency, and executive dysfunction. Although dyslexia is referred to as a genetic disorder, reading ability may also be affected by inadequate exposure to linguistic stimulation due to a lack of a stimulating home reading environment. Socioeconomic status (SES) is defined by parental occupation, educational attainment and household income. Research has shown that SES is positively correlated to reading ability with higher SES children having higher exposure to print in their home during early school learning. Neuroimaging research has shown that socioeconomic inequality can have negative impacts on cognition and brain

development with low SES preschool children showing no activation within lateral prefrontal regions during cognitive tasks compared to their high SES peers. Forty-Six 8-12 year old typical readers and children with dyslexia matched for SES completed neuropsychological testing to examine language, executive functions, and reading ability. Maternal education and household income were collected for all mothers as constructs of SES. In addition, all participants completed two resting state fMRI scans to assess functional connectivity. The results showed differences in the relationship between higher maternal education and functional connectivity of cognitive control networks in dyslexics compared to typical readers. The results suggest higher maternal education may have contrasting roles on the involvement of cognitive control during the reading process for atypical readers compared to children that are typically developing readers. We conclude that higher maternal education may mediate the synchronization of cognitive control networks important for reading acquisition.

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Poster

700. Attention Networks

Location: Hall A

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Program #/Poster #: 700.05/BB73

Topic: H.02. Human Cognition and Behavior

Title: Attentional hypervigilance to and attentional disengagement from test-specific threatening words in students with test anxiety is supported by alterations in alpha and theta frequency power bands in the frontoparietal attentional network

Authors: *E. A. BOURASSA, K. T. STOLL;
Biol. Sci., Mississippi Col., Clinton, MS

Abstract: Test anxiety (TA) affects up to 30% of students and is associated with a 12% decrease in academic performance. Consistent with other forms of anxiety, current research in our lab shows that students with TA have an attentional bias towards test-specific threatening (TST) words, but not generally threatening words. A general question concerning these attentional biases is whether the bias is due to hypervigilance towards threat or failure to disengage attention from threat. To differentiate between these two possibilities, twenty one students (10 low-TA and 11 high-TA) performed a modified rapid serial visual presentation (RSVP) task while connected to a 9-lead electroencephalogram (EEG) to determine whether the high-TA group failed to disengage attention from threat and measure power changes in the theta, alpha, and beta frequency bands in the frontoparietal attentional network (FPAN). Students were classified into low-TA and high-TA groups based on their blue box stress test score. The RSVP consisted of 17 number strings presented for 125 ms each; at position 8, 9, 10, 11, or 12, a word (neutral, N,

generally threatening, or TST) was shown instead of a number string. Three positions following the word, either the target word or a non-target word was shown. Each number string or word was shown in a different color; participants were asked to identify the color of the target word, if present. Continuous EEG data was epoched into 1250 ms segments with 500 ms prior to word presentation used as baseline (target presentation was 375 ms following word presentation). Event-related spectral perturbations (ERSPs) were constructed from trials in which participants responded correctly. The high-TA group had similar accuracy as the low-TA group on target trials containing both N and TST, suggesting a normal ability to disengage attention from threat. However, ERSP analysis showed significant alpha- and theta-band frequency alterations within the FPAN following the presentation of both the word and target. Low-TA participants had increased parietal alpha power following TST compared to N with decreased theta power following target presentation, whereas high-TA participants had decreased parietal alpha power following TST. In the frontal lobes, low-TA participants had decreased alpha/beta power following target presentation not seen in the high-TA group. These results suggest that the attentional bias to threat in TA is due to hypervigilance with attentional recovery following target presentation, these functions are supported by power alterations in the alpha and theta frequency bands in the FPAN, and TA may be distinct from other forms of anxiety requiring further study.

Disclosures: **E.A. Bourassa:** None. **K.T. Stoll:** None.

Poster

700. Attention Networks

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 700.06/BB74

Topic: H.02. Human Cognition and Behavior

Title: Top-down and bottom-up attentional processing in students with test anxiety as measured by electroencephalography

Authors: *G. M. TALKINGTON, E. A. BOURASSA;
Biol. Sci., Mississippi Col., Clinton, MS

Abstract: The attentional control theory of anxiety states that top-down attentional control (centered in the frontal lobes) will be decreased in anxious individuals, while bottom-up attentional capture (centered in the parietal lobes) will be increased. It is hypothesized that test anxiety (TA), a very common entity that is associated with decreased academic performance, would follow the predictions of the attentional control theory. Identifying the alterations in these attentional networks in TA will provide a better understanding of the cognitive deficits associated with TA and inform the development of effective strategies to reduce its impact on students. Electroencephalography (EEG) was measured from students with and without TA during a task requiring the differential activation of these attentional networks to determine if

cortical power was different between these two groups. The task required participants to identify a target triangle based on color and orientation in an array of four triangles; the search condition (which isolates top-down attentional control) contained the target triangle and three triangles of the same color but different orientations whereas the salient condition (which isolates bottom-up attentional capture) contained the target triangle and three triangles of different color and orientations. Twenty participants completed the task; twelve that were classified as highly test anxious and eight that were classified as non-test anxious as determined by the blue box stress test. The continuous 9-lead EEG was epoched into segments that were 1200 ms long with the first 200 ms (pre-target) used as baseline. Event-related spectral perturbations (ERSPs) were constructed from the epoched data. Task accuracy was lower in both conditions in participants with high-TA compared to low-TA. Cortical activity as measured by EEG was significantly lower in the top-down task, specifically in the beta frequency range (12-20 Hz). As predicted, this difference was centered in the frontal lobes. Cortical activity in the parietal lobes was also lower in the bottom-up task, in contrast to our hypothesis. These results may indicate that students with test anxiety have reduced ability to purposefully suppress distracting or task-irrelevant stimuli, decreasing task performance under both conditions. This implies that, in contrast to generalized anxiety disorder, the system of attentional control most influenced by TA is the top-down network.

Disclosures: G.M. Talkington: None. **E.A. Bourassa:** None.

Poster

700. Attention Networks

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 700.07/BB75

Topic: H.02. Human Cognition and Behavior

Support: DGAPA project IN224414-2

Title: Visuo-spatial attention task and handedness: A cerebral electrical activity study

Authors: *S. P. CAÑARTE VARELA, I. Y. DEL RÍO PORTILLO, I. G. GALÁN LÓPEZ; Sleep Lab., Univ. Nacional Autónoma De México, CDMX, Mexico

Abstract: Differences in brain organization and brain processing between right- and left-handers have been described, nevertheless is continue to be an issue of fact. There is also known that visuo-spatial attention processing is different for both hemispheres in relation to handedness. The aim of this study was to analyze brain response and behavioral response between right- and left-handers during visuo-spatial attention task. Fifty stimuli (red and blue circles, 1.6s each) were presented. Stimuli presented in a classical random block design for each group (left- and right-handers). After each run, subjects (n=20 male, n=20 female) responded on a PC keyboard

according to the place they saw the stimuli (right or left side) with their dominant hand and simultaneously gaze on the direction they saw the stimuli (right side if the stimulus were blue or left side if the stimulus were red). For eye movements recording were placed electrodes according to the electrooculogram (EOG).Results showed significant differences on brain activity between left and right handers based on visuo-spatial attention task. Behavioral data analysis in relation to PC keyboard answers, got a greater number of correct answers ($p=0.03$) and a longer reaction time for left-handers. For brain activity, intrahemispheric (INTRAr) correlation was analyzed with electroencephalographic activity ($p<0.05$). Left handers showed differences in theta2 band for INTRAr between F4-C4, F8-T6, C4-T6, T4-T6 including alpha1 between F4-C4 in right hemisphere during the task. Right handers showed differences in delta band for INTRAr between F4-T4, beta1 between F1-T5, F3-O1 and beta2 between F1-O1 for both hemispheres previous the task. These results support the hypothesis that exist different brain functional organization between right- and left-handers on visuo-spatial attention processing.

Disclosures: S.P. Cañarte Varela: None. **I.Y. del Río Portillo:** None. **I.G. Galán López:** None.

Poster

700. Attention Networks

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 700.08/DP11/BB76

ControlExtraData.DynamicPosterDisplay:
Dynamic Poster
Topic: H.02. Human Cognition and Behavior

Support: Fellowship for Basic or Clinical Research (2018-2020) of the ICM Education Committee.

Title: Interaction between exogenous attention and conscious visual perception: An MEG study

Authors: *A. SPAGNA[1], D. J. BAYLE[2], A. CHICA[3], C. TALLON-BAUDRY[4], P. BARTOLOMEO[5];
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Abstract: Do we need attention to become aware of an external object? The relationships between attention and visual perception has fostered an intense debate in cognitive neuroscience. Extensive neuroimaging evidence from the past 25 years does not seem to have been able to unequivocally support the separability or interdependence of these processes. Here we used

magnetoencephalography (MEG) to assess the effect of peripheral non-predictive supra-threshold visual cues on the conscious perception of near-threshold Gabor patches. Eighteen participants underwent MEG recordings while performing an exogenous orienting task, in which peripheral visual cues (small dots presented for 50 ms) oriented attention toward one of two boxes located in the lower left and right quadrants of the display. Three-hundred milliseconds after the visual cue, the Gabor target (duration: 16 ms) was presented with equal probability in the same (valid) or in the opposite (invalid) box indicated by the cue. Participants were then required to perform two tasks: (1) a discrimination task, which required pressing a button to indicate the orientation of the target gratings; (2) a detection task, which required pressing a button to indicate the location of seen targets or whether the target was unseen. At the behavioral level, results showed that exogenous attention increased the percentage of detected targets and biased the observers to report signal occurrence by adopting a more liberal decision criterion, but there was no evidence for an increase in sensitivity due to the presentation of the visual cue. Source reconstruction of MEG recordings in the cue-target period showed that activity in the right temporoparietal junction, an area important for the exogenous orienting of attention, increased for seen *vs*unseen targets. No evidence for the involvement of other brain areas was found in the cue-target period. Source reconstruction in the post-target period showed a widespread increase in activity of areas within the fronto-parietal and the cingulo-opercular networks bilaterally for seen valid trials compared to unseen valid trials, and for seen invalid trials compared to unseen invalid trials. No difference was found between MEG activity in seen valid *vs*seen invalid cue trials. The absence of validity effects at the behavioral level as well as in the MEG recordings was surprising, and possibly due to the cue stimulus used. Despite this negative finding, results of the contrasts between seen and unseen trials separately for the valid and invalid cue confirm that neuronal activity related to exogenous orienting of attention can enhance visual conscious perception.

Disclosures: **A. Spagna:** None. **D.J. Bayle:** None. **A. Chica:** None. **C. Tallon-Baudry:** None. **P. Bartolomeo:** None.

Poster

700. Attention Networks

Location: Hall A

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Program #/Poster #: 700.09/BB77

Topic: H.02. Human Cognition and Behavior

Support: Scholarship for the Master Thesis by the University of Salzburg

Title: Intermodal attention differentially adjusts frequency and phase of entrained oscillations in sensory and non-sensory regions

Authors: *N. SUESS, T. HARTMANN, N. WEISZ;
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Abstract: Continuously extracting behaviourally relevant information from the environment for optimal stimulus processing is one of the crucial functions of attention. Low-frequency phase alignment (~"entrainment") in primary sensory areas with respect to attended / ignored features has been suggested to support this selection function. While activation of frontoparietal areas has been shown to be relevant for top-down selection, entrainment of nonsensory regions has been far less studied in the context of attention. In this MEG study we were interested in how different sensory and non-sensory regions show temporally coordinated activity to rhythmic stimulation dependent on attention. Participants performed an established intermodal selective attention task where low-frequency auditory (1.6 Hz) and visual (1.8 Hz) stimulation were presented simultaneously. We instructed them to either attend to the auditory or the visual stimulation and detect targets while ignoring the other stimulus stream. As expected, highest entrainment was observed in primary sensory areas for the respective stimulation independent from attentional focus. We found higher differences in entrainment between attended and ignored stimulation for the visual modality and that auditory regions can to some extended reflect attention dependent entrainment for visual stimulation. Furthermore, we show phase differences in primary sensory areas for the respective stimulation dependent on attentional focus both present in the auditory and visual modality, suggesting similar processes in both modalities for guiding attention. Importantly, we also found a frontoparietal network which entrains flexibly to the to-be-attended frequencies, suggesting that these higher-order nonsensory regions exploit the temporal structure of stimulation to adjust excitability optimally. Overall, our results suggest that while intermodal attentional focusing acts in particular via phase adjustment at the modality-specific stimulation frequency in primary sensory areas, nonsensory frontoparietal areas adjust their frequency to be in line with the attended modality.

Disclosures: **N. Suess:** None. **T. Hartmann:** None. **N. Weisz:** None.

Poster

700. Attention Networks

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 700.10/BB78

Topic: H.02. Human Cognition and Behavior

Title: The benefit of a hearing aid noise-reduction scheme on selective auditory attention and listening effort in hearing impaired

Authors: *C. GRAVERSEN[1], E. ALICKOVIC[1,2], D. WENDT[1,4], T. S. ALA[1,5], A. GERSTON[1], L. FIEDLER[1], R. K. HIETKAMP[1], T. LUNNER[1,2,4,3];
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of Behavioral Sci. and Learning, Linköping Univ., Linköping, Sweden; [4]Dept. of Hlth. Technol., Tech. Univ. of Denmark, Lyngby, Denmark; [5]Hearing Sciences, Div. of Clin. Neurosci., Univ. of Nottingham, Glasgow, United Kingdom

Abstract: Hearing impaired (HI) listeners report listening as demanding and effortful in challenging environments with multiple speakers to be ignored, while attending to a target speaker. Therefore, hearing-aid signal processing often includes noise-reduction (NR) schemes to support the user in such environments. However, objective outcome measures to quantify the user benefits in such a listening situation are still warranted. To explore the benefit of a NR scheme in HI, electroencephalography (EEG) and pupillometry were used to study the impact of a typical hearing aid NR scheme in different listening conditions on selective auditory attention and listening effort (LE). Selective attention was investigated by the correlation coefficient between stimulus (speech) reconstructed from EEG and actual stimulus, while LE was quantified in terms of pupil dilation and alpha oscillations obtained from EEG. Twenty-two participants were instructed to attend to a target speaker while ignoring competing talkers in a spatial arrangement of loudspeakers. Speech stimuli consisted of 33 seconds of news clips to mimic a realistic listening scenario followed by a control question to obtain sustained attention. Both EEG and pupillometry were recorded in different listening scenarios with changing signal-to-noise (SNR) (3 and 8 dB) and signal-processing of the hearing aid (NR active vs inactive). Results indicate enhanced decoding of attended speech (Figure 1) and reduced LE for high vs. low SNR and active vs inactive NR. In summary, the combination of EEG and pupillometry analysis may in the future lead to better understanding of neural mechanisms involved in aided listening.

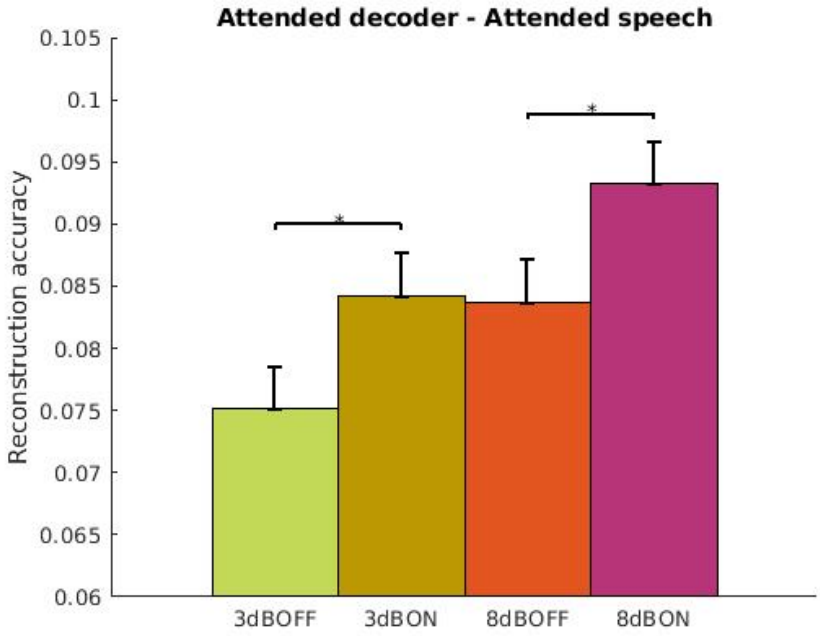

Figure 1: Reconstruction accuracy between reconstructed and actual speech for the four conditions. Active noise-reduction (ON) increased selective auditory attention for both 3 and 8 dB conditions.

Disclosures: **C. Graversen:** A. Employment/Salary (full or part-time):; Eriksholm Research Centre - part of Oticon. **E. Alickovic:** A. Employment/Salary (full or part-time):; Eriksholm Research Centre - part of Oticon. **D. Wendt:** A. Employment/Salary (full or part-time):; Eriksholm Research Centre - part of Oticon. **T.S. Ala:** A. Employment/Salary (full or part-time):; Eriksholm Research Centre - part of Oticon. **A. Gerston:** None. **R.K. Hietkamp:** A. Employment/Salary (full or part-time):; Eriksholm Research Centre - part of Oticon. **T. Lunner:** A. Employment/Salary (full or part-time):; Eriksholm Research Centre - part of Oticon. **L. Fiedler:** A. Employment/Salary (full or part-time):; Eriksholm Research Centre - part of Oticon.

Poster

700. Attention Networks

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 700.11/BB79

Topic: H.02. Human Cognition and Behavior

Support: NIMH Conte Center Grant 1P50MH109429
NIMH Grant R01MH064043
James S. McDonnell Foundation
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Title: The role of cortical alpha-band oscillations during anticipatory gating of spatial attention: An ECoG study

Authors: *X. YANG[1], I. FIEBELKORN[2], O. JENSEN[3], J. PARVIZI[4], R. T. KNIGHT[5,6], S. KASTNER[1,2];
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Abstract: Across the visual attention network, classical effects of selective attention on low frequency suppression have been characterized in human EEG and MEG studies. However, direct cortical measurements of the spatial selectivity and temporal dynamics of alpha-band oscillations in the human brain, and how they are modulated by attention, have not been reported. We recorded electrocorticographic (ECoG) signals in eight epilepsy patients implanted with intracranial electrodes while they were performing a variant of the Eriksen flanker task. Following a spatial cue and a variable delay interval, subjects differentiated between two shapes at the cued location in an array of distracters. Using our probabilistic atlas of the human visual system, we localized electrodes to visual topographic areas and identified those with spatially-selective power profile in the alpha frequency range. We found that low frequency suppression modulated by attention was spatially tuned and showed differential topographic dynamics during

the delay period. Specifically, extrastriate cortex and posterior intraparietal sulcus (pIPS) displayed the classical contralateral alpha suppression and ipsilateral enhancement with respect to the upcoming target location. Surprisingly, anterior intraparietal sulcus (aIPS) showed consistently decreased alpha activity regardless of the cued location. Moreover, we found an anti-correlation between the low frequency activity and the high-frequency broadband (HFB) signals with respect to spatial tuning, especially at pIPS regions. The tuning widths of delay-evoked alpha activity also correlated with HFB signals, further suggesting that these two frequency components were systematically related across the visual hierarchy. We, therefore, investigated the cross-frequency coupling between alpha phase and HFB amplitude within each topographic area and revealed a significant attention effect on coupling (greater ipsilateral than contralateral) observed only in pIPS. We then examined cross-region coupling and discovered that alpha phase of aIPS was significantly coupled with HFB amplitude of pIPS (also greater ipsilateral than contralateral), and this interregional modulation was only found significant in the top-down manner (aIPS to pIPS) but not bottom-up (pIPS to aIPS). In conclusion, these results suggest a parallel yet distinctive representation of spatial information in low and high frequency bands and provide direct neural evidence to support the gating-by-inhibition theory of spatial attention by facilitating a coordinated processing of visual space that may integrate feedback modulation across the visual system.

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Poster

700. Attention Networks

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Topic: H.02. Human Cognition and Behavior

Support: R21 EY027703
NSF GRFP DGE-1247312

Title: Resting-state connectivity fingerprint model predicts individual intra-areal intraparietal sulcus retinotopic organization

Authors: *J. A. BRISSENDEN, D. C. SOMERS;
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Abstract: Human intraparietal sulcus (IPS) contains multiple, retinotopically organized (Swisher et al., 2007) cortical maps. However, the reliable identification of IPS visual field maps in individual subjects requires the collection of a substantial amount of fMRI data and places strong eye-fixation demands on subjects. Connectivity fingerprint models have proven to be a

successful method for predicting area-level organization from diffusion imaging and resting-state connectivity measures (Saygin et al. 2011; Osher et al., 2015, 2019; Tavor et al., 2016; Tobyne et al., 2018). However, these methods have not yet been successfully applied to predict finer scale functional organization, such as that revealed by retinotopic mapping. Here, we applied a connectivity fingerprint model to the Human Connectome Project 7T dataset (N = 181) to characterize individual intra-areal IPS visual responsivity and retinotopic organization. Hierarchical Bayesian regression models were trained to predict vertex-wise IPS population receptive field (pRF) model variance explained (R^2) and polar angle preference estimates from patterns of resting-state functional connectivity. Model performance was evaluated using a split-half cross-validation scheme. Model predictions were found to accurately reflect IPS visual responsivity and polar angle organization in individual subjects. Predicted polar angle maps further allowed for the delineation of boundaries between adjacent intraparietal retinotopic regions, IPS0-3. Recent work indicates that averaging fMRI time series across subjects and then fitting a pRF model produces results that align with previous parcellations of visual areas (Benson et al., 2018). Our connectivity fingerprint model significantly outperforms this group-average model (LH: 0.52 vs. 0.30; RH: 0.50 vs. 0.39). This work presents a method for examining the retinotopic organization in individuals for which the collection of sufficient retinotopic mapping data is difficult. These findings also extend connectivity fingerprinting methods to predict fine-scale gradients in functional organization within a cortical area.

Disclosures: J.A. Brissenden: None. **D.C. Somers:** None.

Poster

700. Attention Networks

Location: Hall A

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Topic: H.02. Human Cognition and Behavior

Support: NSF BCS-1829394
NIH R21 EY027703

Title: 'Connectivity fingerprint' modeling reveals task-specific, individualized patterns of overlapping visual attention and working memory activation in human posterior parietal cortex

Authors: *V. TRIPATHI, S. M. TOBYNE, J. A. BRISSENDEN, A. L. NOYCE, D. C. SOMERS;
Boston Univ., Boston, MA

Abstract: Introduction: Connectivity Fingerprinting (CF) can predict specific task activation patterns in individual subjects using anatomical connectivity (Saygin et. al. 2012) or resting state functional connectivity (Tavor et. al. 2016; Tobyne et. al. 2018). However, it remains unclear

whether the CF approach reveals an individual's broad-scale network supporting several cognitive functions(e.g. the dorsal attention network) or if it can capture fine-scale task-specific activation within a common network. Methods: We examined fMRI data from 3 tasks known to strongly activate posterior parietal cortex: Multiple Object Tracking (MOT, n=9), Visual Short-Term Memory - Change Detection (VSTM-CD, n=9) and Visual 2-back vs. Auditory 2-back working memory (VAWM, n=14) along with resting-state data. For each task, we constructed CF models using ridge regression to relate functional connectivity to task activation and a nested leave-one-subject-out cross-validation procedure for model parameter tuning. CF models predicted task activation for every cortical surface vertex within a search space, which spanned posterior parietal cortex, by applying an individual subject's connectivity matrix to the model. Task-specific CF models consisted of the set of weights corresponding to each parcels relative importance to predicting the search space. We performed permutation testing to get distributions for the weights which were compared across tasks. Results: CF modelling was highly effective in predicting individual-subject activation patterns in each of the three tasks (MOT: R=0.67; VSTM: R=0.71; VAWM: R=0.61). While the CF models exhibited some parcel connections common to all 3 tasks, significant task-level differences were observed in the model structure. Weights for parietal and temporoparietal regions were particularly informative in the MOT model, visual area weights in the VSTM model, and temporal regions weights in the VAWM task. Conclusions: CF models make task-specific activity predictions within posterior parietal cortex for individual subjects and these differences are observable in the estimated model coefficients. This demonstrates that CF modelling goes beyond large-scale resting-state networks to make task-specific predictions. More broadly, this work demonstrates the utility of CF modelling in revealing fine scale networks even for tasks that involve similar cognitive processes and colocalized brain activation such as working memory and attention.

Disclosures: V. Tripathi: None. **S.M. Tobyne:** None. **J.A. Brissenden:** None. **A.L. Noyce:** None. **D.C. Somers:** None.

Poster

700. Attention Networks

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Program #/Poster #: 700.14/BB82

Topic: H.02. Human Cognition and Behavior

Support: CONICYT
ICM P10-001-F
P09-015-F

Title: Beta band activity reflects anticipatory sensorimotor planning during covert visual attention oculomotor dual task

Authors: *J. TORRES-ELGUETA[1], P. MALDONADO[2];
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Abstract: It has been proposed that orientation of visual attention is coupled to oculomotor planning, giving that saccade planning leads to facilitation of the visual processing of targets at the same visual locus. However, there is evidence of complete mechanistic independence between both processes. If visual attention depends on oculomotor planning, we expect to find interference between both processes when each one is directed to a different locus. This interference would manifest itself through a drop of saccadic behavior or a different time course of electrophysiological markers. Nine subjects (4 male) performed the dual task in order to track the location of an attentional focus by discriminating the identity of a peripheral target (OD), while they have to perform a saccade to a target that is in the same location of the primary task (congruent trial), or to a neighboring site (incongruent, INC1 and INC3). Each trial begins with the gaze on a central fixation which is replaced by an arrow whose direction and color indicate the side of the OD and the position of the saccade, respectively. The saccade was withheld during a variable time until a Go signal. We found that target discrimination was significantly higher for incongruent trials compared to but there was no difference between congruent and INC1. During post CUE period, oscillatory activity (Beta band) showed a spectral power decrease at posterior electrodes, contralateral to the cued target, compared to ipsilateral, both in congruent and INC1. Such lateralization of beta had an earlier time course in INC1 than congruent trials. During the Go period, beta band showed clear lateralization of spectral power in congruent trials and was not present in incongruent trials. Our results suggest that there is no interference, without a time cost for the direction of saccade and visual attention to different sites. However, the different time course of beta band activity during post CUE period may reflect an anticipatory process for sensory-motor integration, which avoids a time cost in the post GO period. The experiment showed no evidence of interdependence between visual attention orienting and oculomotor planning. The results suggest a dissociation between the two processes and no interference between them.

Disclosures: J. Torres-Elgueta: None. **P. Maldonado:** None.

Poster

700. Attention Networks

Location: Hall A

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Program #/Poster #: 700.15/BB83

Topic: H.02. Human Cognition and Behavior

Support: Natural Sciences and Engineering Research Council Discovery Grant

Canadian Foundation for Innovation Leaders Opportunity Fund infrastructure grant

Title: Individual attention-emotion differences in spontaneous neural connectivity during rest

Authors: *K. CHEEMA[1], A. SHAFER[2], R. BAHKTIARI[1], M. MOORE[3], F. DOLCOS[3], A. SINGHAL[1];
[1]Univ. of Alberta, Edmonton, AB, Canada; [2]Wayne State Univ., Detroit, MI; [3]Univ. of Illinois, Urbana, IL

Abstract: Background. Recent work from our group using simultaneous EEG-fMRI recordings has shown multi-modal evidence in support of the two major neural circuits involved in emotion-cognition interactions. These circuits include hubs in dorsolateral prefrontal cortex (dlPFC) and ventrolateral prefrontal cortex (vlPFC). While several task-based studies have outlined the neural circuitry associated with these two key regions, their intrinsic connectivity is not fully clear. Moreover, it remains open as to how the connectivity of these networks relates to the individual differences in attention and emotional processing. In this study, we employed a simultaneous EEG-fMRI protocol to further characterize the intrinsic connectivity of dlPFC and vlPFC in healthy controls, and examine how the spontaneous resting-state connectivity of the two circuits relate to individual differences in attention and emotion processing. **Methods**. 20 healthy adults (18-31 years old, 13 females) completed the Emotion Regulation Questionnaire (ERQ; Gross & John, 2003) and the Test of Variables of Attention (TOVA; Greenberg, 2011). During scanning, participants were asked to close their eyes for 5 minutes and remain still. The resting-state analysis was performed using the CONN toolbox to examine the resting state connectivity for right dlPFC and vlPFC. Finally, the ERQ and TOVA scores were correlated with connectivity patterns of right dlPFC and vlPFC. Both positive and negative connections from the two hubs were analyzed. **Results**. As expected, dlPFC was intrinsically connected to areas related to executive functioning, while vlPFC displayed spontaneous connections with areas associated with emotional processing. These two hubs were also both connected with amygdala and cingulate cortex. Only right dlPFC was found to be negatively correlated with medial prefrontal cortex (part of the default mode network), indicating the functional significance of dlPFC network for attention processing. Finally, better performance on sustained attention (TOVA) and emotion regulation (ERQ) was associated with stronger intrinsic connectivity from right vlPFC. **Conclusion**. This study provides emerging evidence for the presence of distinct but separate spontaneous networks for the two prefrontal cortices associated with emotion-cognition interactions. It is critical to understand the brain circuitry responsible for emotion-attention interaction to better understand how this circuitry is impaired in mood and anxiety disorders.

Disclosures: K. Cheema: None. **A. Shafer:** None. **R. Bahktiari:** None. **M. Moore:** None. **F. Dolcos:** None. **A. Singhal:** None.

Poster

700. Attention Networks

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Program #/Poster #: 700.16/BB84

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant R01NS078396
NIH Grant 1R01MH109954-01

Title: Anticorrelated inter-network electrophysiological activity varies dynamically with attentional performance and behavioral states

Authors: *A. KUCYI[1], A. L. DAITCH[2], O. RACCAH[3], B. ZHAO[4], C. ZHANG[4], M. ESTERMAN[5], M. ZEINEH[1], C. HALPERN[1], K. ZHANG[4], J. ZHANG[4], J. PARVIZI[1]; [2]Lab. of Behavioral and Cognitive Neurosci. (LBCN), [1]Stanford Univ., Stanford, CA; [3]Neurol. & Neurolog. Sci., Stanford Univ., Palo Alto, CA; [4]Capital Med. Univ., Beijing, China; [5]Boston Univ. Med. Sch., Boston, MA

Abstract: The default mode network (DMN) is thought to exhibit infraslow, negatively correlated (or “anticorrelated”) activity with dorsal attention (DAN) and salience (SN) networks across various behavioral states. To investigate the fine-grained dynamics of activity across these networks, we used human intracranial electroencephalography (iEEG) in a unique cohort of 7 neurosurgical patients with simultaneous recordings within core nodes of the three networks (posteromedial cortex within DMN, dorsal posterior parietal cortex within DAN, and dorsal anterior insula within SN). Pre-operative resting state fMRI confirmed that these implanted electrode sites were functional connected with their constituent networks within individuals. During iEEG recordings, participants performed multiple runs of a visual continuous performance task requiring sustained attention, and spontaneous activity was also recorded during wakeful rest and sleep. During attentionally-demanding stimulus processing, the three network-specific sites showed dissociable profiles of high-frequency broadband (HFB) activity: DAN and SN sites showed task-evoked HFB power increases (with an error monitoring signal in the SN but not DAN), while DMN sites showed HFB power decreases. Inter-network, continuous anticorrelation of infraslow HFB activity was found consistently during task performance but during wakeful rest or sleep, anticorrelation only emerged intermittently and in tandem with expression of task-like brain states. Critically, on a finer timescale, task-evoked DAN and SN activations preceded DMN deactivations by hundreds of milliseconds. Moreover, greater lagged, but not zero-lag, DMN-DAN anticorrelation was associated with better attentional performance. These findings have implications for interpreting antagonistic network relationships and confirm the behavioral importance of time-lagged inter-network interactions.

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Poster

700. Attention Networks

Location: Hall A

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Program #/Poster #: 700.17/BB85

Topic: H.02. Human Cognition and Behavior

Title: Personalized neuromodulation for attention networks

Authors: *B. L. DECK[1], B. YEAGER[1], J. ZIMMERMAN[2], A. KELKAR[1], B. ERICKSON[1], J. D. MEDAGLIA[1];
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Abstract: Attention to simple stimuli has been shown to dissociate into three separate but interacting networks using task-evoked fMRI. However, our understanding of how these networks comport with networks estimated from modern precision fMRI mapping approaches is unclear. Here, we test whether applying transcranial magnetic stimulation (TMS) to three distinct networks estimated within subjects, evaluated using modern approaches yield dissociable effects on behavior. We hypothesize that inhibitory TMS to the cingulo-opercular network (CO), dorsal attention network (DAN), and a fronto-parietal executive control network (FP) individually will reduce performance on alerting, orienting, and executive control behavioral efficiency, respectively. In this study individualized intrinsic connectivity systems were identified in subjects based on previously collected resting-state fMRI data. An iterative mapping procedure was used in a normative template of 18 distributed systems are registered to each subject's fMRI data and system labels are iteratively updated based on the correlation of voxel time-series to the time-series of the 18 distributed systems. The attention network task (ANT) was administered to participants before and after continuous theta-burst (cTBS) TMS delivered to both the left CO network and the FP network (as a control) both in the middle frontal gyrus. Efficiency scores were calculated for the ANT based on previous literature. Based on each ANT efficiency score, we observed that alerting and executive control became slower while orienting became faster after performing cTBS on the left CO network. Our results show that inhibitory stimulation applied to the CO network not only inhibits the network stimulated but also inhibits normal function of the FP network. We provide evidence that the inhibition of both of these networks may allow the DAN network to perform better at orienting an individual's attention. These results point to the need for additional neuromodulation studies that clarify the relationship between modern precisely mapped networks and attention performance. Our results further

suggest that subject-specific attention interventions could be supported by precision fMRI network mapping.

Disclosures: B.L. Deck: None. **B. Yeager:** None. **J. Zimmerman:** None. **A. Kelkar:** None. **B. Erickson:** None. **J.D. Medaglia:** None.

Poster

700. Attention Networks

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 700.18/CC1

Topic: H.02. Human Cognition and Behavior

Title: Differential functional patterns of the human posterior cingulate cortex during activation and deactivation: A meta-analytic connectivity model

Authors: *J. BUSLER, J. YANES, R. BIRD, M. REID, J. ROBINSON;
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Abstract: The posterior cingulate cortex (PCC), a cortical hub, facilitates and modulates a diverse set of neural network operations. The PCC activates when emotional stimuli are encountered, displays functional connectivity to frontoparietal networks indicating its role in attention and cognitive control, and is a pivotal component of the default mode network. Moreover, the PCC has been shown to be involved in a range of psychiatric and neurological disorders. However, very little is known about the specific activated/deactivated functional profiles of the PCC. We employed a dual-analytic approach using robust quantitative meta-analytical connectivity modeling (MACM) and ultra-high field, high resolution resting state functional magnetic resonance imaging (rs-fMRI) to identify state-specific functional activity patterns of the human PCC. We defined the PCC region of interest (ROI) using the Harvard-Oxford Structural Probability Atlas (thresholded at 50% probability, distributed with FSL neuroimaging analysis software. Whole-brain meta-analytic co-activation and co-deactivation profiles were generated for the PCC ROI using the BrainMap database. In addition, using tools within Mango imaging analysis software, we conducted behavioral and paradigm analyses on resultant functional profile differences between the activation and deactivation meta-analyses. The MACM results provided evidence for regions of convergence for PCC co-activation and co-deactivation (i.e., left medial frontal gyrus, left amygdala, and left anterior cingulate) as well as regions of divergence specific to either PCC activation (i.e., bilateral inferior frontal gyri) or PCC deactivation (i.e., left parahippocampal gyrus). Resting state connectivity analyses showed widespread connectivity similar to that of the PCC co-activation-based MACM, but also demonstrated additional regions of activity, including bilateral superior parietal regions and right superior temporal regions. Behavioral and paradigm analyses showed significant behavioral domain and paradigm classes associated with PCC co-activation but not for PCC co-

deactivation. These analyses provide additional insight into the dynamic functional activity patterns of the human PCC as it switches between activated, deactivated, and resting states and associatively improves our understanding of PCC function via a multi-state, multi-method assessment that may elucidate models of disease.

Disclosures: **J. Busler:** None. **J. Yanes:** None. **R. Bird:** None. **M. Reid:** None. **J. Robinson:** None.

Poster

700. Attention Networks

Location: Hall A

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Program #/Poster #: 700.19/CC2

Topic: H.02. Human Cognition and Behavior

Support: This work was supported by funding from the Federal Ministry of Education and Research to SV (BMBF, 01GQ1401).

Title: Resting - state functional connectivity of the right temporoparietal junction relates to belief updating and attentional reorienting

Authors: *A.-S. KÄSBAUER[1], P. MENGOTTI[1], G. FINK[1,2], S. VOSSEL[1,3];
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Abstract: Whereas the resting-state functional connectivity (rsFC) pattern of the right temporoparietal junction (rTPJ) has been characterized by multiple studies [1], little is known about the link between rTPJ-rsFC and cognitive functions. The first evidence for a significant relationship between rsFC networks and deficits in the domain of attention has been provided by studies in stroke patients [2]. Given a putative involvement of rTPJ in both reorienting of attention and the updating of probabilistic beliefs [3], the present study aimed at characterizing the relationship between rsFC of rTPJ with dorsal and ventral attention systems and these two cognitive processes.
Twenty-three healthy participants (14 females, mean age 27 years, all right-handed) performed a modified location-cueing paradigm allowing for the assessment of belief updating and attentional reorienting. Resting-state fMRI was recorded before and after the task. To study the rsFC of rTPJ, seed-based correlation analysis with a coordinate derived from a previous fMRI and TMS study was used. The rsFC pattern of this rTPJ region was characterized at the whole-brain level. Using a ROI-based approach with key nodes of the dorsal and ventral attention systems, correlations of each behavioral parameter with rsFC before the task, as well as with changes in rsFC after the task were analyzed.

The whole-brain rsFC pattern of the present rTPJ region resembled the pattern described by previous studies. Regarding the link between connectivity and behavior, weaker rsFC of rTPJ and the right intraparietal sulcus before the task was associated with faster updating of beliefs about the validity of the spatial cue. Moreover, an increase of the interhemispheric rsFC of rTPJ and left TPJ after the task was related to faster belief updating as well as faster reorienting. These results are in line with task-based connectivity studies. Moreover, they extend existing patient studies on the role of interhemispheric interactions for optimal behavioral performance [2]. In conclusion, the present findings argue for mutual interactions between cognitive processing and resting-state connectivity architectures.

[1] Kucyi A, Hodaie M, Davis KD (2012) J Neurophysiol. 108(12): 3382-3392.
[2] Baldassarre A, Ramsey L, Hacker CL, Callejas A, Astafiev SV, Metcalf NV, Zinn K, Rengachary J, Snyder AZ, Carter AR, Shulman GL, Corbetta M (2014) Brain. 137(12): 3267-3283.
[3] Mengotti P, Dombert PL, Fink GR, Vossel S (2017) J Neurosci. 37(22): 5419-5428.

Disclosures: **A. Käsbauer:** None. **P. Mengotti:** None. **G. Fink:** None. **S. Vossel:** None.

Poster

700. Attention Networks

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 700.20/CC3

Topic: D.07. Vision

Support: NIH Grant MH111868
NIH Grant MH116170

Title: Effective brain stimulation is linked to functional network markers

Authors: S. LAGANIERE[1], J. XIE[2], W. CHEONG[2], I. LEE[2], U. NAWAZ[3], R. O. BRADY, JR[4], M. ESTERMAN[5], ***M. A. H. HALKO**[3];
[1]Neurol., Beth Israel Deaconess Med. Ctr., Boston, MA; [2]Harvard Med. Sch. / Beth Israel Deaconess Med. Ctr., Boston, MA; [3]Harvard Med. Sch. / Beth Israel Deaconess Med., Boston, MA; [4]Beth-Israel Deaconess Med. Ctr., Boston, MA; [5]VA Boston Healthcare Syst., Boston, MA

Abstract: Despite growing advances in the field of neuromodulation, not all participants and patients respond to non-invasive brain stimulation. The emergence of the study of large scale brain networks has allowed investigation of communication between brain regions independent of tasks or symptomology.
In a first experiment, we used voxelwise whole-brain analysis to identify a cerebellar-prefrontal cortex network linked to the negative symptoms of schizophrenia with resting state functional connectivity (n=44). We then tested in n=11 participants if network modulation (twice-daily, 5

days) with cerebellar-targeted transcranial magnetic stimulation (TMS) would be linked to symptom improvement. In a second experiment, we repeated the stimulation in healthy participants (n=26) within single sessions. We obtained large-scale network connectivity measures before and immediately after stimulation. Concurrent with network collection, participants performed a continuous performance task. The dose intensity of cerebellar TMS was varied across three separate sessions in each participant.
In schizophrenia patients, we identified a cerebellar-prefrontal cortex network deficiency was linked to negative symptoms. In the TMS cohort, the magnitude of increased connectivity following stimulation directly corresponded to negative symptom improvement ($r=-0.809$). In healthy participants, the absolute machine intensity of stimulation was not related to improved attentional improvement (d'), but modulation of the default network and dorsal attention network with stimulation intensity is predictive of subsequent improvement ($p=0.015$).
In conclusion we show that a comprehensive approach to mental illness can be taken where functional connectivity imaging is used to identify networks which correspond to symptoms. This same approach can be translated into healthy participants for briefer duration experiments to parameterize network modulation using cognitive performance as a surrogate for symptom measures.

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Poster

701. Language Disorders

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 701.01/CC4

Topic: H.02. Human Cognition and Behavior

Title: Anosognosia for alexia without agraphia: Implications for understanding anosognosia, right brain reading and right brain logic

Authors: *E. L. ALTSCHULER;
Metropolitan Hosp., New York, NY

Abstract: In1965 Geschwind called alexia without agraphia (AwoA), originally described by Dejerine in 1892, the first disconnection syndrome. Indeed, a lesion to the left visual cortex combined with a lesion of the splenium of the corpus callosum disconnects intact vision in the right cortical hemisphere from the language centers in the left brain (in a right handed individual) rendering the patient unable to read. Writing is intact as the left-brain language centers—Wernicke, Broca's areas—are intact as are the white matter tracts connecting them. Study of patients with AwoA has the potential to yield insights on a number of conditions. For example, I saw a patient who after a large stroke affecting the left visual cortex and splenium of the corpus

callosum could not read any text correctly but was able to write normal sentences spontaneously and to dictation. When asked to read, her response bore no connection to the text before him. When pressed on this she said there may have been some mistakes due to a vision problem secondary to something in her eye. When told that examination showed there was nothing in her eye, she said it was still a problem as there was a feeling of something in the eye. The patient's visual acuity was normal and the she could instantly find even a small mark on a piece of paper. Thus the patient had anosognosia for her AwoA. This is the third such example we have seen of this (Multari, Ramachandran & Altschuler, 2011; Williams, Patira & Altschuler, 2016). Conversely to (incorrect) attempts to read English, when shown a page of Chinese text, the patient immediately said, "I cannot read this because it is written in a foreign language." In our previously two reported cases the patient responded similarly. This suggests that the anosognosia for AwoA is due to a vacuum of afferent information. The patient could sometimes identify individual letters, but could not read even a two-letter word. It will be interesting to study the length of words that other patients with AwoA can read to assess the reading ability of the right brain. Finally, studying patients with AwoA may give an unprecedented opportunity to assess the capacity of the right brain for reasoning and logic: Recently we have described a method, using question stimuli presented either as pictures or words, e.g., does a bone go with a dog, cat (or do not know the answer), to assess whether or not Wernicke's aphasia patients understand or not that they do not understand language (Hartman et al., & EL Altschuler, 2017). This method can be used with the picture stimuli—processed by the brain—as the test stimuli and the same questions asked verbally which should be able to be answered normally by the left brain as (positive) control stimuli.

Disclosures: E.L. Altschuler: None.

Poster

701. Language Disorders

Location: Hall A

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Program #/Poster #: 701.02/CC5

Topic: H.02. Human Cognition and Behavior

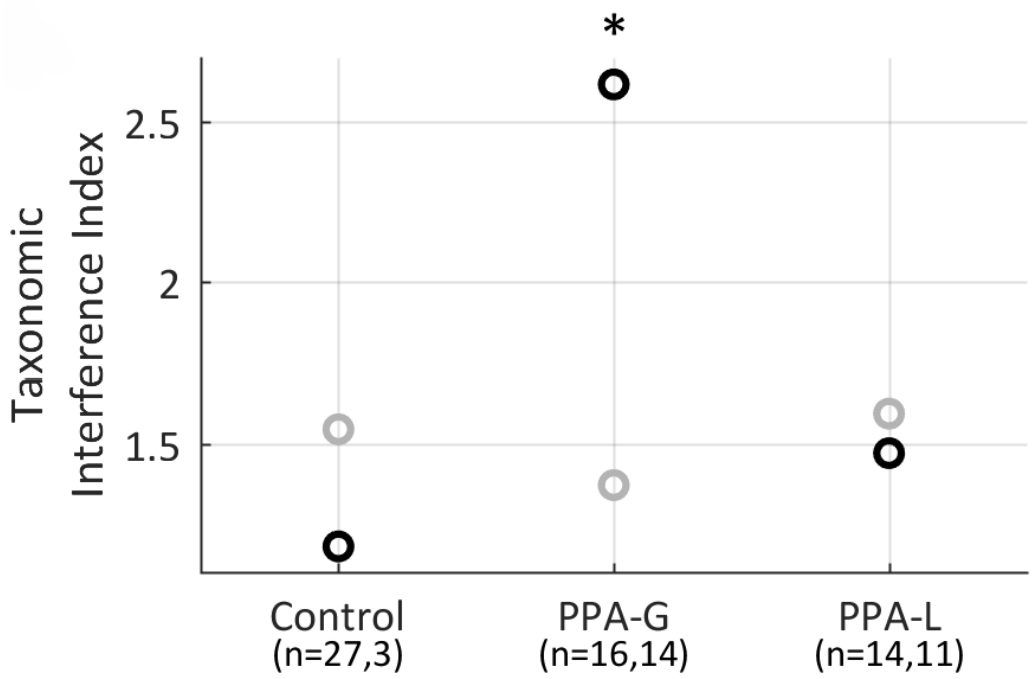
Support: NIH Grant NS047987
NIH Grant R01008552
NIH Grant AG056258
NIH Grant AG013854
NIH Grant NS075075

Title: Semantic component of phonemic paraphasias in agrammatic primary progressive aphasia

Authors: *M. J. NELSON[1,2], S. MOELLER[1], A. BASU[1], L. CHRISTOPHER[5], E. ROGALSKI[1,3], M. GREICIUS[5], S. WEINTRAUB[1,4], B. BONAKDARPOUR[1,4], R. HURLEY[1,6],

M.-M. MESULAM[1,4];
[1]Mesulam Ctr. for Cognitive Neurol. and Alzheimer's Dis., [2]Dept. of Neurolog. Surgery, [3]Dept. of Psychiatry and Behavioral Sci., [4]Dept. of Neurol., Northwestern Univ. Feinberg Sch. of Med., Chicago, IL; [5]Dept. of Neurol. and Neurolog. Sci., Stanford Univ., Stanford, CA; [6]Dept. of Psychology, Cleveland State Univ., Cleveland, OH

Abstract: Phonemic paraphasias in language-impaired patients are thought to reflect deficits in phonological (post-semantic) stages in the process of language production. Here we present evidence that phonemic paraphasias in non-semantic primary progressive aphasia (PPA) may also be driven by an underlying deficit in the semantic representation of words. Agrammatic and logopenic PPA patients and control participants performed a word-to-picture visual search task where they were asked to match a stimulus noun to one of 16 object pictures, one of which was the correct target. Participants were subsequently asked to name the same items. We measured the taxonomic interference (ratio of time spent viewing related versus unrelated foils) during the search task for each item. Target items that elicited a phonemic paraphasia during object naming elicited increased taxonomic interference (semantic blurring) during the search task in agrammatic PPA patients but not in logopenic PPA patients. These results suggest a semantic (pre-phonological) basis for phonemic paraphasias in at least one variant of PPA. The findings are also consistent with cascade models of phonological production, presumably reflecting impaired inhibition of competing phonological representation in instances where semantic access has lost its robustness.



Disclosures: **M.J. Nelson:** None. **S. Moeller:** None. **E. Rogalski:** None. **S. Weintraub:** None. **B. Bonakdarpour:** None. **R. Hurley:** None. **M. Mesulam:** None.

Poster

701. Language Disorders

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

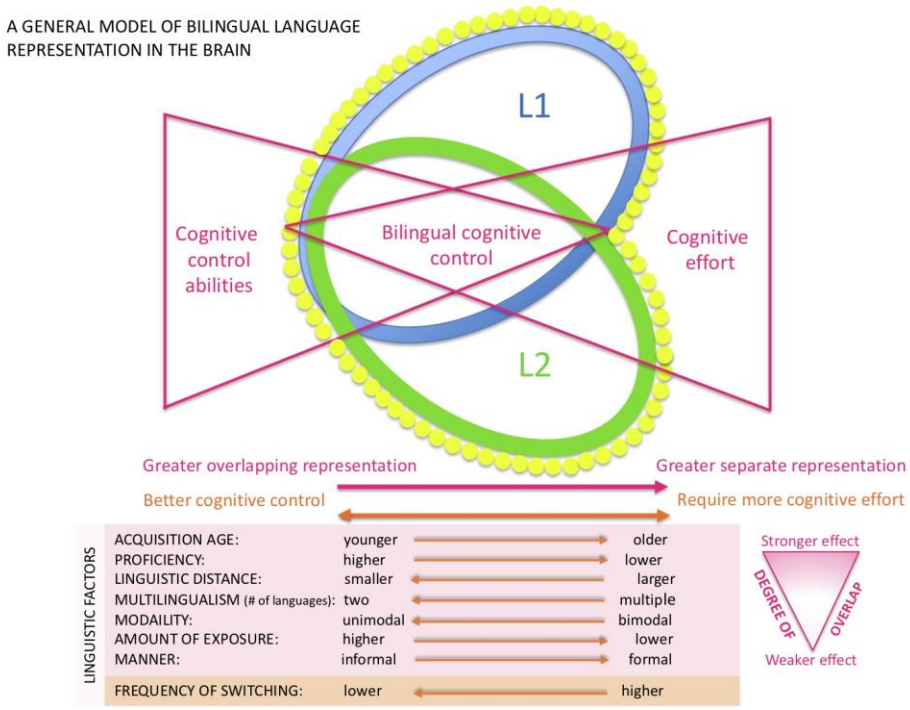
Program #/Poster #: 701.03/CC6

Topic: H.02. Human Cognition and Behavior

Title: Factors modulating the organization of languages in the bilingual brain: A systematic review

Authors: *M. M. POLCZYNSKA[1], S. Y. BOOKHEIMER[2];
[1]Univ. of California Los Angeles, Los Angeles, CA; [2]Psychiatry and Biobehavioral Sci., UCLA, Los Angeles, CA

Abstract: There have been numerous studies on linguistic factors that predict the representation of bilingualism in the brain, many of which have been based on patient data. The factors include age of acquisition of the second language (L2), proficiency level of L2, the amount of exposure to each language, manner of L2 acquisition (implicit vs. explicit), the linguistic distance between the first language (L1) and L2, multilingualism, the modality of acquisition (oral vs. sign language) and the frequency of language switching. However, there is a need for general organizing principles that incorporate all these linguistic factors explaining how the factors modify the degree of functional overlap between L1 and L2 in the brain. Here, we review bilingual studies on clinical language mapping. Methods available for study in patient mapping, with invasive techniques in particular, are much more vast than those available in healthy volunteers. We performed a literature search of articles published in English through January 2019 using four databases (e.g., PubMed). We included 29 studies with 208 participants. The reviewed data show several significant generalized principles of the neural organization of languages. Here we present two of the findings: (1) All the studies focusing on shared vs. separate language organization in bilinguals reported a tremendous degree of functional separation between L1 and L2 that is far more extensive than what is widely assumed, (2) Early L2 acquisition is associated with a more significant functional overlap between L1 and L2, in contrast to late L2 acquisition. This paper introduces a general model of bilingualism that integrates and organizes principles of bilingual representation in the brain (see the Figure). The reviewed studies validate the model. The main conclusion stemming from this review is that there is a high amount of separation between L1 and L2, therefore, it is crucial to pre-surgically map *all* languages that the patient needs to communicate in post-surgically. The results of the review will inform both basic research and clinical language mapping.



Disclosures: **M.M. Polczynska:** None. **S.Y. Bookheimer:** None.

Poster

701. Language Disorders

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 701.04/CC7

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant DC013828

Title: Electrocorticographic recordings enable intraoperative language network mapping

Authors: ***B. LIPKIN**[1], J. PLASS[1], S. KAKAIZADA[3], C. VALDIVIA[3], O. SAGHER[2], S. HERVEY-JUMPER[3], D. BRANG[1];
[1]Psychology, [2]Neurosurg., Univ. of Michigan, Ann Arbor, MI; [3]Neurosurg., Univ. of California, San Francisco, CA

Abstract: Brain tumors and epilepsy can be life-threatening pathologies requiring neurosurgical treatment. To offer patients a high post-operative quality of life, neurosurgical procedures must strike a fine balance between removing pathological tissue, while preserving vital cognitive networks. The most common approach to identifying healthy cognitive functions relies on

extensive cortical stimulation mapping (CSM) during awake neurosurgery, in which electrical stimulation temporarily disrupts cortical functions, thus identifying critical areas. However, only ~1/3 of brain tumor patients meet the clinical requirements for this procedure, limiting its utility. Furthermore, CSM is time consuming and can be non-specific about cognitive functions localized to a region. To improve the efficacy and precision of intraoperative mapping, we assessed the use of intracranial recordings (electrocorticography; ECoG) as a supplement to CSM. Data were acquired from electrodes implanted along the left peri-sylvian language cortex in neurosurgical tumor patients (n=7) during a series of speech production tasks: text reading, word repetition, audio naming, picture naming, and syntax production. ECoG recordings were time-locked to speech onset for each task and filtered to track changes in mean population spiking rates (high gamma power: 70-150 Hz) at each electrode. Preliminary results suggest that the timing of ECoG responses can be used to distinguish between nearby pre-motor (motor planning) and primary motor (motor execution) activity during speech production. Using these event-locked recordings, we confirmed a temporally specific activation cascade during speech onset from superior temporal gyrus (STG) through Broca's area to primary motor cortex, as was previously observed in epilepsy patients, extending this model to a new patient population and lending validity to intraoperative ECoG. Ongoing analyses are examining the specificity and selectivity of ECoG results relative to both CSM and functional deficits following tumor removal.

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Poster

701. Language Disorders

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 701.05/CC8

Topic: H.02. Human Cognition and Behavior

Support: Rutgers University Busch Biomedical Grant

Title: Overextension of the concrete semantic processing network in autism

Authors: *H. LEVINSON, L. COULANGES, M. J. ROSENBERG-LEE, W. W. GRAVES; Psychology, Rutgers Univ., Newark, NJ

Abstract: Autism spectrum disorder affects roughly 1 in 59 US children, almost half of whom have average to above average intellectual functioning. While basic verbal skills are intact in this group, issues with social pragmatics and abstract language persist. It remains unknown whether the basis of these issues is social or linguistic in nature. In neurotypicals (NT), cortical networks supporting semantics and social cognition largely overlap, notably in the inferior parietal lobe

and medial prefrontal cortex. A separate line of research has identified the anterior temporal lobe (ATL) as a primary hub for semantic and social knowledge representation, with graded specialization of function. For example, the ventral ATL (vATL) has been associated with concrete concepts, and the superior ATL (sATL) for abstract and social concepts. We examined differences in resting state functional connectivity between ASD and NT groups using abstract social (sATL) and concrete semantic (vATL) seed regions. A sample of 120 right-handed males was selected from the Autism Brain Imaging Data Exchange-II (ABIDE-II) database (see table). One striking pattern that emerged was the relative paucity of significant differences in functional connectivity between the groups. The significant differences that did emerge were specific to right vATL connectivity. There was heightened connectivity in the ASD group between the vATL and (1) right anterior superior temporal sulcus, a region involved in abstract-social concept processing, and (2) right posterior cingulate, a core default mode region involved in concrete semantics. Thus, seeding a region associated with concrete semantics revealed an over recruitment of the concrete network into regions usually associated with more abstract processing in NTs. Although exploratory, these results suggest heightened connectivity between brain regions that process concrete semantics and those for more abstract social processing as a potential neural basis for the challenges with abstract social processing often encountered by people on the autism spectrum. These challenges typically manifest as a tendency to interpret statements literally, the neural basis of which we are currently investigating in a separate task-based study.

Phenotype Summary from the ABIDE-II sample

	ASD	**NT**	***p***
N	59	61	
Avg Age (SD)	15.3 (3.1)	16.1 (3.3)	0.18
Full-Scale IQ (SD)	110.4 (12.2)	113.6 (11.9)	0.16
Verbal IQ (SD)	111.5 (13.3)	115.6 (11.7)	0.08
Mean Framewise Displacement (mean FD)	0.11	0.10	0.52
Age range was 12-24 for both groups. Groups did not significantly differ in age, FIQ, VIQ or mean FD			

Disclosures: H. Levinson: None. **L. Coulanges:** None. **M.J. Rosenberg-Lee:** None. **W.W. Graves:** None.

Poster

701. Language Disorders

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 701.06/CC9

Topic: H.02. Human Cognition and Behavior

Title: Severity not fluency is the clinical hallmark of aphasia

Authors: *K. WAKAIZUMI[1,2], R. JABAKHANJI[1,2], R. HURWITZ[1], S. ASHALE[1], E. BAVVITT[1], L. CHRNERY[1], M. N. BALIKI[1,2];
[1]Shirley Ryan AbilityLab, Chicago, IL; [2]Physical Med. and Rehabil., Northwestern Univ., Chicago, IL

Abstract: The cortical language system is thought to be a paradigmatic example of a modular functional system that is necessary for explaining the variability, and neuro-psychological dissociations of language impairments in aphasia, such as comprehension (Wernicke's aphasia) and fluency (Broca's aphasia). We challenge these ideas using data-driven approaches to identify the principal aspects of chronic aphasic performance, and their neural bases.
We applied principal component analysis (PCA), and network-based statistics to identify unique components of language impairments assessed using the Western Aphasia Battery-Revised (WAB-R) in 187 patients with chronic stroke aphasia. All language properties exhibited high inter-correlations and dependency. PCA identified one component with a high eigenvalue (7.47) and a high percentage of explained variance (62.2%). In addition, aphasic performances showed little clustering and topological properties similar to that of random networks.
We also used a data-driven approach to identify different classes of patients with unique behavioral properties, and contrasted them to classical diagnostic classifications of aphasia type. We used k-means and hierarchical clustering paradigms in half of our sample (discovery group, n=94) and validated our result in the other half of the data (validation group, n=93). We observed that patients robustly segregated into two major groups identified by the total propensity of their symptoms (i.e. mild and severe). The classes (mild and severe) showed significant segregation based on the aphasia quotient (AQ) score (Accuracy > 90%, $p<0.01$), but not the fluency score (Accuracy = 55%, $p>0.8$). Clinical diagnosis, such as Broca's and Wernicke's, did not follow the same classification ($p>0.5$, chi-square test), except for Anomic aphasia which mostly classified as mild. Finally, we used validated functional and anatomical neuroimaging methods to identify the neural properties of each class. We observed that total lesion size was not associated with severity of aphasia. Furthermore, resting-state fMRI analysis showed that patients in the severe group exhibited decrease connectivity within the left side of the default mode network. Overall, we show that data-driven approaches can improve our understanding of brain-behavior relationships in stroke aphasia. Our results challenge the classical modular functional systems view for aphasic impairments and indicate the need for an improved data driven framework for understanding, studying, and managing aphasia.

Disclosures: K. Wakaizumi: None. **R. Jabakhanji:** None. **R. Hurwitz:** None. **S. Ashale:** None. **E. Bavvitt:** None. **L. Chrnery:** None. **M.N. Baliki:** None.

Poster

701. Language Disorders

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Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 701.07/CC10

Topic: H.02. Human Cognition and Behavior

Support: R01DC014976 award to the Baylor College of Medicine from the National Institute on Deafness and Other Communication Disorders

Title: A new method for comparing the predictive validity of brain lesion-behavior mappings

Authors: *J. S. PATTERSON, J. F. MAGNOTTI, T. T. SCHNUR;
Baylor Col. of Med., Houston, TX

Abstract: Lesion-behavior mapping (LBM) is used to identify causal relationships between brain regions and behavior. LBM techniques provide a voxel-wise mapping between brain damage and individual differences in behavior that enable accurate prediction of behavior from lesion patterns. A common use of LBMs is to find the brain regions uniquely associated with different behaviors. Problematically, there is currently no accepted method for determining if two LBMs are significantly different. Most often, researchers compare the LBM output values (e.g., beta weights) either by subtraction or by correlation. However, a more principled statistical criterion remains elusive. Here, we propose a statistical method for comparing two LBMs based on the notion of predictive validity. Two LBMs are different if and only if they provide unique predictive power for the two behaviors assessed. The method produces as output a single statistical test that allows researchers to determine if the LBMs trained on separate behaviors provide equivalent predictive accuracy as a single LBM trained on the average of the two behaviors.

To validate our method, we assessed its ability to correctly identify brain-behavior relationships in two simulations for which the ground truth was known: the two behaviors resulted from damage to different brain regions *vs.* the same brain region. The lesion data came from a dataset of 131 persons with aphasia due to left MCA chronic stroke (source: Moss Rehabilitation Research Institute's Neuro-Cognitive Rehabilitation Research Patient Registry). We created LBMs from the simulated behavior and the lesion data using a sparse multivariate LBM technique (SCCAN; Pustina et al., *Neuropsychologia*, 2018). For each simulation, our new method compared the predictive validity of the LBMs trained on each behavior independently *vs.* a single LBM trained on the averaged behavior. The method correctly identified when the LBMs were similar (paired Wilcoxon $p = 0.46$) and when they were different ($p = 0.003$). In summary, our approach provides a statistical method to objectively determine whether two behavioral deficits are driven by similar patterns of brain damage. The technique works regardless of how the LBMs were generated and can be generalized to situations of more than two behaviors.

Disclosures: **J.S. Patterson:** None. **J.F. Magnotti:** None. **T.T. Schnur:** None.

Poster

701. Language Disorders

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 701.08/CC11

Topic: H.02. Human Cognition and Behavior

Title: Auditory perception and theta activity in specific language impairment

Authors: *I. G. GALÁN[1], N. LAGARDA[1], M. GALICIA[2];
[1]UNAM, Mexico City, Mexico City, Mexico; [2]Natl. Rehabil. Inst., Mexico City, Mexico

Abstract: Phonemes are the smallest contrasting unit of language that distinguishes the meaning of words (Pulvermüller & Fadiga, 2010), that allow perceptual equivalence within a given language (Binder, 2016) and established during the development through the input of the environmental language. The Specific Language Impairment (SLI) proposes an auditory deficit that could hypothesize a posible immaturity in the auditory cortex as a dificulty in the perception of language sounds wich would impact on the development of defined phonological representations. The theta band frequency (4-8 Hz) has been use in the study of linguistic cortical networks and the processing of words and syllables, associated to temporal regions (Carmona et al., 2014; Turken & Dronkers, 2011). ERD/ERS (event-related de-synchronization /synchronization) can be an indirect measurement of functional specificity of neuronal groups mediated by maturational processes to understand the characteristics of language processsing. The objective of this work was to compare phonemic perception skills in children with SLI and children with typical development (TD) through neuropsychological evaluation and quantitative EEG measurement (ERD/ERS) in theta band. We studied 22 children aged 5-6 years divided in two groups: SLI = 12, TD = 10. The phonemic perception performance was assessed using "ENI" Battery (Matute et al., 2007) and EEG recording was made during phonemic stimulation to obtain the ERD/ERS. We used non parametric methods to analize the data. This results indicated lower scores in phonemic perception of children with SLI compared with children with TD, the difference was significant ($Z = 17{,}500$, $p < .05$) with an average range of 7.96 for SLI children and 15.75 for TD. We also made a correlation analysis between the phonemic perception performance and ERD/ERS, the results showed that TD group presented negative association in T3 derivation, $r = -0.72$, $p = 0.04$; meanwhile, SLI presented in F7, $r = -0.87$, $p = 0.05$. This results showed that phonemic perception is influenced by perceptual expectations and phonemic aference (Arnal et al., 2016). In relation to phonemic perception, a greater involvement of left frontal regions in children with SLI could indicate a differential functioning of the linguistic network that explains the lower phonemic perception abilities in these children, which could be interpreted as a compensatory mechanism in the face of poor sensory processing.

Disclosures: **I.G. Galán:** None. **N. Lagarda:** None. **M. Galicia:** None.

Poster

701. Language Disorders

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 701.09/CC12

Topic: H.02. Human Cognition and Behavior

Support: HMRF Grant 02130846, Hong Kong SAR

Title: Impaired neural pitch encoding associated with autism spectrum disorders in Cantonese-speaking children

Authors: J. LAU[1], X. KANG[1], C. TO[2], M. LOSH[3], *P. C. WONG[1];
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Abstract: One feature observed in individuals with Autism spectrum disorders (ASD) is atypical pitch processing. Pitch, in tone languages including Cantonese, conveys word meaning. Impairment of pitch processing thus not only affects their social and emotional communication, but also structural language. This research investigates linguistic pitch processing deficits in Cantonese-speaking children with ASD. We test a version of the Weak Central Coherence (WCC) hypothesis, which posits that impairment to pitch processing associated with ASD is associated with increased sensitivity to local cues at fundamental levels of auditory processing. Despite such hyper-sensitivity to local cues, pitch processing is ultimately impaired due to impairment in the processing of global cues at higher-level processing. We investigated lexical tone processing at behavioral and neural levels of children diagnosed with ASD (N=30) versus those who are typically developing (TD, N=32). Behavioural lexical tone processing was investigated with a tone categorical perception task. Neural encoding of three lexical tones was tested by examining the Frequency-following Response (FFR), a phase-locking electrophysiological component known to provide a faithful `snapshot' of neural auditory encoding with high fidelity. We found that linguistic pitch processing is impaired at both behavioral [marked by less sharp categorical perception (β =-0.13679, Z=-2.889, p=0.0039)] and neural levels [marked by less robust FFR peak autocorrelation [$F(1,60) = 4.222$, p=0.0443], indexing lower pitch encoding fidelity] compared to TD controls. Contrary to the WCC hypothesis which predicts hyper-sensitivity at fundamental levels of processing, results point to a general linguistic pitch processing impairment associated with ASD across the hierarchy of the auditory pathway. This research has identified behavioral and neurophysiological correlates to linguistic pitch processing deficits in Cantonese-speaking children with ASD. An understanding of the behavioral and neural characteristics of their language abilities could lead to better

treatment for language and communication deficits in ASD in the long run, especially those children who are learning a tone language.

Disclosures: **J. Lau:** None. **X. Kang:** None. **C. To:** None. **M. Losh:** None. **P.C. Wong:** None.

Poster

701. Language Disorders

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 701.10/CC13

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant DC006740

Title: Left perisylvian cortex damage selectively impairs pseudoword spelling

Authors: ***J. J. PURCELL**[1], J. SHEA[2], G. PETROZZINO[2], R. WILEY[2], B. RAPP[2];
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Abstract: Spelling involves retrieving orthographic knowledge from orthographic long-term memory (OLTM) or computing phoneme-to-grapheme correspondences (PGC), and then processing the letter information via orthographic working memory (OWM) prior to producing a written or oral spelling response. Although recent work has used lesion symptom mapping to identify regions associated with OLTM in the inferior frontal gyrus and ventral occipitotemporal cortex and with OWM in the left parietal cortex (Rapp et al., 2015), this work did not test for regions uniquely associated with PGC. In this study, we address this knowledge gap by using a recently refined multivariate lesion-symptom mapping technique (DeMarco & Turkeltaub 2018) to examine the brain basis of PGC, while simultaneously accounting for impairments in either OLTM, OWM or auditory comprehension deficits. We studied 33 participants with post-stroke, chronic dysgraphia (age range 36-80; 15 female). The JHU Dysgraphia battery was used to measure of pseudoword spelling, length effects (i.e. worse spelling for long vs short words) and frequency effects (i.e. worse spelling for low vs high frequency words). Linear mixed effects models were used to obtain beta estimates for the severity of impairment in pseudoword spelling, frequency effects, and length effects in each participant; these served as estimates of damage to the PGC, OWM, and OLTM systems respectively. To account for impairments phonological input processing, we also included a pseudoword auditory discrimination (PALPA1; Kay et al., 1992). Each participant had a T1-weighted MRI scan. Enantiomorphic normalization was used to standard lesions (Nachev et al. 2008). To identify brain regions selectively associated with PGC, we used support vector regression lesion-symptom mapping (SVR-LSM; DeMarco and Turkeltaub, 2018). This analysis accounted for other variables such as frequency effect, length effect, lesion volume, age, digit span, and PALPA1. We found that impairment in PGC was associated with damage to the anterior supramarginal gyrus, pre/post-central gyri, and dorsal

IFG. Second, severity of auditory comprehension impairment (PALPA1) was exclusively associated with damage to the superior temporal gyrus. These findings fit with previous literature reporting that impairments in PGC in spelling - along with phonological input deficits - were associated with damage to left Perisylvian cortex (Henry et al. 2007). We extend this work by demonstrating that impaired PGC in spelling were restricted to damage dorsal to the Sylvian fissure.

Disclosures: **J.J. Purcell:** None. **J. Shea:** None. **G. Petrozzino:** None. **R. Wiley:** None. **B. Rapp:** None.

Poster

701. Language Disorders

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 701.11/CC14

Topic: H.02. Human Cognition and Behavior

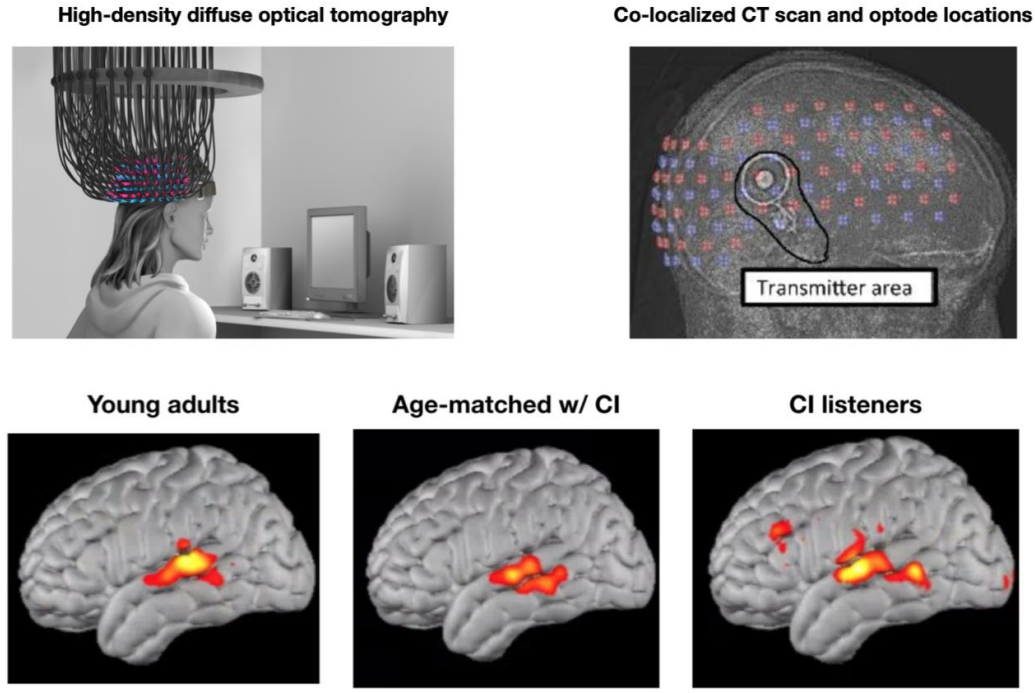
Support: NIH Grant R21 DC016086
NIH Grant R21 DC015884

Title: Dorsolateral prefrontal cortex supports speech perception in listeners with cochlear implants

Authors: A. SHERAFATI[1], N. DWYER[1], M. S. HASSANPOUR[2], A. T. EGGEBRECHT[1], J. B. FIRSZT[1], J. P. CULVER[1], ***J. E. PEELLE**[1];
[1]Washington Univ. in St. Louis, Saint Louis, MO; [2]Dept. of Ophthalmology and Visual Sci., Moran Eye Institute, Univ. of Utah, Salt Lake City, UT

Abstract: Cochlear implants (CIs) are neuroprosthetic devices that can restore hearing to patients with profound hearing loss, but with a loss of acoustic detail compared to healthy biological hearing. The brain networks required to extract meaning from this degraded signal are poorly understood. Here we use high-density diffuse optical tomography to quantify source-localized cerebral blood flow in adult patients with cochlear implants during spoken word perception. Patients all had unilateral right-side cochlear implants, and ranged in age from 31-72 years. We compared brain activity in CI patients to a group of young adults, and to a separate group of age- and sex-matched controls. Participants listened to lists of single, unrelated words in a block design, with 15 seconds of spoken words alternating with 15 seconds of silence. Each participant listened to 12 blocks of words (about 6 minutes of data). We recorded regional changes in blood flow using near infrared spectroscopy and a large field-of-view cap with 96 sources and 92 detectors, covering large portions of the occipital, temporal, and frontal lobes.Source localized results were analyzed using a voxelwise general linear model framework in standard space. We found that while listeners with normal hearing showed speech-related

activity in temporal cortex, CI listeners additionally showed activity in left dorsolateral prefrontal cortex. This frontal activation is consistent with a need to rely on executive resources to compensate for a degraded acoustic signal.



Disclosures: **J.E. Peelle:** None. **A. Sherafati:** None. **J.B. Firszt:** None. **N. Dwyer:** None. **A.T. Eggebrecht:** None. **J.P. Culver:** None. **M.S. Hassanpour:** None.

Poster

701. Language Disorders

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 701.12/CC15

Topic: H.02. Human Cognition and Behavior

Title: Ablation and resection for mesial temporal lobe epilepsy: Analysis of neuropsychological performance in language and memory

Authors: *K. TOMBRIDGE[1], C. DONOS[1], L. MOSS[2], J. JOHNSON[1], J. BREIER[2], P. ROLLO[1], N. TANDON[1,3];
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Abstract: INTRODUCTION: Brain activation studies using fMRI and electrocorticography have frequently been used to map language and memory in stroke and epilepsy patients. Voxel-wise lesion-based symptom mapping (VLSM) techniques, typically conducted in stroke patient populations, are vital in delineating the anatomical organization of language. This technique does not consider both important pre-morbid individual differences and reorganization that occurs after damage. Accounting for these factors will maximize the predictive power that connectivity has on behavioral outcome. By applying this technique in a controlled-lesioned epileptic patient population, we can disambiguate the components of the temporal lobe.
METHODS: To elucidate the cognitive impact, lesioned tissue was related to neuropsychological assessments in a sample of 63 patients who underwent surgery to treat mTLE. These patients underwent one of the surgical techniques: Anterior Temporal Lobectomy (ATL; n=42) or Laser Interstitial Thermal Therapy (LITT; n=21), in the left, language-dominant hemisphere. Pre- and post-operative behavioral and neuroimaging measures were conducted to measure pre-surgical differences and post-surgical functioning. The neuropsychological test battery included measures of verbal fluency, naming, and memory (semantic, verbal, and spatial). Lesion volumes were outlined using a post-operative T1 contrasted MRI in MRIcron software. Seizure outcomes were measured using Engel classification. VLSM and percent damage of brain region were analyzed with neuropsychological subtests.
RESULTS: In both ATL and LITT, post-surgical declines in verbal memory were found. Region-based analyses provided a distinct relationship between percent damage to anterior temporal lobe sub-regions and neuropsychological task performance. Comparison of neuropsychological outcomes between surgery types showed significant differences in verbal learning, auditory memory, and visual memory. No significant impact on naming was detected within the ablation surgical group.
CONCLUSIONS: This study leverages a unique patient population for the comparison of the effects of lesions on individuals' cognition. Consequently, we can better quantify the functional organization of language-dominant temporal lobe and the impact ATL and LITT surgeries have on cognitive outcomes. This will inform future refinement of psycholinguistic models of language as well as provide insights to design surgical interventions for mTLE that minimize cognitive deficit.

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Poster

701. Language Disorders

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 701.13/CC16

Topic: H.02. Human Cognition and Behavior

Support: MOST 107-2410-H-007-036

Title: The neural correlates of emotional influence on semantic processing in alexithymia

Authors: *S.-H. LEE[1], C.-L. YU[1], T. CHEN[2], C.-C. LIAO[2];
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Abstract: Alexithymia has been found as a major risk factor for a variety of psychiatric disorders, including somatoform disorders, panic disorders, drug addiction, and alcoholism (Waller & Scheidt, 2004). Individuals with alexithymia demonstrate disabilities in both affective and cognitive dimensions characterized by identifying, analyzing, and verbalizing the emotions of the self (Vorst & Bermond, 2001). Specifically, alexithymia has been thought as a linguistic deficit in processing emotions of self and also in understanding the emotions of others (Moseley et al., 2015). Thus, individuals with alexithymia may show both affective and semantic deficits, demonstrating disruptions in both emotion-related regions and semantic-related regions in the brain. However, the neural correlates of this interaction is not clear. In the current study, we aimed to use event-related fMRI to examine the neural correlates of emotional influence on semantic processing in alexithymia. In order to have a better understanding of the emotional influence on semantic processing, we aimed to adopt an emotional semantic judgment task. In the semantic judgment task, association strength (strong, weak) and emotional valence (negative, neutral) are independently varied. This systematic manipulation allowed for a more precise determination of the role of emotion in processing meaning. In the current study, we conducted analyses for the individuals with high alexithymia in the contrast of [(Negative strong association > Neutral strong association) - (Negative weak association > Neutral weak association)]. The results revealed significant activation in the left inferior parietal lobule (IPL), supporting the semantic integration for the incoming semantic information into a larger unit of concept for stronger association pairs. In addition, the results also demonstrated significant activation in right temporal parietal junction (TPJ), medial prefrontal cortex (mPFC) and precuneus, suggesting the engagement of self-recognition over negative emotion. Our current analyses gave an overview of the networks of the impact of emotion over semantic processing in individuals with high alexithymia. Thus, we may evaluate the dysregulation of brain regions associated with emotional processing and semantic processing and the inter-connection between these brain regions for both high and low alexithymia groups in our future research.

Disclosures: S. Lee: None. **C. Yu:** None. **T. Chen:** None. **C. Liao:** None.

Poster

702. Genomic and Proteomic Techniques

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 702.01/CC17

Topic: I.02. Systems Biology and Bioinformatics

Title: LiP-MS: A novel approach to probe protein (mis)folding and drug-protein interactions

Authors: *Y. FENG[1], L. MALINOWSKA[2], L. VERBEKE[1], N. BEATON[1], R. BRUDERER[1], L. REITER[1], P. PICOTTI[2];
[1]Biognosys AG, Schlieren-Zurich, Switzerland; [2]Inst. for Mol. Systems Biol., ETH Zurich, Zurich, Switzerland

Abstract: Background Protein misfolding and aggregation are commonly observed phenomena in a wide range of neurodegenerative diseases. For example, aggregates of the amyloid-beta (Aβ) peptide and of the protein alpha-Synuclein (αSyn) are formed in brains of Alzheimer's disease (AD) and Parkinson's disease (PD) patients, respectively. (Mis)folding and aggregation events of these disease-related proteins have been extensively investigated in vitro. However, little is known about their structure-function/toxicity relationship in vivo, largely due to the lack of experimental tools that can assess protein structural features in complex biological matrices. To address this challenge, we developed a strategy combining limited proteolysis (LiP) and quantitative mass spectrometry (MS) that enable the proteome-wide probing of protein structural alterations directly in cell and tissue lysates. We showcase the power of this approach in two major applications that are highly relevant to drug development and discovery in the neuroscience space.
Results In the first application of LiP-MS, we deployed this method to compare in vitro and in situ structures of αSyn. We generated a library of structure-specific proteolytic signatures using well-characterized structures of αSyn prepared from the recombinant protein. We then measured the proteolytic signatures of αSyn in cells overexpressing αSyn and used in vitro reference structures in a mathematical framework for predicting the αSyn structural composition in cells. As a second application, we developed dose-response (DR) LiP-MS for drug target deconvolution. Detection and quantification of LiP-peptides allowed us to probe small molecule drug-binding sites and to estimate binding affinities (IC50) in cellular lysate. To demonstrate the performance of this workflow, we profiled the target space for a specific kinase inhibitor, selumetinib (SE), as well as a broad-band inhibitor, staurosporine (ST). Our approach successfully identified the known target MEK1 for SE while for the unspecific ST, we found a significant enrichment of kinase targets in our drug-binding candidate list.
Conclusions We present a method that enables two key applications to address unmet needs in neurodegeneration research. On the one hand, LiP-MS can be employed to assess the structural landscape of disease-related proteins in clinically relevant cells and tissues. On the other hand, LiP-MS has demonstrated its capabilities as a powerful target deconvolution and identification strategy, regardless of the specificity of the compound.

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Poster

702. Genomic and Proteomic Techniques

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 702.02/CC18

Topic: I.02. Systems Biology and Bioinformatics

Support: TRN512243

Title: Integrative proteomics and pathway analyses reveal perturbed mitochondrial signaling in ApoA2-kocout mice brain

Authors: M. KHALIFA[1], *S. AZZAM[2], J.-E. DAZARD[2], K. STROHL[2];
[1]St. George's Univ. Sch. of Med., St. George's, Grenada; [2]Case Western Reserve Univ., Cleveland, OH

Abstract: Apolipoprotein A2 (ApoA2) is a brain apolipoprotein. ApoA2 gene and its downstream interactions have broad effects on breathing and fictive brainstem phrenic rhythm stability (Gillombardo et al, 2017). The lack of fundamental information relevant to its unexpected CNS presence and potential effects at cellular level leads one to further investigate the topic. To address this and understand system-level perturbations mediated by ApoA2 presence (ApoA2-WT mouse) or absence (ApoA2 knockout (KO) mouse), we performed integrative omics profiling and pathway analyses. Our previous proteomics data showed no ApoA2 protein in the KO mouse; and a lesser abundance of the protein in WT brainstem, and hypothalamus in comparison to either WT liver or plasma (P=0.0001). In this study, label-free expression proteomics and phosphoproteomics profiles of brain tissue from WT (n = 8) and ApoA2-KO (n = 8) were acquired by LC-MS/MS (LTQ Orbitrap). LC-MS/MS raw files were imported into Rosetta Elucidator^{TM} software for peptides identification and quantification. To reduce the dimensionality of the data, and reduce the error rates, pre-filtered proteins with at least two quantified peptides were analyzed for differential expression using a Bayesian ANOVA model. To examine how APOA2 KO-induced differential proteomic expressions predict the downstream changes in APOA2 KO-induced phosphorylation signaling pathway(s), we integrated both omics-datasets using Partial Least Square (PLS) and Kinase-Substrate Enrichment Analysis (KSEA) approaches. While Bayesian ANOVA yielded a total of 387 unique annotated proteins (209 up- and 178 down-regulated) and 162 unique annotated proteins (127 up- and 35 down-regulated) from label-free and phosphoproteomics data, respectively, PLS revealed a subset of differentially expressed proteins correlated with 22 activated kinases/phosphatases proteins upon ApoA2-KO. Analyzing this integrated data by two novel pathways tools, Ingenuity Pathway Analysis (IPA) and Crosstalker, identified mitochondrial function (oxidative phosphorylation, citric acid cycle and respiratory electron transport) as the top dysregulated canonical pathway. This finding is consistent with our previous quantitative

proteomic and pathway analyses of liver tissue that have indicated an effect of ApoA2 on mitochondrial electron transport chain. In conclusion, integrative omics profiling and pathway analyses identify protein, and kinase, activity perturbations in mitochondrial signaling as a consequence of ApoA2 loss with implication for energy homeostasis and cellular bioenergetics systems in the brain.

Disclosures: **M. Khalifa:** None. **S. Azzam:** None. **J. Dazard:** None. **K. Strohl:** None.

Poster

702. Genomic and Proteomic Techniques

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 702.03/CC19

Topic: I.02. Systems Biology and Bioinformatics

Support: AHA 19POST34380239
AHA 18EIA33890055
NIH HL134850
NIH HL084207

Title: Transcriptomic changes in the arcuate nucleus of the hypothalamus in response to prolonged high fat diet: Insights from single-nucleus RNA-sequencing

Authors: *G. DENG, L. L. MORSELLI, S. A. SAPOUCKEY, V. A. WAGNER, A. E. KWITEK, J. L. GROBE, H. CUI;
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Abstract: Selective leptin resistance (SLR) is a pathological state caused by prolonged high fat diet (HFD) feeding in which cardiovascular responses to leptin are preserved, but metabolic effects are attenuated. Thus, SLR is hypothesized to contribute to obesity-associated hypertension, but the mechanisms causing SLR are unclear. Neurons expressing agouti-related peptide (*Agrp*) within the arcuate nucleus (ARC) represent a major target for leptin signaling and may play a role in SLR. Previous studies in various rodent models indicate that while shorter-term (4-14 weeks) HFD feeding suppresses ARC *Agrp* expression, this suppression is lost with longer-term (10-20 weeks) exposure. Further, 10 weeks of 45% HFD (D12451) feeding is sufficient to cause SLR in wildtype C57BL/6J mice. To examine the transcriptomic changes induced by prolonged HFD exposure specifically in *Agrp* neurons, we performed single-nucleus RNA-sequencing on nuclei isolated from ARC of *ad libitum* fed male C57BL/6J mice fed chow diet (7013; CD, n=5) or 45% HFD (n=6) from 8 to 18 weeks of age. At 18 weeks, fat mass (+10.1±1.4 vs +3.2±0.4g, $p<0.01$) was increased in mice fed HFD vs CD, energy expenditure was decreased (feed efficiency: 17±2 vs 12±1 mg/kcal, $p<0.05$), and caloric intake was normal (10±1 vs 9±1 kcal/d after correction for body mass, $p=0.3$). After pooling replicates and filtering

out nuclei with low quality reads, a total of 6,621 (CD) & 14,396 (HFD) nuclei remained. Unbiased clustering (Seurat) identified 22 cell-type clusters, including one cluster with high expression of *Agrp* (n=136 CD & 453 HFD cells). HFD caused differential expression of 73 genes in this cluster, including genes previously implicated in energy balance such as *Grm5* (69% of CD, FDR q<0.01). Interestingly, although 10 weeks of HFD feeding increased circulating leptin (119±43 vs 486±148 pg/mL, p<0.05), *Agrp* expression was increased (126%, FDR q<0.01) and Ingenuity Pathway Analysis revealed gene expression perturbations in canonical pathways implicated in the pathogenesis of obesity, including "Leptin Signaling in Obesity" and "Protein Kinase A (PKA) Signaling." These results correlate dysregulated *Agrp* expression within ARC *Agrp* neurons with the development of SLR, and may implicate altered PKA signaling in this process.

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Poster

702. Genomic and Proteomic Techniques

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 702.04/CC20

Topic: I.02. Systems Biology and Bioinformatics

Support: Support from the Knut and Alice Wallenberg Foundation

Title: A new tool for exploring gene and protein expression and localisation in human, pig and mouse brain

Authors: *N. MITSIOS[1], W. ZHONG[2], E. SJOSTEDT[1], P. OKSVOLD[2], F. EDFORS[2], F. NORRADIN[3], C. ADORI[1], A. LIMISZEWSKA[1], S. KHEDER[1], C. LINDSKOG[3], F. PONTEN[3], L. FAGERBERG[2], T. HOKFELT[1], Y. LUO[4], M. UHLEN[1,2], J. MULDER[1];
[1]Dept. of Neurosci., Karolinska Inst., Stockholm, Sweden; [2]Sci. for Life Lab., KTH Royal Inst. of Technol., Stockholm, Sweden; [3]Dept. of Immunology, Genet. and Pathology, Uppsala Univ., Uppsala, Sweden; [4]Ctr. for Regenerative Med., BGI, Shenzhen, China

Abstract: The Human Protein Atlas (HPA, http://www.proteinatlas.org) is a public online database that provides an integrated overview of protein expression and location in all major human organ and tissue types. Within this portal, we have now created a brain-centric sub atlas, where a similar approach is used to provide a comprehensive overview of protein expression in the main anatomical structures of the human, mouse and pig brain. RNA expression levels in the major anatomically defined regions of the mammalian brain are compared and used for classification of all human protein-coding genes (one-to-one orthologous genes) in human, pig and mouse. Antibody-based protein profiling in human and mouse enable spatial resolution

down to almost single cell level. Thus, we provide additional information on the detailed localization of proteins in cells compared to ISH, with proteins located at synaptic compartments being a clear example of targets that benefit of this antibody-based investigation. Thanks to such multi-omics approach, we have found several genes with an expression profile unique to the human brain when compared to mouse and pig. Notably, among all investigated brain regions, the cerebellum had the highest level of variation when compared to other brain regions or when compared with other species.

Disclosures: **N. Mitsios:** None. **W. Zhong:** None. **E. Sjostedt:** None. **P. Oksvold:** None. **F. Edfors:** None. **F. Norradin:** None. **C. Adori:** None. **A. Limiszewska:** None. **S. Kheder:** None. **C. Lindskog:** None. **F. Ponten:** None. **L. Fagerberg:** None. **T. Hokfelt:** None. **Y. Luo:** None. **M. Uhlen:** None. **J. Mulder:** None.

Poster

702. Genomic and Proteomic Techniques

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 702.05/CC21

Topic: I.02. Systems Biology and Bioinformatics

Support: The Human Protein Atlas project is funded by the Knut & Alice Wallenberg foundation

Title: Introducing the HPA Brain Atlas, a brain-centric sub atlas with regional expression maps of the human, pig and mouse brain

Authors: *E. SJOSTEDT[1], W. ZONG[2], N. MITSIOS[3], P. OKSVOLD[2], F. EDFORS[2], F. H. NORRADIN[5], C. ADORI[3], A. LIMISZEWSKA[3], S. KHEDER[3], C. LINDSKOG[5], F. PONTEN[5], L. FAGERBERG[2], T. G. HOKFELT[6], Y. LUO[7], M. UHLEN[2], J. MULDER[4];
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Abstract: Identifying the molecular organization of the brain, at the regional, cellular and sub cellular levels is important to provide detailed molecular information to advance our understanding of the brain physiology and disease. In the Human Protein Atlas (HPA) we use an integrated omics approach based on transcriptomics analysis and antibody-based mapping to better understand protein expression and localization. We now created a brain-centric sub atlas, where a similar approach is used to provide a comprehensive overview of protein expression in the main anatomical structures of the human, mouse and pig brain. The transcriptomics analysis of the basic brain structures (olfactory bulb, cerebral cortex, hippocampal formation, amygdala,

basal ganglia, hypothalamus, thalamus, midbrain, pons, medulla oblongata and cerebellum) reveals the fundamental molecular organization of the mammalian brain, but also unique features not shared by all 3 species. Antibody-based protein profiling in human and mouse enable spatial resolution down to single cell details. Serial sections of the mouse brain provide a full brain overview for a selection of over 250 targets, available as online virtual microscope of high-resolution images. And more than 800 genes were selected for protein mapping in human, in collaboration with the Tissue Atlas. By combining the brain-centric perspective with the whole-body view, established in an updated version in the HPA Tissue Atlas, we are able to classify protein-coding genes based on the expression level and group genes into different categories. Genes with higher expression in brain compared to other tissue types are highlighted as "brain elevated" (in total 2587 genes) and when comparing the expression levels within brain, 1059 genes are classified as regionally elevated. This unique strategy enables comparison of expression within brain to the whole-body perspective. And for the first time we facilitate a gene based comparison of RNA expression in three different mammalian brains, side by side, grouped into the major regions of the brain.

Disclosures: **E. Sjostedt:** None. **W. Zong:** None. **N. Mitsios:** None. **P. Oksvold:** None. **F. Edfors:** None. **F.H. Norradin:** None. **C. Adori:** None. **A. limiszewska:** None. **S. kheder:** None. **C. lindskog:** None. **F. Ponten:** None. **L. Fagerberg:** None. **T.G. Hokfelt:** None. **Y. Luo:** None. **M. Uhlen:** None. **J. Mulder:** None.

Poster

702. Genomic and Proteomic Techniques

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 702.06/CC22

Topic: I.02. Systems Biology and Bioinformatics

Support: CDTI IDI-20180117 from CDTI, Spanish Ministry of Science, Innovation and Universities

Title: Chemoproteomics identifies key KDM1A interactors and unravels mechanisms of action of vafidemstat on aggressive behavior and cognition

Authors: M. M. P. LUFINO, C. MASCARÓ, D. ROTLLANT, C. BUESA, *T. MAES; Oryzon Genomics S.A., Cornella de Llobregat, Spain

Abstract: Epigenetic dysregulation plays an important role in neurodegenerative and psychiatric disorders. Vafidemstat (ORY-2001) is an orally available, brain-penetrant KDM1A/MAO-B inhibitor. Vafidemstat is currently in PhIIa clinical trials in Alzheimer's disease (AD), Multiple sclerosis and in aggression. We previously reported that vafidemstat restores the cognitive deficit and behavior alterations including aggression in SAMP8 mice; and the responsiveness of

immediate-early genes (IEG) in their prefrontal cortex following exposure to stress. Recent data from the PhIIa basket trial in aggression indicate that vafidemstat also reduces aggression in patients with BPD and ADHD. KDM1A is a FAD-dependent amine oxidase recruited to active chromatin by transcription factors (TFs) and demethylates primarily H3K4me2/1 marks, thus repressing gene expression. We analyzed the KDM1A interactome in human neuroblastoma cells using a biotinylated KDM1A chemoprobe that binds specifically to the active enzyme. KDM1A-containing complexes were pulled down and analysed by mass spectrometry. This chemoproteomics approach permitted identification of components of the core KDM1A complex including RCOR and HDAC proteins, in addition to KDM1A-recruiting TFs ZMYM2, ZNF516 and ZNF217. KDM1A-interactor ELISAs on neuroblastoma cells and on human hippocampal tissue confirmed the interactions detected by MS and identified several other KDM1A-recruiting TFs, including REST, ZNF878, OVOL2, SRF and GTF2I. The last two TFs are particularly interesting as they control the transcription of the IEG *Fos* and have been involved in cognition and behavior. *GTF2I* duplication is involved in autism spectrum disorders in the 7q11.23 duplication syndrome. SRF is important for activity-dependent gene expression and its loss in the forebrain of rodents impairs acute stress-associated immediate and long-term coping mechanisms, learning and memory. KDM1A transcription regulation circuits are complex, and the role of many TFs that recruit KDM1A in the brain is still largely unknown and requires further studies. Nevertheless, the identification of SRF and GTF2I as key elements in the mechanism of action of vafidemstat provides solid support for the observed therapeutic activity of this compound in cognition and behavior.

Disclosures: **M.M.P. Lufino:** A. Employment/Salary (full or part-time):; ORYZON GENOMICS S.A. **C. Mascaró:** A. Employment/Salary (full or part-time):; ORYZON GENOMICS S.A. **D. Rotllant:** A. Employment/Salary (full or part-time):; ORYZON GENOMICS S.A. **C. Buesa:** A. Employment/Salary (full or part-time):; ORYZON GENOMICS S.A.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ORYZON GENOMICS S.A. **T. Maes:** A. Employment/Salary (full or part-time):; ORYZON GENOMICS S.A.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ORYZON GENOMICS S.A..

Poster

702. Genomic and Proteomic Techniques

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 702.07/CC23

Topic: I.02. Systems Biology and Bioinformatics

Support: Hartwell Foundation to J.N.S
2018 NARSAD Young Investigator Grant to Y-Z.W

CHDI Foundation to J.N.S

Title: Determining cell-type specific striatal synaptic proteomes in mice

Authors: *H. WANG[1], Y.-Z. WANG[2], J. N. SAVAS[1];
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Abstract: Mammalian synapses display a high degree of structural and functional diversity. The large number of neuron and neurotransmitter types make it extremely challenging to isolate the proteome of a single type of synapse with biochemistry, micro dissection, or cell sorting. Until recently, our understanding of the synaptic proteome has been limited by composite measures of heterogeneous synaptosome biochemical fractions. We set out to develop a modular tool kit in order to systematically measure many different discrete synapse types in the mouse brain. We merged several previously described tools to leverage a new set of probes based on BioID (a biotin ligase, BirA*). We fused BirA* to the pre- and post- synaptic membrane localization domains from pre-mGRASP (BirA*-pre) or post-mGRASP (BirA*-post). We characterized our probes in cultured hippocampal neurons and found that about 90% BirA*-pre puncta co-localized with the excitatory synapse marker VGluT1 but only 20% with the inhibitory synapse marker VGAT. Similarly, 80% of the BirA*-post puncta colocalized with PSD95 but 40% with Gephyrin. In this way we aim to achieve promiscuous biotinylation of synaptic proteins interacting with the probe or in close proximity. The biotinylated proteins are pull-down by streptavidin or anti-biotin antibodies and analyzed by tandem mass spectrometry-based proteomic analysis. To test the tools, we stereotactically delivered them as viruses to several basal ganglia circuits: 1) targeting synapses at direct or indirect pathway spiny projection neurons (e.g. dSPNs or iSPNs) in striatum that are affected in autism spectrum disorder (ASD); 2) targeting synapses at striatopallidal projection that is affected in Huntington's disease (HD). With IHC we found that both BirA*-pre and BirA*-post successfully facilitated biotinylation within striatum without recruiting astrocytes or microglia. In our proteomic analysis on wild-type striatum samples, we quantified 1,740 proteins at similar levels in both cell types, 842 proteins specific for dSPNs, and 77 for iSPNs. Additional bioinformatic analysis showed that the BirA*-post datasets were enriched for proteins known to localize to postsynaptic membranes and presynaptic proteins in BirA*-pre datasets. These data documented our progress towards obtaining a near complete draft of specific synaptic proteome. In the future we will apply our probes to a panel of synapses in mouse models of HD and ASD. It is our hope that by determining how discrete synaptic proteomes are remodeled we will gain new insight on how synapse are hampered during diseases.

Disclosures: **H. Wang:** None. **Y. Wang:** None. **J.N. Savas:** None.

Poster

702. Genomic and Proteomic Techniques

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

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Topic: I.02. Systems Biology and Bioinformatics

Support: FI Grant
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PIRG-GA-2009-256413
2014-SGR-200
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Rockefeller University

Title: A universal evolution-based nomenclature for the oxytocin and vasotocin ligand and receptor families

Authors: *C. THEOFANOPOULOU[1], G. GEDMAN[2], J. A. CAHILL[4], C. BOECKX[5], E. D. JARVIS[3];
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Abstract: Oxytocin (*OT*) and vasopressin/vasotocin (*VT*) are neurotransmitter ligands that function through specific receptors to control a diverse set of brain functions. Here we performed genome analyses in 34 species spanning all major vertebrate lineages and 4 outgroup invertebrate lineages to resolve orthology and the evolution of oxytocin and vasotocin ligands and receptors (*OT*, *VT* and *OTR-VTRs*). We included genomes of newly re-sequenced species with long-read technology that filled in gaps and corrected errors in previous shorter-read assemblies, some of the former being assemblies contributed by the G10K Vertebrate Genomes Project (VGP; https://vertebrategenomesproject.org). We performed pair-wise BLAST/BLAT analyses, analyzed gene synteny from microchromosomal to macrochromosal scales, across and within species, and performed phylogenetic tree inference of genes families. Our findings support the claim that *OT* and *VT* are adjacent paralogous genes resulting from a local duplication, which we infer was through DNA transposable elements near the origin of vertebrates, with *VT* the parental gene. We identified six *OTR-VTR*s among vertebrates, and propose they arose from a single invertebrate-like *VTR* through a combination of whole genome and large segmental duplications at the origin of vertebrates, followed by lineage-specific losses and gains. Based on these findings we propose a universal evolution-based nomenclature for the oxytocin and vasotocin ligand and receptor gene families, where they be given the same

orthologous names across vertebrates and paralogous names relative to each other, according to their relationships and evolutionary history. This terminology and vertebrate-wide perspective should prevent further confusion and errors of orthology and paralogy due in part to differential naming in the pre-genomic era, allow easier translation of findings across vertebrates, foster more informative design of functional experiments across species, and further understanding of their evolution.

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Poster

702. Genomic and Proteomic Techniques

Location: Hall A

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Topic: I.02. Systems Biology and Bioinformatics

Support: California Tobacco-Related Disease Research Program (TRDRP) Grant 251P003
TRDRP grant 24RT-0023H
NIMHD/NIH Accelerating Excellence in Translational Science (AXIS) grant 2U54MD007598
NHLBI/NIH grant 1R01HL135623-01
NIDA/NIH grant 1R41DA044788-01

Title: A mouse model for chronic intermittent electronic cigarette exposure exhibits nicotine pharmacokinetics resembling human vapers

Authors: *X. M. SHAO[1,2], B. LOPEZ[2], D. NATHAN[2], J. WILSON[2], E. BANKOLE[2], H. TUMOYAN[2], A. MUNOZ[2], J. ESPINOZA-DEROUT[2], K. M. HASAN[2], S. CHANG[2], C. DU[3], A. P. SINHA-HIKIM[2], K. LUTFY[4], T. C. FRIEDMAN[2];
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Abstract: The use of electronic cigarettes has increased in recent years, particularly among youths. Animal models for e-cigarette exposure with pharmacokinetics resembling human e-cigarette users are lacking. We developed an e-cigarette aerosol exposure system for rodents and a chronic intermittent delivery method that simulates e-cigarette users who vape episodically during wakefulness and abstain during sleep. Mice were exposed to e-cigarette in a programmed schedule at very low, low, medium, and high doses defined by duration of each puff, number of puffs per delivery episode and frequency of episodes in the dark phase of a 12/12-h circadian cycle for 9 consecutive days. The plasma nicotine/cotinine levels and their time courses were

determined using LC/MS-MS. We assessed the body weight, food intake and locomotor activity of Apolipoprotein E null mice exposed to chronic intermittent e-cigarette aerosol. Plasma nicotine and cotinine levels were positively correlated with exposure doses. Nicotine/cotinine levels showed a circadian variation as they increased with time up to the maximum nicotine level of 21.8 ± 7.1 ng/mL during the daily intermittent e-cigarette exposure in the 12-h dark phase and then declined during the light phase when there was no e-cigarette delivery. Chronic e-cigarette exposure to ApoE-/- mice decreased body weight, food intake and increased locomotion. Our rodent e-cigarette exposure system and chronic intermittent exposure method yield clinically relevant nicotine pharmacokinetics associated with behavioral and metabolic changes. The methodologies are essential tools for *in vivo* studies of the health impacts of e-cigarette exposure on CNS, cardiovascular, pulmonary, hepatic systems, metabolism and carcinogenesis.

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Poster

702. Genomic and Proteomic Techniques

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 702.10/CC26

Topic: I.02. Systems Biology and Bioinformatics

Support: NIH EY018607
Sigma Xi GIAR

Title: Strain-dependent sexual dimorphism in the cns: Proteomic analysis of the mouse retina

Authors: ***J. C. HARMAN**[1], J. J. GUIDRY[2], J. M. GIDDAY[1];
[1]Ophthalmology, Physiology, Neurosci. Ctr. of Excellence, Biochem., Louisiana State Univ. Hlth. Sci. Ctr., New Orleans, LA; [2]Biochemistry-Proteomics Core Facility, LSUHSC, New Orleans, LA

Abstract: The neuroscience research enterprise depends on preclinical models to gain insight into human physiology and pathophysiology. While studies in rodents have historically represented a large fraction of this endeavor, studies of strain-dependent differences are rare. Only recently have calls been made to systematically include females. In our efforts to understand disease, we often consider the resting, baseline condition as only a control, and not as the very foundational basis for such disease. To document the significance of these shortcomings at the phenotypic level, we undertook a quantitative proteomics approach to analyze the retina of adult mice, with strain and sex as independent variables. Retinae were harvested from 5 male and

5 female mice of both the inbred C57Bl/6J (B6) strain (Jackson Labs, Bar Harbor ME), and the outbred Swiss Webster-ND4 (SW) strain (Envigo, Indianapolis IN), during daylight hours under resting conditions. Retinae were processed for MS3 analysis on a Fusion Orbitrap mass spectrometer using Tandem-Mass-Tags for quantification. Approximately 4000 unique proteins were identified in the both the inbred and outbred retinae. 77 proteins were differentially expressed (at levels >1.5 fold) between male and female mice in B6. In SW mice, 76 proteins showed sex-dependent expression differences. Downstream bioinformatic analysis implicates many of these proteins as enriched in metabolic pathways. Of note, only about 25% of the differentially expressed proteins were identical between strains. These data indicate that, in the resting state, significant differences exist in the adult retinal proteome of inbred and outbred mice, and that the adult retinal proteome exhibits a number of distinct, sex-dependent differences unanticipated for a tissue unrelated to reproductive fitness. On the one hand, these differences provide a phenotypic foundation for the epidemiological findings that the incidence of many neurological diseases varies by sex. On the other hand, these differences also raise serious caution about assuming the physiologic and anatomic ubiquity, as well as the translational relevance, of preclinical neuroscience research results derived from studies based on a single inbred or outbred strain, or a single sex.

Disclosures: **J.C. Harman:** None. **J.J. Guidry:** None. **J.M. Gidday:** None.

Poster

702. Genomic and Proteomic Techniques

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 702.11/CC27

Topic: I.02. Systems Biology and Bioinformatics

Support: Fred Murphy Jones & Homer Lindsey Bruce Endowed Fellowship

Title: Dissecting individual differences in alcohol sensitivity using *C. elegans*

Authors: *B. L. CLITES[1], K. EVANS[2], E. ANDERSEN[2], J. T. PIERCE[1];
[1]Inst. for Cell. and Mol. Biol., Univ. of Texas at Austin, Austin, TX; [2]Dept. of Mol. Biosci., Northwestern Univ., Evanston, IL

Abstract: Despite its high heritability, the genetic basis of alcohol use disorder (AUD) remain poorly understood. Attempts at genome-wide association studies (GWAS) for AUD in human populations have largely failed, due to a lack of controls for life history and an inability to precisely measure AUD phenotypes. To overcome these limitations, we are conducting a GWAS for alcohol sensitivity, the best predictor of later life alcoholism, using 250 whole-genome sequenced *C. elegans* wild-isolates. We have already identified four significant loci associated with resistance to acute alcohol intoxication: one near the known alcohol target BK-channel, and

three at novel sites never before implicated in alcohol response. We are now using CRISPR gene-editing to identify and functionally characterize causal variants at these loci. A more complete knowledge of the genetic underpinnings of AUD will contribute to a better understanding of the neuronal and behavioral dynamics that lead to alcohol abuse.

Disclosures: **B.L. Clites:** None. **K. Evans:** None. **E. Andersen:** None. **J.T. Pierce:** None.

Poster

702. Genomic and Proteomic Techniques

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Topic: I.02. Systems Biology and Bioinformatics

Support: NIH Grant U01 MH106876
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Title: Best practices for mosaic variant discovery in the human brain using whole-genome sequencing data

Authors: *T. B. BAE[1], .. BRAIN SOMATIC MOSAICISM NETWORK[2];
[1]Dept. of Hlth. Sci. Research, Ctr. for Individualized Med., Mayo Clin., Rochester, MN; [2]Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: Mosaic mutations, which arise post-zygotically and exist in only a subset of the cells of a single individual, are common in brain development of healthy individuals and may contribute to brain-related disorders. Despite the advent of high-throughput sequencing technologies, the accurate detection of mosaic variants is still challenging due to their presence in a very low proportion of cells. The Brain Somatic Mosaicism Network (BSMN), which is a multi-institutional initiative for the comprehensive understanding of somatic mosaicism in the human brain, generated a whole-genome sequencing data resource from the human brain to develop, optimize, and evaluate the performance of methods for mosaic variant discovery. First, we simulated mosaic variants at various allele frequencies by mixing and sequencing the DNA of four unrelated individuals. Using this data, we evaluated the performance of commonly used tools for the purpose of mosaic variant discovery. This exercise revealed that the naive application of germline variant calling from a single sample or somatic variant calling from paired samples (as typically done in cancer studies) is neither precise nor sensitive. Next,

different labs produced several replicates of whole-genome sequencing data of bulk cortical tissue and dural fibroblasts from a reference healthy human brain including standard Illumina 250X deep sequencing, linked read sequencing by 10X, and sequencing of 12 single cell neurons amplified by multiple displacement amplification. We then developed and applied several analytical approaches for calling and filtering mosaic variants from these data. Through validation experiments and the consideration of multiple orthogonal supporting evidence for 400 candidate mosaic calls, we identified a set of 44 true mosaic variants. Guided by the validation results, we derived consensus best practices for mosaic variant discovery that achieves 80%-95% precision with 70%-95% sensitivity towards the validated set. This data resource and best practices implementation will be made available to the scientific community.

Disclosures: T.B. Bae: None. **.. Brain Somatic Mosaicism Network:** None.

Poster

702. Genomic and Proteomic Techniques

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 702.13/CC29

Topic: I.02. Systems Biology and Bioinformatics

Support: U54 MD007584
P20 GM103466
P20 GM113134
17CON-87879

Title: Cell type specific analysis of selenium-related genes in brain

Authors: A. R. SASUCLARK[1], V. KHADKA[1], ***M. W. PITTS**[2];
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Abstract: Selenoproteins are a unique class of proteins that play key roles in redox signaling in the brain. This unique organ is comprised of a wide variety of cell types that includes excitatory neurons, inhibitory neurons, astrocytes, microglia, and oligodendrocytes. Whereas selenoproteins are known to be required for neural development and function, the cell-type specific expression of selenoproteins and selenium-related machinery has yet to be systematically investigated. Due to advances in sequencing technology and investment from the NIH-sponsored BRAIN initiative, RNAseq data from thousands of cortical neurons can now be freely accessed and searched using the online RNAseq data navigator at the Allen Brain Atlas. Hence, we utilized this newly developed tool to perform a comprehensive analysis of the cell-type specific expression of selenium-related genes in brain. Select proteins of interest were further verified by means of multi-label immunofluorescent labeling of mouse brain sections. Of potential significance to neural selenium homeostasis, we report co-expression of selenoprotein P (SELENOP) and

selenium binding protein 1 (SELENBP1) within astrocytes. These findings raise the intriguing possibility that SELENBP1 may negatively regulate astrocytic SELENOP synthesis and thereby limit downstream Se supply to neurons.

Disclosures: **M.W. Pitts:** None. **A.R. Sasuclark:** None. **V. Khadka:** None.

Poster

702. Genomic and Proteomic Techniques

Location: Hall A

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Program #/Poster #: 702.14/CC30

Topic: I.02. Systems Biology and Bioinformatics

Support: VIDI Grant 723.012.102
VENI Grant 863.13.020
ERC starting grant 71601

Title: Unravelling mGluR5 dynamic interactions, signaling, and mGluR-LTD mediated protein synthesis using multilayered mass spectrometry-based proteomics approaches

Authors: *C. A. G. H. VAN GELDER, R. PENNING, C. C. HOOGENRAAD, H. D. MAC GILLAVRY, M. ALTELAAR;
Utrecht Univ., Utrecht, Netherlands

Abstract: Long term depression (LTD), or activity regulated reduced synaptic strength, is a form of plasticity that is key in many brain processes (e.g. learning, memory) and in disorders such as autism. This desensitization is the result of chemical stimulation of the metabotropic glutamate receptor 5 in the dendritic spines of hippocampal neurons results in LTD, which leads to internalization of AMPA-type glutamate receptors. We use a variety of mass spectrometry-based proteomics approaches to study the molecular mechanisms of mGluR5-LTD in primary hippocampal and cortical neurons. Low sample amounts and local, dendritic protein synthesis in very short time points are challenging characteristics of these neuroproteomics experiments. Utilizing specialized proteomics approaches, including highly sensitive Fe(III)-IMAC cartridges in an automated platform to enrich for phosphorylated peptides and azide labeled methionine replacement azido homo alanine (AHA) for the labeling and enrichment of newly synthesized proteins. This allowed for the creation of a proteome wide and unbiased map of LTD signaling routes, as well as the identification of key kinases in these pathways. Moreover, we use APEX2, a chemical biology approach utilizing biotin labeling of proximal proteins, to map the mGluR5 interactome. Stimulation of the mGluR5-APEX2 fusion construct with H_2O_2 allows for rapid, 60 second, biotinylation of proximal proteins, creating a snapshot of the mGluR5 interactome in space and time in living cells. This led to the identification of novel, and location dependent mGluR5 interactors, further confirming a differential role of intracellular mGluR5.

Disclosures: C.A.G.H. van Gelder: None. **R. Penning:** None. **C.C. Hoogenraad:** None. **H.D. Mac Gillavry:** None. **M. Altelaar:** None.

Poster

702. Genomic and Proteomic Techniques

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 702.15/CC31

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Support: NIDA R03DA045833
NIDA R03DA045350

Title: Bench-marking behavioral effects of methamphetamine in casper zebrafish for the development of photoaffinity probes

Authors: *A. WISNER, A. HORTON, F. S. HALL, F. WILLIAMS, I. SCHIEFER;
Univ. of Toledo, Toledo, OH

Abstract: Background*:* Novel synthetic psychostimulants (i.e., 'bath salts') have begun to replace common drugs of abuse like methamphetamine (MA) and 3,4-methylenedioxymethamphetamine (MDMA) in recreational drug markets. The rate at which novel synthetic psychostimulants are produced has rapidly outpaced their pharmacological evaluation in mammalian animal models. The zebrafish has become a widely used model in neurobehavioral research due to its high-throughput capabilities and diverse behavioral repertoire. This work aims to utilize the Casper zebrafish line ($roy^{-/-}$; $nacre^{-/-}$) with photoaffinity labeling techniques to assess the behavioral effects of psychostimulants and identify the associated drug targets. Methods: Adult Casper zebrafish are transferred from the home tank into an exposure chamber for a 20 min waterborne exposure of varying equimolar concentrations of either MA (5-65 mg/L) or an equimolar amount of a novel methamphetamine related photoreactive probe (named MAP). Fish were then transferred to a novel tank and their behavior tracked and analyzed via a collection of freeware programming functions (available at http://iEthology.com/ and https://www.r-project.org/). Behavioral data was assessed for MA and MAP's ability to elicit a change in zebrafish locomotor and anxiety-related behavior in the novel tank test paradigm. Results/Conclusion: We successfully bench-marked a dose-response curve for MA and MAP in the Casper zebrafish line. MAP elicited similar behavioral changes as MA in the novel tank test, albeit MAP appears to be slightly more potent than MA at lower doses.

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Poster

702. Genomic and Proteomic Techniques

Location: Hall A

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Program #/Poster #: 702.16/CC32

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Support: NIDA Grant R03DA045833
NIDA Grant R03DA045350

Title: Methamphetamine probe synthesis and *in vivo* psychostimulant target identification

Authors: *A. HORTON[1], A. WISNER[2], E. TACKIE-YARBOI[1], K. HAGOOD[1], T. CHAU[3], F. S. HALL[4], F. WILLIAMS[2], I. T. SCHIEFER[1];
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Abstract: Background: Psychostimulant drugs have long been abused by every culture throughout history. Advances in synthetic chemistry techniques have introduced an ever growing variety non-naturally occurring psychostimulatory molecules ripe for abuse. Many of these drugs of abuse come from a class of molecules known as phenethylamines. Examples of commonly abused phenethylamines include methamphetamine (MA), a Schedule II psychostimulant, MDMA (commonly referred to as 'Ecstasy'), and a variety of synthetic cathinones (i.e., 'bath salts') which are new to the marketplace and have yet to be fully regulated or rigorously evaluated scientifically. Gaining a more complete understanding of the drug targets, mechanism of action (MOA), and toxicity associated with novel synthetic psychoactive agents is an important step to effectively treat substance abuse disorders, long term toxicity, and episodic lethality. This work seeks to utilize a novel experimental platform employing transparent pigment-free zebrafish (known as "casper" fish), photoaffinity labeling, and click chemistry to define target receptors of these agents. Methods/Results: We synthesized a novel MA-like photoreactive probe (named MAP), employing a Grignard dependent synthetic strategy, and demonstrated that upon irradiation with UV light (i.e., black light), MAP readily converts (half-life = 3.2 min) to a highly reactive intermediate which will react with proteins in close proximity, presumably its target proteins. Efficacy of the probe relative to MA was confirmed using the zebrafish novel tank test. After recording effects on behavior, the fish were irradiated with UV light to covalently modify target proteins/receptors. The brain tissue was homogenized and we performed click chemistry to visualize the protein targets by SDS PAGE and fluoroimaging. Conclusion: MAP displays similar activity to MA in its ability to elicit behavioral changes as assessed in the zebrafish novel tank test. Protein targets were visualized through click chemistry and proteomic validation of targets is ongoing. *In vivo* photoaffinitly labeling using casper

zebrafish represents a novel tool which allows for target ID in a live system capable of providing distinct phenotypic behavioral readouts upon exposure to CNS agents.

Disclosures: **A. Horton:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Psyneurgy Pharmaceuticals. **A. Wisner:** None. **E. Tackie-Yarboi:** None. **K. Hagood:** None. **T. Chau:** None. **F.S. Hall:** None. **F. Williams:** None. **I.T. Schiefer:** None.

Poster

702. Genomic and Proteomic Techniques

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 702.17/CC33

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

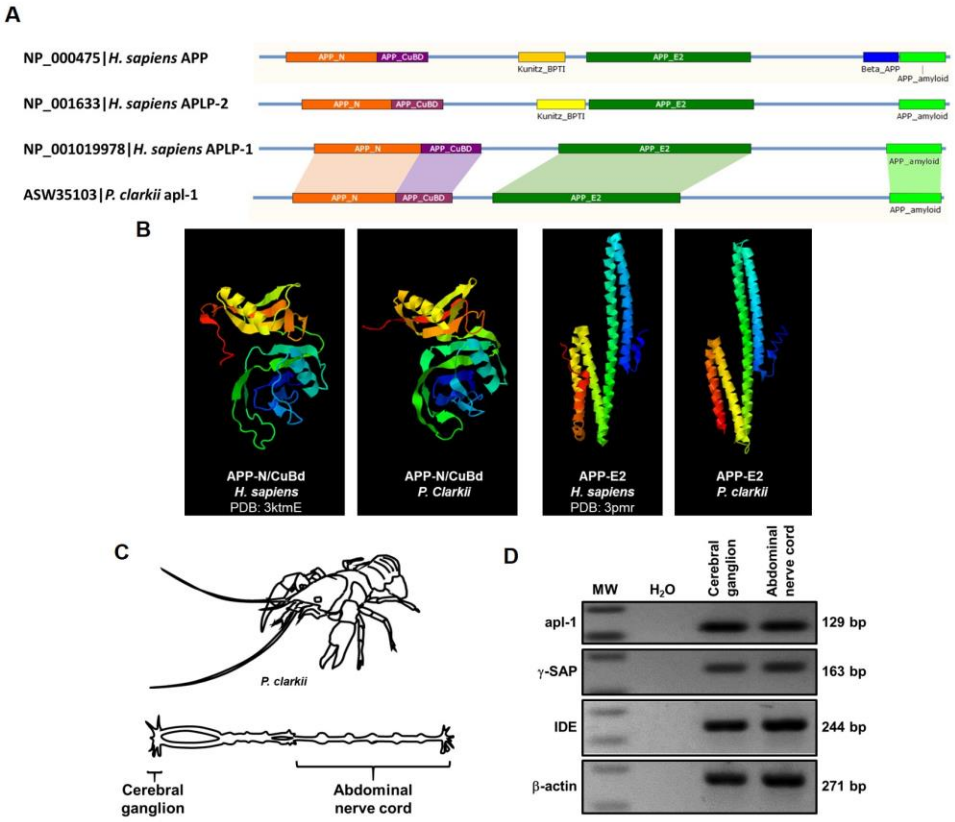
Support: ISSSTE-010.2015
PAPIIT-UNAM Grant IN214817

Title: Molecular and *in silico* characterization of the amyloid precursor-like protein (apl-1) in the red swamp crayfish

Authors: *M. LARA-LOZANO[1,2], G. CALDERÓN-ROSETE[3], N. B. PÉREZ-SILVA[4], C. FLORES DE LOS ÁNGELES[4], C. PIÑA-LEYVA[1,2], L. RODRÍGUEZ-SOSA[3], J. A. GONZALEZ-BARRIOS[2];
[1]DFBN, Ctr. de Investigación y de Estudios Avanzados del IPN, Ciudad de México, Mexico; [2]Servicio de Medicina Genómica, Hosp. Regional 1o de Octubre, ISSSTE, Ciudad de México, Mexico; [3]Dept. de Fisiología, Facultad de Medicina, Univ. Nacional Autónoma de México, Ciudad de México, Mexico; [4]Dept. de Ciencias Biológicas, Univ. Popular Autónoma del Estado de Puebla, Puebla, Mexico

Abstract: The amyloid precursor protein (APP) and the amyloid precursor-like proteins 1 and 2 (APLP-1/2) are growth factors related to neuronal differentiation, migration of NPC, neurite outgrowth and proper synaptic function. The red swamp crayfish (*Procambarus clarkii*) is an animal model used in physiology and environmental biotechnology studies; however, gene information of this crayfish are scarce. We sequenced the transcriptome of the abdominal nerve cord of *P. clarkii* by NGS. So far, we have assembled 309 sequences *de novo*; from these, we identified a gene related to human APP gene family named amyloid precursor-like 1 (apl-1) and three genes related to the APP processing: the γ-secretase activating protein (γ-SAP), the insulin-degrading enzyme (IDE) and the integral membrane protein 2B (ITM2B). In this work, we made *in silico* analysis of the apl-1 gene (KY974303) and protein (ASW35103.1). Structural analysis of apl-1 reveals four domains: APP-N from 41 to 143 aa; APP-CuBD from 146 to 201 aa; APP-E2 from 243 to 431 aa; and APP-amyloid from 644 to 695 aa (Table; Figure A and B).

Additionally, we evaluated the transcription of apl-1, γ-SAP, and IDE by RT-PCR. Interestingly, there is a high transcription activity for γ-SAP and IDE genes in the cerebral ganglion and the abdominal nerve cord (Figure C and D). In conclusion, *in silico* analysis of P. clarkii apl-1 shows structural homology to human APLP-1. Interestingly, the APP-amyloid region of apl-1 preserves the peptide sequence "GYENPTY" that is strongly conserved among species from tapeworm to human. These data describe the crayfish as a possible study model to compare the molecular and physiological roles of the APP family.



Identity matrix of P. clarkii apl-1.

	APP_N	**APP_CuBD**	**APP_E2**	**APP_amyloid**
APP	44%	46%	35%	51%
APLP-1	35%	44%	32%	38%
APLP-2	39%	46%	35%	49%

The percentages indicate the identity of the domains of the crayfish apl-1 with respect to human APP family

Disclosures: M. Lara-Lozano: None. **G. Calderón-Rosete:** None. **N.B. Pérez-Silva:** None. **C. Flores de los Ángeles:** None. **C. Piña-Leyva:** None. **L. Rodríguez-Sosa:** None. **J.A. Gonzalez-Barrios:** None.

Poster

703. Optical Methods: Applications

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 703.01/CC34

Topic: I.04. Physiological Methods

Support: ANR-11-LABX-0015
ANR-18-CE19-0024-02

Title: Imaging axonal sodium influx at high spatial and temporal resolution

Authors: *L. FILIPIS, M. CANEPARI;
Liphy-Cnrs UMR5588, Saint Martin D'Heres, France

Abstract: Recording the activity of voltage-gated Na^+ channels in the axon initial segment (AIS) is of extreme importance at understanding the origin of neuronal excitability and to explore the channelopathies associated with this fundamental phenomenon. Using the Na^+ indicator Asante natrium green-2 excited by a 520 nm laser and the ultrafast CMOS camera DaVinci2K, we have been able to monitor Na^+ influx in the AIS associated with a single action potential, at 10 kHz with a spatial resolution of ~1 µm in layer-5 neocortical pyramidal neurons in brain slices of the mouse. We could combine at the same resolution Na^+ imaging either with membrane potential imaging, using the voltage sensitive dye JPW1114, or with Ca^{2+} imaging using the low-affinity indicator FuraFF using a 405 nm laser. From these data, we could precisely monitor the spatial profile of Na^+ influx in the AIS, estimating Na^+ lateral diffusion, or spatially correlate Na^+ entry either with the generation of the action potential of with the concomitant Ca^{2+} influx. We could confirm that the critical all-or-none activation of voltage-gated Na^+ channels starting the action potential occurs at 20-30 µm from the cell body and more proximal voltage-gated Na^+ channels are activated as the action potential back-propagates towards the soma. Finally, we pharmacologically blocked voltage-gated Na^+ channels to further assess the technique. Our methodological achievement opens the gate to the full understanding of the complex ion channel activity underlying the action potential generation.

Disclosures: L. Filipis: None. **M. Canepari:** None.

Poster

703. Optical Methods: Applications

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 703.02/CC35

Topic: I.04. Physiological Methods

Title: Ultra compact miniature fluorescence microscope for simultaneously imaging neuronal activities from two brain areas in freely moving mice

Authors: *F. XUE, K. ZHANG, P. LAU, Q. ZHU, G.-Q. BI;
Univ. of Sci. and Technol. of China, Hefei, China

Abstract: Miniature fluorescence microscopes have been successfully used in the study of behaviorally relevant neuronal population activity in freely moving animals. However, currently available devices are still not sufficient for simultaneously studying activity in two or more areas in the mouse brain, a task that requires an even smaller and more lightweight solution. Here, by optimizing opto-mechanical design, together with high density interconnect (HDI) PCB and 3D printing, we develop an ultra-compact microscope that is much smaller and lightweight than currently available systems, and allows for a mouse to carry two of them in the same time. Using this system, we successfully recorded behavior-triggered neuronal activities in different brain areas in freely moving mice expressing calcium sensitive fluorescent protein GCaMP6.

Disclosures: **F. Xue:** None. **K. Zhang:** None. **P. Lau:** None. **Q. Zhu:** None. **G. Bi:** None.

Poster

703. Optical Methods: Applications

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 703.03/CC36

Topic: I.04. Physiological Methods

Support: JST PRESTO #JPMJPR1689
JSPS KAKENHI #15KK0209
JSPS KAKENHI #17H02222

Title: A battery-less, ultra-small wireless optical stimulator

Authors: *T. PAKPUWADON[1], N. WUTHIBENJAPHONCHAI[1], M. HARUTA[1], K. SASAGAWA[1], T. TOKUDA[2], J. OHTA[1];
[1]Nara Inst. of Sci. and Technol., Ikoma, Nara, Japan; [2]Tokyo Inst. of Technol., Meguro-ku, Japan

Abstract: This research aims to realize a CMOS-based battery-less, implantable optogenetic stimulator. We developed a CMOS-integrated optical power receiver chip that can drive an InGaN blue LED, and then integrated the chip with an external capacitor and the blue LED. For reducing size and weight of the device, we integrated the photovoltaic (PV) cells onto the CMOS chip. The volume and weight of the device are approximately 1 mm^2 and 2.3 mg. The operation of the device starts with the device is illuminated with IR light, the capacitor is charged with the current generated by the integrated PV cells. When the voltage of the capacitor is high enough to operate the LED, a control circuit supply power to operate the blue LED. After that, the voltage of the capacitor drops, the control circuit stops to supply power to the LED. Then, the capacitor voltage starts to increase toward next operation. With this functionality, the device can be used to perform on-brain optical stimulations in freely moving animals. We can illuminate the head of the animal with this device to perform the optical stimulation.

Disclosures: T. Pakpuwadon: None. **N. Wuthibenjaphonchai:** None. **M. Haruta:** None. **K. Sasagawa:** None. **T. Tokuda:** None. **J. Ohta:** None.

Poster

703. Optical Methods: Applications

Location: Hall A

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Program #/Poster #: 703.04/CC37

Topic: I.04. Physiological Methods

Support: JST, CREST
KAKENHI

Title: Simultaneous, multi-site imaging of deep brain regions related to feeding behavior in freely-moving GCaMP6 transgenic mice using an implantable micro-imaging device

Authors: *M. S. GUINTO, Y. OHTA, M. KAWAHARA, M. HARUTA, K. SASAGAWA, J. OHTA;
Nara Inst. of Sci. and Technol., Ikoma, Japan

Abstract: Feeding behavior is regulated by neural circuits that are primarily implicated in the processing of satiety, reward and pleasure, of which many critical regions are located in the deep brain. Currently, imaging methods available for studying these regions are still difficult to implement without interfering with the normal behavior of an awake, freely-moving mouse. To this end, here we report a scheme for investigating the neural mechanisms of feeding behavior in

mice using an implantable micro-imaging device developed in our laboratory. The micro-imaging device consists of a CMOS-based image sensor chip and a μ-LED excitation light source embedded on a flexible printed substrate and is designed to minimize invasiveness with its streamlined structure. Fluorescence emission from putative somas expressing GCaMP6 was used to indicate neuronal activity. Following deep-brain implantation, neuronal activities in the lateral and arcuate nucleus of the hypothalamus, portions of the striatum, and the amygdala were recorded in GCaMP6 transgenic mice. We also report recent improvements in the implantation protocol and environmental lighting for observing the behavior of the mouse, in addition to the emission filter applied to the sensor area, which have reduced the occurrence of artifacts in the fluorescence recordings. Moreover, the miniature size (0.5-mm device width) and relatively light weight (~20 mg) of the device has enabled simultaneous imaging of multiple sites across the mesocorticolimbic circuit to yield new insights on how distant regions interact with one another during specific behavioral sequences that characterize feeding. Our previous study shows that distinct patterns of fluorescence have been observed in different brain regions over a range of behavioral states (e.g., grooming, eating, sleeping) exhibited by the animal. Taken together, this work presents a new platform designed to access deep brain regions and monitor neuronal activity from calcium dynamics in freely-moving mice, opening avenues to establish links between robust patterns of neural activity with complex behaviors such as feeding.

Disclosures: **M.S. Guinto:** None. **Y. Ohta:** None. **M. Kawahara:** None. **M. Haruta:** None. **K. Sasagawa:** None. **J. Ohta:** None.

Poster

703. Optical Methods: Applications

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 703.05/CC38

Topic: I.04. Physiological Methods

Support: BMBF (German Federal Ministry of Education and Research) project RAPID3D (FKZ 13N14537).

Title: A comparison of remote focusing strategies for two-photon functional imaging

Authors: ***J. C. DONOVAN**[1], F. HUHN[2], T. O. HELMBRECHT[1], J. KAPPEL[1], M. DAL MASCHIO[3], G. RAPP[2], H. BAIER[1];
[1]Max Planck Inst. of Neurobio., Martinsried, Germany; [2]Rapp OptoElectronic GmbH, Wedel, Germany; [3]Dept. of Biomed. Sci., Univ. of Padua, Padua, Italy

Abstract: Many common forms of functional imaging record from a single plane, but brains consist of interconnected circuits that extend in three dimensions. Volumetric imaging is crucial for capturing network activity associated with rare behaviors, or in combination with 3D

holographic photostimulation. There are many techniques that enable fast volumetric functional imaging; however, two-photon approaches are preferred for deep imaging and for use in light-sensitive visual experiments. Experiments investigating multiple interconnected regions would often be best served by recording in multiple distinct subvolumes, to avoid the high power and other challenges associated with recording from large volumes. Common two-photon microscopes rapidly scan a laser focus in XY, and with the addition of an element for rapid focusing in Z can flexibly scan different subvolumes without optical reconfiguration. Here we compare several fast Z scanning configurations, two based on remote focusing (where a second objective is refocusing by a moving mirror) and one based on an Optotune electrically tunable lens. We characterize and compare performance in terms of speed, power efficiency, range, and point spread function (PSF). The remote focusing approaches outperform the electrically tunable lens in speed, but are more complex to setup and increase pulse dispersion. For fast point-scanned volumes, the limited dwell time per voxel can reach challenging signal to noise levels, thus we examine strategies for improving signal and determining the optimal volume rate. We demonstrate large volume and multi-subvolume scanning *in vivo* with larval and juvenile (~3 weeks) zebrafish, and show the usefulness of these approaches for simultaneous recording of visual responses across multiple brain areas.

Disclosures: **J.C. Donovan:** None. **F. Huhn:** A. Employment/Salary (full or part-time):; Employee of Rapp Optoelectronic. **T.O. Helmbrecht:** None. **J. Kappel:** None. **G. Rapp:** A. Employment/Salary (full or part-time):; Head of Rapp Optoelectronic. **H. Baier:** None. **M. Dal Maschio:** None.

Poster

703. Optical Methods: Applications

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 703.06/CC39

Topic: I.04. Physiological Methods

Support: KCL “Developmental Neurobiology” PhD studentship
Wellcome Trust Investigator Award (095589/Z/11/Z)
NC3Rs grant (NC/P002420/1)

Title: Imaging the axonal action potentialwith genetically-encoded voltage sensors

Authors: *V. GONZALEZ SABATER, M. RIGBY, J. BURRONE;
Developmental Neurobio., King's Col. London, London, United Kingdom

Abstract: The axonal action potential (AP) has traditionally been considered an all-or-none event that encodes information in its firing frequency. A handful of recent studies now suggest multiple factors can influence the AP waveform. However, due to the relative inaccessibility of

the mammalian axon to electrophysiological methods, such studies are either limited to a few large synapses, or rely on indirect measures of axonal voltage. Recent advancements in the development of genetically-encoded voltage sensors (GEVIs) open the possibility of visualizing the presynaptic AP in small en-passant varicosities with enhanced temporal and spatial resolution.
We performed a comparative analysis of two state-of-the-art GEVIs: Ace2N-mNeon-4AA (Gong et al. 2015) and Archon2 (Piatkevich et al. 2018), and assessed whether their kinetics and sensitivity are sufficient to monitor the AP waveform in dissociated hippocampal neurons. Simultaneous whole-cell patch-clamp recordings and somatic voltage imaging performed at a frame rate of ~ 3KHz allowed a detailed characterization of the kinetics of each probe during an AP in control conditions and following drug-induced alterations of the AP waveform. Using local extracellular somatic stimulation with a bipolar electrode, we also measured the AP waveform along the axon and in presynaptic boutons, identified by genetic markers. Repeated imaging of these probes provided measures of the signal-to-noise ratio, as well as bleaching rates and overall probe stability. We find that both GEVIs can reliably report the AP waveform, but with different kinetics and sensitivities.
We then went on to measure the AP waveform along the axon with GEVIs in order to investigate factors that govern its shape and plasticity. We used specific pharmacology to assess the role of different types of potassium channels in shaping the axonal AP waveform. We found that the axonal AP width and amplitude increase upon pharmacological blockade of voltage-gated and G protein-activated potassium channels, but not large conductance calcium-activated potassium channels. In contrast, we did not observe AP amplitude modulation in the soma.
Our observations underline the importance of axonal properties in shaping the AP and suggest the possibility of local analogue signal computation. We next aim to further investigate physiological factors that govern the axonal AP waveform and its plasticity, whilst simultaneously imaging genetically-encoded sensors of Ca2+ or neurotransmitter release.

Disclosures: **V. Gonzalez Sabater:** None. **M. Rigby:** None. **J. Burrone:** None.

Poster

703. Optical Methods: Applications

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 703.07/DP14/CC40

ControlExtraData.DynamicPosterDisplay:
Dynamic Poster
Topic: I.04. Physiological Methods

Support: NS090473
EY007023
EB022726

Title: Label free characterization of attenuation lengths of cortical regions via three photon microscopy in awake mice

Authors: *M. YILDIRIM[1], M. HU[1], P. SO[2], M. SUR[3];
[1]Picower Inst. for Learning and Memory, [2]Dept. of Biol. Engin., [3]Dept. of Brain and Cognitive Sci., MIT, Cambridge, MA

Abstract: Our understanding of large population activity of cortical neurons has been greatly advanced by two-photon microscopy. However, due to light scattering and absorption, it is still a challenge to be able to imaging neurons at deep layers. Moreover, the attenuation length of the cortex may change from area to area depending on its structure. Thus, it is critical to characterize the attenuation length of the area of interest in order to precisely image/modulate cortical and subcortical regions. Current state of art for determining the attenuation length of any cortical region is to label blood vessels with high absorption cross-section dyes injected retro-orbitally in anesthetized mice. However, these injections do not last long enough to characterize multiple brain regions at once so multiple retro-orbital injections are required. Attenuation lengths of multiple cortical regions in awake mice has never been reported. Here, we developed two label-free methods to characterize attenuation lengths in multiple brain regions in awake mice via our custom-made three photon microscope. The first method is based on imaging blood vessels in the cortex and axonal tracts in the white matter via third-harmonic generation (THG) microscopy. The second method is to ablate four different depths in the cortex with varying pulse energy. THG imaging of blood vessels is advantageous since it is practical for multi-site imaging whereas it is disadvantageous since it relies on both excitation and emission wavelengths. Ablation is a more precise method since it relies on only the excitation wavelength whereas it is disadvantageous since it creates small lesions in multiple depths. We performed these imaging and ablation experiments in several brain regions including primary visual cortex (V1), and somatosensory cortex (S1) in four awake mice. Comparing the attenuation length between these regions obtained with THG imaging and ablation, we concluded that ablation experiments consistently generate 10% longer attenuation lengths compared to those obtained with THG imaging. Also, we found that there were significant differences in attenuation lengths between cortical regions. For example, V1 has an attenuation length of 254.0 ±8.1 μm whereas S1 has an attenuation length of 312.0 ±10.2 μm. Our work shows that the attenuation lengths of cortical regions in awake mice can be reliably estimated by performing label-free THG imaging of blood vessels at 1300 nm wavelength. These measurements place fundamental constraints on two-photon imaging depths and three-photon imaging power for analysis of cortical activity.

Disclosures: **M. Yildirim:** None. **M. Sur:** None. **P. So:** None. **M. Hu:** None.

Poster

703. Optical Methods: Applications

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 703.08/CC41

Topic: I.04. Physiological Methods

Support: NIH Grant GM081739
NIH Grant MH107515
NIH Grant NS099429
NIH Grant HD087011

Title: Longitudinal imaging of calcium functional connectivity in the developing mouse cortex

Authors: *R. M. RAHN[1], L. M. BRIER[2], A. R. BICE[2], J. D. DOUGHERTY[3], J. P. CULVER[2]; [1]Radiology, Genet. and Psychiatry, [2]Radiology, [3]Genet. and Psychiatry, Washington Univ. In St. Louis, Saint Louis, MO

Abstract: Functional connectivity (FC) networks in human infants have been previously shown to vary in their development, with sensorimotor areas showing more connectivity than association cortex in infancy. However, the developmental trajectory of FC changes between infancy and adulthood is not well-characterized. We therefore used longitudinal mesoscopic calcium imaging to evaluate functional connectivity across development in the cortex of transgenic mice expressing the genetically-encoded calcium indicator GCaMP6f under the *Thy1* promoter. We collected calcium and hemoglobin resting-state data at five developmental timepoints (postnatal day 15 (P15), P22, P28, P35, and P60) proximal to developmental milestones such as eye-opening and critical periods such as that for vision. Fluorescence imaging of the cortex was performed transcranially (using a chronic optical window affixed to the intact skull) and by sequential LED illumination (λ=470nm (GCaMP6 fluorescence excitation), 530nm, 590nm, 625nm) and sCMOS detection. Seed-based functional connectivity for all timepoints displayed characteristically high correlation for homotopic contralateral regions and passed quality control metrics with a manageable signal-to-noise ratio typical of adult data collected on the fluorescence imaging system. Vascular and cranial bone-derived features were used to perform image registration, benefiting group-based analysis. Survival to adulthood following window placement surgery and imaging at P15 was high (92%), and mice windowed at P14 display similar quality data at later timepoints as well. Calcium data within the delta frequency band, 0.4-4.0 Hz, produce stable, consistent FC maps with 30s or more of imaging, as has been found in previous adult studies. Taken together, these results indicate that mesoscopic optical intrinsic signal imaging permits longitudinal study of cortical dynamics across development in the mouse, and preliminary analysis suggests region-specific developmental trajectories for functional connectivity. The methodology shows great potential for elucidating the functional

architecture typical of specific developmental timepoints both in healthy controls and disease or injury models.

Disclosures: R.M. Rahn: None. **L.M. Brier:** None. **A.R. Bice:** None. **J.D. Dougherty:** None. **J.P. Culver:** None.

Poster

703. Optical Methods: Applications

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 703.09/CC42

Topic: I.04. Physiological Methods

Title: Fluoropolymer nanosheet as a candidate for an artificial dura for long-term two-photon imaging of the mouse brain *in vivo*

Authors: *T. TAKAHASHI[1,2], H. ZHANG[3], R. KAWAKAMI[4], K. YARINOME[5], Y. OKAMURA[5,3], T. NEMOTO[6,2];
[1]Res. Inst. for Electronic Science, Hokkaido Univ., Sapporo, Japan; [2]Grad. Sch. of Information Sci. and Technology, Hokkaido Univ., Sapporo, Japan; [3]Micro/Nano Technol. Ctr. Tokai Univ., Kanagawa, Japan; [4]Ehime Univ., Toon, Japan; [5]Grad. Sch. of Engineering, Tokai Univ., Kanagawa, Japan; [6]Hokkaido Univ., Sapporo, Japan

Abstract: *In vivo* two-photon microscopy has become widely used for deep tissue imaging. For *in vivo* imaging of the deep regions in mouse brains, open skull method is used to make a cranial window. In this operation, the dura mater was sometimes removed. Otherwise, thickening of the dura on the inner surface of the coverslip was frequently observed after a week post-surgery, that deteriorated the transparency of the window (Heo et al., 2016) and the optical path of the microscope (Goldey et al., 2014). However, removing the dura tended to cause inflammation and bleeding in the brain, which was not compatible with long-term imaging. In the previous meeting, we proposed newly-developed fluoropolymer nanosheet"PEO-CYTOP" as a sealing material for the chronical cranial window instead of glass coverslip (Takahashi et al., Program No. 796.05. San Diego, CA: Society for Neuroscience, 2018). At that time, we demonstrated that PEO-CYTOP nanosheets immediately stopped bleeding, though the dura was not removed. In this study, we examined the facilitation of PEO-CYTOP nanosheets after removing the dura, especially for a long-time observation over several months. First, we confirmed that sealing with PEO-CYTOP nanosheets also successfully suppressed bleeding from the brain surface even when the dura was removed. Next, for the protection of the brain from mechanical damages, we inserted and glued a round glass coverslip (2.7 mm diameter round, about 0.17 mm thickness, #1S, Matsunami Glass, Japan) in the cranial hole sealed with PEO-CYTOP nanosheet. In addition, the regrowth of the dura was suppressed inside the window and kept the transparency up to 14 weeks post-surgery. From these results, we tried to achieve two-photon imaging in

Thy1-EYFP-H transgenic mice (over 8 week-old, male) (Feng et al., 2000) to access the effect to deep imaging. As a result, we could observe same axons and neurons over at 700 μm depth corresponding to layer 6 of the cerebral cortex up to 14 weeks post-surgery. To summarize, PEO-CYTOP nanosheets could be a component for artificial dura in living mouse brain. In future, the nanosheets will be applied as an artificial dura to other animals including rats and marmosets for long-term imaging in deep regions of living brains.

Disclosures: T. Takahashi: None. **H. Zhang:** None. **R. Kawakami:** None. **K. Yarinome:** None. **Y. Okamura:** None. **T. Nemoto:** None.

Poster

703. Optical Methods: Applications

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 703.10/CC43

Topic: I.04. Physiological Methods

Support: ERC NEURO-PATTERNS
NIH U01 NS090576
NIH U19 NS107464

Title: High-efficiency *in vivo* stimulation of neurons using two-photon holographic illumination

Authors: A. FORLI[1], M. PISONI[1], Y. PRINTZ[2], O. YIZHAR[2], *T. FELLIN[1];
[1]Optical Approaches to Brain Function Lab., Inst. Italiano di Tecnologia, Genova, Italy; [2]Dept. of Neurobio., Weizmann Inst., Rehovot, Israel

Abstract: Optical techniques to simultaneously image and manipulate neuronal activity with high spatial resolution in the intact mammalian brain promise to be fundamental tools to causally investigate how ensembles of cells drive behavior. In order to achieve cellular-resolution two-photon (2P) stimulation over large number of cells, efficient generation of action potential (AP) firing by 2P stimulation is required. Towards this goal, we combined a new high conductance soma-targeted excitatory opsin (stCoChR) with 2P holographic illumination using a low-repetition rate laser source and a non collinear optical parametric amplifier at 920 nm. stCoChR expression in principal cells and interneurons was achieved in the mouse cortex through injections of adeno-associated viruses. We measured efficiency and resolution of 2P stimulation by combining holographic illumination with juxtasomal electrophysiological recordings from stCoChR-expressing neurons of layer 2/3 *in vivo*. We found that stCoChR-positive cells reliably increased their AP firing rate in response to brief 2P holographic illumination with an extended circular shape covering their soma. AP frequency increase during stimulation was proportional to the average illumination power and significant responses to 2P holographic stimulation were observed at low average power levels *per* cell (average power under the objective: 0.25 mW - 5

mW depending on the repetition rate). Latency to first AP was in the range 4 - 21 ms and the AP jitter in the range 0.2 - 8.7 ms. These results demonstrate high-efficiency 2P activation of a blue-shifted soma-targeted opsin that can be used for effective large scale stimulation of distributed neural networks in the intact mouse cortex.

Disclosures: **A. Forli:** None. **M. Pisoni:** None. **Y. Printz:** None. **O. Yizhar:** None. **T. Fellin:** None.

Poster

703. Optical Methods: Applications

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 703.11/CC44

Topic: I.04. Physiological Methods

Title: Multi channel fiber photometry based mapping of axonal terminal activity in freely moving mice

Authors: *H. QIN[1,2], X. CHEN[3], J. LU[4], L. FU[2], W. JIN[3];
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Abstract: Fiber photometry has been increasingly popular in neuroscience research in freely behaving animals. In combination of the use of genetically encoded Ca^{2+} indicators, it serves as an efficient approach for real time monitoring of neural activity in neuronal somata, dendrites and axonal terminals. Here, we demonstrated a new version of multi-channel fiber photometry used for functional mapping in sub-regions of axonal terminals. To reduce the recording range of each channel, we chose a wee type of fiber with a core diameter of only 50 μm. A fast and sensitive sCMOS was equipped to simultaneously detect the Ca^{2+} signals of multi-channel. Optical fibers were integrated into a bundle, with the neighboring channel close to a distance of ~250 μm, to delivery excitation light to and collect the emission light from different sub-regions of neural projections. The design of the bundle shape and channel number were flexible according to the specific recording situation. The sample rate of the system was 100 frames/s, which was restricted to the maximal frame rate of sCMOS. Through theoretical analysis and experiment testing, we got the recording depth of 200-250 μm and found that there was no interference among different channels. Using a Ca^{2+} indicator GCaMP5G, we demonstrate the feasibility of this system for recording the activities in axonal terminals from the medial entorhinal cortex layer II (MECII) to the hippocampal dentate gyrus (DG) in freely moving mice. We detected spatially separated Ca^{2+} signals at four different sites at the DG. Therefore, our multi-channel fiber photometry provides a simple but powerful method for functional mapping

of axonal terminals in a spatially confined brain area of freely moving animals.
Keywords: multi-channel; fiber photometry; integrated probe; axonal terminals.

Disclosures: **H. Qin:** None. **X. Chen:** None. **J. Lu:** None. **L. Fu:** None. **W. Jin:** None.

Poster

703. Optical Methods: Applications

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 703.12/CC45

Topic: I.04. Physiological Methods

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VISGEN_734862

Title: Functional imaging of long neuronal processes and network in behaving animal in any arbitrary tilted plane in 3D

Authors: *M. MAROSI[1], K. OCSAI[1], T. TOMPA[1], Z. MEDVECZKY[2], G. SZALAY[1], G. KATONA[2,1], B. ROZSA[1,2];
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Abstract: Understanding neural computation requires the detection of processes in all three dimensions simultaneously, as dendritic integration *in vivo* in the neural tissue takes place in an intricate network of neural connections with elements, most of the time, not parallel to the surface. Conventional functional microscopy methods are limited to 2-dimensional planes parallel with the front lens of the microscope and the cortical surface. Imaging through cortical layers was only possible either non-simultaneously or with highly invasive methods (ie: microprisms).
Using two-photon acusto-optical (AO) microscopy we presented already a method the overcome the limitation of the 2-dimensional scanning, by a random-access point scanning method (Katona et al 2012), we later complemented with the 3D drift AO scanning (Szalay et al 2016). 3D drift AO scanning can extend each scanning point to small 3D lines, surface or volume elements, preserving fluorescence information for fast off-line motion correction. With this method *in vivo* motion artifacts can be effectively eliminated, allowing fast 3D measurement of over 100 dendritic spines with 3D lines; hundreds of somata with squares and cubes; multiple spiny dendritic segments with surface and volume elements.
However, this earlier solution contained some limitation regarding the scanning patterns and acquisition speed. Here we present a complex scanning solution which can exploit the full

capabilities of the 3D scanning options, providing virtually compromise-free ROI scanning options. This technique allows us to measure various scanning patterns on any arbitrary tilted frame, with 40 Hz scanning speed for a full field imaging and up to 3Khz on special scanning patterns. This feature makes it possible to record raster videos of all cortical layers simultaneously or record individual neurons with their entire apical dendrites, or obliquely running neural elements with high speed.
Here we present our results from the visual cortex (V1) of awake behaving mice involved in a visual task and show calcium events occurring along the entire length of the cortical pyramidal neuron's soma and apical dendrites and within a group of neurons. On these elements we record local dendritic spikes.

Disclosures: **M. Marosi:** None. **K. Ocsai:** None. **T. Tompa:** None. **Z. Medveczky:** None. **G. Szalay:** None. **G. Katona:** None. **B. Rozsa:** None.

Poster

703. Optical Methods: Applications

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Support: This project has received funding from the H2020 EXCELLENT SCIENCE - European Research Council (ERC) under grant agreement ID n. 692943 BrainBIT

Title: Spatiotemporal features of large scale motor-evoked calcium activity patterns

Authors: ***A. SCAGLIONE**[1,2], E. CONTI[1,2], A. ALLEGRA MASCARO[1], F. S. PAVONE[1,2]; [1]LENS, European Lab. for Non-linear Spectroscopy, Univ. of Florence, Sesto Fiorentino, Italy; [2]Dept. di Fisica e Astronomia, Univ. of Florence, Firenze, Italy

Abstract: Understanding the link between brain function and behavior represents a fundamental question in modern neuroscience. Recent advancements in imaging techniques, such as widefield calcium imaging, are especially well suited to address this question by allowing to monitor neural activity of large cortical areas in awake behaving animals. In this study, we wondered if the information contained in the calcium activity patterns over a large portion of the cortex is sufficient to discriminate motor evoked output from baseline activity on a single trial basis. Intact skull widefield calcium imaging was acquired while Thy1-GCaMP6f mice performed a motor task. Briefly, mice were head-fixed under a microscope and placed on a robotic platform were at the beginning of each trial their left arm is passively extended. Animals were then delivered a milky reward when they pulled the left arm to target position when cued with a tone. Next, we use a Euclidean distance based classifier to assign trials to two different classes: either 1) baseline, a 75 ms period of activity collected at random before the task started or 2) motor-

outcome, a 75 ms period of time around the time of the successful pull. Our results show that: 1) we can successfully discriminate rewarded pulls from baseline activity on a single trial basis with high accuracy in all subjects (about 80% averaged across all subjects); 2) activity across all imaged cortical areas contributed similarly to the performances of the classification and 3) classification performances increased significantly (about 60% in average) as early as 400 msec before time of pull and were highest at the motor onset. Taken together these results suggest that large scale motor evoked calcium activity patterns are distributed over a large portion of the cortex in a small time window (800 msec) supporting the idea that different cortical areas act in concert over a short temporal scale to produce the motor output.

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Poster

703. Optical Methods: Applications

Location: Hall A

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Topic: I.04. Physiological Methods

Support: MIUR (Ministero dell'Università e della Ricerca), University of Genoa.

Title: Study of RuBi-GABA uncaging by non-linear photoactivation and patch clamp technique in cerebellar granule cells

Authors: *E. GATTA[1], M. COZZOLINO[1,2], V. BAZZURRO[1], E. ANGELI[1], P. BIANCHINI[2], A. DIASPRO[1,2], M. ROBELLO[1];
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Abstract: RuBi GABA is a photoactivatable molecule whose activity can be controlled by a pulse of light. These probe compounds are prepared via covalent appendage of a light-sensitive protecting group "the cage" (RuBi) to a signaling molecule (GABA). With the cage bound, the signaling molecule is unable to activate its receptor [Diana D., J Am Chem Soc., 2014]. One photon (UV-VIS light) and two-photon (700-900nm) absorption can be used to break the "cage" binding. The uncaged molecule becomes active and can bind on $GABA_A$ receptor site [Rial Verde E.M., Front Neural Circuits., 2008]. Uncaging technology and fluorescence microscopy coupled to patch clamp technique provide approach to detect a selected biological target in a temporally and spatially confined way. We analyzed how the change of physical parameter such as uncaging distance, exposure time, laser power, linear and non-linear photoactivation influence the measurements and we determine how these parameters change the modality and efficacy of the GABA release and consequently the $GABA_A$ response. Specifically, localization precision can be improved using advanced fluorescent optical methods, in particular, we used the super-

resolved and non-linear fluorescence microscopy [Diaspro A., BioMedical Engineering OnLine, 2006]. These allow exploring the release of caged GABA topically applied *in situ* at defined concentration and in a specific region of neuronal cells for mapping the localization and the functional distribution of $GABA_A$ receptors in cerebellar granule cells *in vitro.* We aim to achieve a $GABA_A$ receptors super resolved map in cerebrellar granule cells or within brain slices integrated by electrical measurements. Specific blocking factors can be used to identify receptor type (on the basis of subunit composition) presence in different neuronal regions. Finally, we are able to explore the responses generated by specifics drugs in different regions of neuron. Localization precision can be improved by using advanced fluorescent optical methods as the ones in use in super resolved and non-linear fluorescence microscopy.

Disclosures: E. Gatta: None. **V. Bazzurro:** None. **E. Angeli:** None. **M. Robello:** None. **M. Cozzolino:** None. **P. Bianchini:** None. **A. Diaspro:** None.

Poster

703. Optical Methods: Applications

Location: Hall A

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ControlExtraData.DynamicPosterDisplay:
Dynamic Poster
Topic: I.04. Physiological Methods

Support: NSF GRANT DBI-1707312
NIH GRANT NS096669
NYSCIRB C32630GG

Title: *In vivo* three-photon excited fluorescence imaging of neural activity in the spinal cord of awake, locomoting mice

Authors: *Y.-T. CHENG[1], K. M. LETT[2], S. DENOTTA[3], D. RIVERA[2], S. HU[2], J. RAIKIN[2], D. G. OUZOUNOV[4], T. WANG[4], J. CRUZ HERNANDEZ[2], I. BASTILLE[2], N. NISHIMURA[5], J. R. FETCHO[1], C. XU[4], C. B. SCHAFFER[6];
[1]Neurobio. and Behavior, [2]Meinig Sch. of Biomed. Engin., [3]Col. of Vet. Med., [4]Applied and Engin. Physics, [5]Biomed. Engin., [6]Biomed Engin., Cornell Univ., Ithaca, NY

Abstract: Nonlinear optical microscopy and genetically encoded calcium indicators (e.g. GCaMP) enable recording of the activity of large numbers of neurons in the central nervous system of awake, behaving rodents. Much of this work has focused on cortical activity, and anatomical regions that are more difficult to access optically have received less attention. The rhythmic limb movements that underlie locomotion are controlled by spinal cord interneurons in central pattern generator (CPG) circuits. Measuring activity in these CPG circuits in locomoting

animals could help uncover how alternating limb motion and different locomotor speeds are produced, as well as how this fails in movement disorders. We developed an implantable chamber that provides long-term optical access to the spinal cord, and have shown that mice can be trained to run on a treadmill while they are held firmly by the implanted chamber. We found only modest differences in the gait cycle between spine-fixed and free-running mice. The spine-fixed mice had a slightly longer stance phase in their gait, and while they ran with a similar speed to free-running mice they spent about half as much time running. The white matter on the dorsal surface of the spinal cord is highly optically scattering and limits the maximum depth that even scattering insensitive imaging modalities, such as two photon excited fluorescence, can reach. We imaged fluorescently-labeled blood vessels and neural processes to a depth of only 150 µm in mouse spinal cord before losing image contrast due to increased background. Due to the longer excitation wavelengths used and the higher order nonlinear excitation process, three-photon excited fluorescence microscopy (3PEF) enables deeper imaging into scattering samples. In the mouse spinal cord we imaged fluorescently labeled blood vessels to a depth of 500 µm with 3PEF, limited by the optical power we could apply before causing thermal damage. The V2a neurons are excitatory interneurons that have been implicated in shaping the left-right alternation of limbs during locomotion and which express the embryonic transcription factor chx10. We crossed chx10-cre mice with TIGER-line GCaMP6s reporter mice and now aim to use 3PEF to correlate V2a neuron activity patterns to limb movements.

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Poster

703. Optical Methods: Applications

Location: Hall A

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Topic: I.04. Physiological Methods

Support: NSF Miniature Brain Machinery traineeship
Neuroscience Program at UIUC

Title: Multiple scale quantitative analysis of white matter connectivity on a MYRF knock-out mouse model using spatial light interference microscopy (SLIM)

Authors: *J. A. MALDONADO[1], C. BEST[2];
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Abstract: The brain architecture is organized hierarchically and is extended from the nanometric scale to the centimeter scale, however most studies on neurodegeneration, due to resources and time are limited to only a few orders of magnitude. De-myelinating diseases display significant alterations in all the seven orders of magnitude depending on the disease stage. Here our goal is to do a multi-scale analysis on a mouse Myrf knock-out transgenic model of de-myelination using Spatial Light Interference Microscopy (SLIM) combined with standard immunohistochemical methods.
Our study focused on three brain regions: the corpus callosum, anterior commissure; motor cortex optic nerve and spinal cord. We quantify variations in both gray and white matter.
To analyze our data, we use fiber orientation analysis, density mapping and optical related measures to quantify fiber and myelin integrity respectively in 4um tissue slices, and across 16 um reconstructed tissue volume blocks. Our results show that MYRF knock-out mice fibers continuity, and density in corpus callosum and other areas of concentrated white mater were significantly decreased compared to the controls. Subtle changes in mature oligodendrocyte number were also observed.

Disclosures: J.A. Maldonado: None. **C. Best:** None.

Poster

703. Optical Methods: Applications

Location: Hall A

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Program #/Poster #: 703.17/CC50

Topic: I.04. Physiological Methods

Title: Complex event analysis for neurotoxic profiling of compound effects on human iPSC-derived neural spheroid 3D cultures

Authors: *O. SIRENKO[1], C. CRITTENDEN[1], F. ZANELLA[2], R. GORDON[2], C. CARROMEU[2];
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Abstract: To speed up the development of more effective and safer drugs, there is an increasing need for more complex, biologically relevant, and predictive cell-based assays for drug discovery and toxicology screening. Human iPSC-derived neural 3D co-cultures (microBrain 3D platform) have been developed as a high throughput screening platform that more closely resembles the constitution of native human cortical brain tissue. Neural spheroid 3D cultures are a physiologically relevant co-cultures of iPSC-derived functionally active cortical glutamatergic and GABAergic neurons co-differentiated and matured with astrocytes from the same donor. 3D neural spheroids contain a neural network enriched in synapses, creating a highly functional neuronal circuitry and display spontaneous synchronized, readily detectable calcium oscillations. Here, we describe a method for the complex analysis of calcium oscillations that allows

detection and multi-parametric characterization of oscillation peaks that include the oscillation rate, peak width and amplitude, characterization of secondary peaks, waveform irregularities, and several other read-outs. In addition, cellular and mitochondrial toxicity were assessed by high-content imaging.
For assay characterization, we used a set of neuromodulators with known mechanisms of action affecting GABA, NMDA and dopamine targets. Then we characterized the neurotoxic profile of a set of 30 known neurotoxic or seizurogenic drugs, including anticancer compounds, antipsychotics, and antibiotic, as well as selected environmental chemicals. Our results show that neural 3D cultures when paired with complex event analysis and cytotoxicity assays form a promising, biologically-relevant system for assessing the neurotoxic potential of pharmaceutical drugs and environmental toxins.

Disclosures: **O. Sirenko:** A. Employment/Salary (full or part-time):; full time employment, Molecular Devices. **C. Crittenden:** A. Employment/Salary (full or part-time):; Employment, Molecular Devices. **F. Zanella:** A. Employment/Salary (full or part-time):; full time employment, StemoniX. **R. Gordon:** A. Employment/Salary (full or part-time):; Employment, StemoniX. **C. Carromeu:** A. Employment/Salary (full or part-time):; Employment, StemoniX.

Poster

703. Optical Methods: Applications

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Topic: I.04. Physiological Methods

Support: NSF Grant CBET-1631912
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Title: Imaging odor associated neural activity in piriform cortex and hippocampus using gradient index lenses

Authors: *C. MCCULLOUGH[1], M. MA[2], D. RAMIREZ-GORDILLO[2], G. FUTIA[1], B. OZBAY[1], N. AREVALO[2], D. RESTREPO[2], E. GIBSON[1];
[1]Bioengineering, [2]Cell & Dev. Biology, Neurosci. Program, Univ. of Colorado Anschutz Med. Campus, Aurora, CO

Abstract: Olfaction is a crucial sense for navigating environment, assessing threats, mating, and eating. Yet, olfaction is one of the least understood sensory modalities because of the inherently complex space it samples. Brain regions known to process olfactory information include the piriform cortex (PCTX) and hippocampus (HC). Substantial progress has been made understanding the role of PCTX and HC in olfaction using electrical recordings to identify single unit and large ensemble activity in these regions. Multiphoton imaging of neural activity in these

regions would allow for spatial localization of cells and cell specific recording selectivity using viral expression or transgenic models. However, PCTX and HC are located approximately 2 mm and 5 mm below the surface of the brain respectively, beyond the imaging depth of 3-photon imaging. To overcome this depth restriction, we have used implanted gradient index (GRIN) lenses: rod shaped lenses of small diameter. Here we present our progress using GRIN lenses to record high signal-to-noise GCaMP6 activity in PCTX and HC of mice participating in odor discrimination tasks. Additionally, we present our progress developing a device to incorporate electrical recording alongside optical recording through a GRIN lens.

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Poster

703. Optical Methods: Applications

Location: Hall A

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Program #/Poster #: 703.19/CC52

Topic: I.04. Physiological Methods

Title: Live cell imaging of 3D primary cortical microtissue via AAV-induced fluorescence

Authors: *S. BROWN[1], E. ATHERTON[2], A. ALLAWALA[1], D. BORTON[1,3,4];
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Abstract: Reliable performance of devices implanted in the brain for the purpose of recording neural activity relies heavily on the stability of the tissue environment surrounding the device. One of the greatest challenges in optimizing device performance is the onset of acute inflammation and a chronic foreign body response that often occurs at the device-tissue interface upon implantation. In developing effective neural implants and devices, detailed and thorough characterization of the device-tissue interface is paramount. We have previously demonstrated an *in vitro* model of the neuroinflammatory response using cultured three-dimensional primary cortical microtissues for evaluating interface passivation solutions. A major limitation in our understanding of the device-tissue interface the lack of dynamic visualization and quantification of the foreign-body response, including adaptation of neural infrastructure and composition around implanted devices. Here, we present a live cell imaging platform for real time capture of the dynamic neuroinflammatory response to an electrode in a three-dimensional neural microtissue via virally mediated expression of fluorescent reporter proteins in three key cell types: neurons, astrocytes, and microglia. This model of induced fluorescence allows for the capability of a longitudinal analysis of the neural microenvironment in a single microtissue

without the implementation of traditional cross-sectional studies using fixed sample immunohistochemical staining. We provide continuous visualization and quantification of the cellular response by tracking the morphological and migrational dynamics of the three cell types during the foreign-body induced inflammatory response to chronically implanted electrodes. The application of fluorescent tagging via viral transduction to monitor cell-specific dynamics offers a new perspective on the device tissue interface with real time longitudinal visualization of the device-tissue microenvironment.

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Poster

703. Optical Methods: Applications

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Topic: I.04. Physiological Methods

Support: NIH 5DP1MH110234-02 Pioneer Grant

Title: Identifying active neural circuits in freely moving, adult fruit flies with the optogenetic tool CaMPARI

Authors: *K. A. EDWARDS[1], M. B. HOPPA[2], G. BOSCO[1];
[1]Mol. and Systems Biol., [2]Biol. Sci., Dartmouth Col., Hanover, NH

Abstract: Linking neural circuitry to behavior by mapping active neurons *in vivo* is a challenge. Currently, genetically encoded calcium (Ca^{2+}) indicators (GECIs) allow quantitative identification of active neurons during behavior, but can only be viewed in a restricted area of the brain and limit the movement of the behaving organism. Alternatively, staining of immediate early genes, such as Arc and cFos, can label highly active neurons within the entire brain but the temporal resolution is poor. To overcome these spatial-temporal challenges, CaMPARI (calcium-modulated photoactivatible ratiometric integrator) was engineered from the circular permutation of the photoconvertible protein, EosFP, and attachment to the Ca^{2+} binding protein, Calmodulin, and its associated peptide, M13. This combination of components allows photoconversion to occur specifically in the presence of high intracellular Ca^{2+} in an active neuron. The photoconversion can then be quantified by taking the ratio of the red channel signal to the green channel signal. CaMPARI promises the ability to trace active neurons during specific stimulus; however, CaMPARI's uses in adult fruit flies have been limited to photoconversion with a laser during fly immobilization and, in some cases, with the head cuticle removed. Here, we demonstrate our setup allows photoconversion of multiple freely-moving intact adult flies during a stimulus. Fruit flies were placed in a Petri dish with filter paper wet with acetic acid (pH=2) or neutralized acetic acid (pH=7) and exposed to photoconvertible light (60 mW 405 nm) from an

LED for 30 min (500 ms on, 200 ms off). Immediately following photoconversion, whole flies were fixed and imaged by confocal microscopy. The red:green ratio was quantified for the DC4 glomerulus, a convergence of neurons expressing *Ir64a*, an ionotropic receptor that senses acids in the fruit fly antennal lobe. Flies exposed to acetic acid showed 1.6-fold greater photoconversion than flies exposed to neutralized acetic acid. These results were recapitulated using apple cider vinegar (4-fold greater photoconversion). These results indicate that CaMPARI can be used to label neurons in intact, freely-moving adult flies and will be useful for identifying the circuitry underlying complex behaviors.

Disclosures: K.A. Edwards: None. **M.B. Hoppa:** None. **G. Bosco:** None.

Poster

703. Optical Methods: Applications

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Topic: I.04. Physiological Methods

Support: NIH/NINDS R24 NS098536
Boston University Neurophotonics Center

Title: 1p2c: A miniscope for multiplexed single-photon imaging of two spectrally distinct fluorescent reporters in freely-behaving animals

Authors: W. W.-S. YEN[1], *D. P. LEMAN[1], J. R. CLEVENGER[2], N. PERKINS[2], H. FAWCETT[2], W. A. LIBERTI, III[3], T. NGUYEN[2], I. G. DAVISON[1], A. CRUZ-MARTIN[1], T. J. GARDNER[1], T. M. OTCHY[1];
[1]Dept. of Biol., [2]Dept. of Biomed. Engin., Boston Univ., Boston, MA; [3]Univ. of California Berkeley, Berkeley, CA

Abstract: The combination of genetically encoded fluorescent indicators and miniaturized, head-mounted fluorescence microscopes (“miniscopes”) offers the ability to record the activity of large populations of neurons in freely-behaving small animals. The freedom of movement afforded by miniscopes enables imaging during a wide range of naturalistic behaviors that have been challenging (if not impossible) to study in traditional head-fixed preparations. The availability of reporters that fluoresce at spectrally separable wavelengths has made it possible to target functionally distinct cell populations for simultaneous imaging, providing insight into how the activity of two neuronal populations are correlated to specific behaviors. However, currently available miniscope systems are limited to capturing fluorescent signals within a single spectral band. Here, we present an expanded-capability miniscope based on our open-source FinchScope project that overcomes this limitation.
We have developed a two-color system based on multiplexing of excitation wavelengths that can

be used to simultaneously image spectrally distinct fluorescent reporters. Frame sync signals from the CMOS sensor are used to toggle the excitation LEDs on alternative frames at rates up to 60 Hz, providing two imaging streams at 30 Hz resolution. The intensity of each illumination channel can be independently controlled by our software package. Our current GRIN-lens based optical path is designed for GCaMP and jRCaMP, avoiding the photo-switching effects associated with other red-shifted calcium sensors such as jRGECO. This system will also allow identification of genetically identified cell types within networks broadly labeled with single-wavelength activity sensors, such as anatomically defined populations that project to different target areas, identified by retrograde labeling. We demonstrate these capabilities in bench-top characterization, ex-vivo histological slices, and in-vivo recordings from awake, freely-moving animals.
Overall, dual-color imaging - in conjunction with advances in genetically-targeted fluorescent reporters - will enable improved access to the activity of functionally distinct ensembles within heterogeneous neural circuits. Future miniscope development efforts will aim at further improving image quality and reducing the chromatic aberration that is inherent to GRIN-lens based multi-color systems.

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Poster

703. Optical Methods: Applications

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NIH 5R01NS061908
DoD MURI W911NF-12-1-0594
Simons Foundation Collaboration on Global Brain
McKnight Foundation

Title: SCAPE microscopy for high-speed 3D neuronal imaging of behaving larval and adult *Drosophila*

Authors: *W. LI, V. VOLETI, R. VAADIA, N. MISHRA, E. SCHAFFER, W. B. GRUEBER, E. M. C. HILLMAN;
Mortimer B. Zuckerman Mind Brain Behavior Inst., Columbia Univ., NEW YORK, NY

Abstract: It is a major challenge to understand functional neuronal circuits across the whole brain. The current methods we use to observe neuronal activity represent a major bottleneck in addressing biological problems, even for small animal model such as *Drosophila*. Our method, Swept Confocally Aligned Planar Excitation (SCAPE) microscopy offers the ability to image a large 3D volume (e.g. 1000x800x250um) at speeds exceeding 10 volumes per second, while preserving sufficient spatial resolution to identify cellular level neuronal activity. Together with different genetically encoded fluorescent indicators, SCAPE enables us to observe neuronal activity across a much larger population of neurons of freely crawling *Drosophila* larva and head-fixed behaving adult *Drosophila*.
Here, two research projects using high-speed SCAPE imaging will be presented. Taking advantage of the high-speed and large field of view of SCAPE microscopy, we were able to image freely crawling *Drosophila* larvae and characterize the full set of proprioceptive neurons during crawling and turning in dendrites, axons and soma. With the same setup, we are also able to image the entire adult head-fixed *Drosophila* brain at cellular resolution. Using both dense pan-neuronal or sparse subset labels, we are able to record and identify brain-wide functional circuits with olfactory stimuli while the fly was walking on an air suspended ball. Latest developments of SCAPE microscopy for different applications will also be shown.

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Poster

703. Optical Methods: Applications

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Topic: I.04. Physiological Methods

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Title: Novel molecular strategies for *in vivo* dual-color imaging

Authors: *J. F. NORMAN, B. RAHSEPAR, J. NOUEIHED, J. A. WHITE;
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Abstract: Calcium imaging has provided neuroscientists with the ability to monitor the activity of large networks of neurons *in vivo*. Novel molecular tools allow simultaneous imaging of multiple cell types, in order to better understand their real-time interactions and how they related

to behavior. We compared two strategies to record simultaneously from distinguishable CaMKII-positive pyramidal cells and GAD2-positive inhibitory interneurons. In the first, transgenic strategy, GAD2-tdTomato transgenic mice were injected with jGCaMP7f expressed under the synapsin promoter. In second, double-virus strategy, AAV viral injections in GAD2-cre mice were used to drive expression of cre-dependent tdTomato and synapsin-promoted jGCaMP7f. In principle, both strategies should allow us to record from both neuronal subtypes, and distinguish interneurons based on the presence of the tdTomato signal. Our preliminary results indicate that transgenic expression of tdTomato appears to limit expression of the calcium indicator, whereas the double-virus strategy allows for greater co-expression. We have quantified the statistics in brain slices and showed that the double-virus strategy leaves around half of the GAD2+ neurons labeled with tdTomato fluorophore co-expressing jGCaMP7f. In contrast, in response to our transgenic strategy, fewer than 10% of interneurons co-expressed the calcium indicator and tdTomato. Consistent with these results, *in vivo* calcium recordings from double-virus animals show substantially more jGCaMP7f-based activity than obtained using the transgenic strategy. These results, currently being followed up using immunohistochemical analysis, suggest that the double-virus method is much preferred for dual-color recordings from separate, identified cell types.

Disclosures: **J.F. Norman:** None. **B. Rahsepar:** None. **J. Noueihed:** None. **J.A. White:** None.

Poster

703. Optical Methods: Applications

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 703.24/CC57

Topic: I.04. Physiological Methods

Support: NIDA CEBRA award #R21DA044010

Title: Use of nIRCat to image the development of dopamine release in a wild-derived mouse with protracted adolescence

Authors: *G. S. PROUNIS, L. WILBRECHT;
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Abstract: In order to achieve independence adolescent mammals must disperse from the natal site and be motivated to engage in high-risk exploration for distal resources. Changes in striatal dopamine (DA) systems are believed to play a role in regulating these motivational changes. The scope of this transition may be muted in strains of mice engineered in the lab, as these animals are far removed from ecological selective pressures. The steppe mouse (Mus spicilegus) is a wild-living species closely related to typical lab mice (derived from Mus musculus domesticus) distinctly characterized by its protracted adolescent development when compared to other mice.

We posit that steppe mice exhibit phenotypes shaped by ecological selection which, proximal to adolescence, reflect changes that are critical for dispersal. These changes include increased locomotion, risk taking, and novel object investigation, and may correlate with patterns of dopamine signaling in the striatum. We examined the behavior of steppe mice at various post-weaning ages (postnatal day (P) 22-120) within an open field apparatus; notably, this marked the first instance of exposure to a novel environment, an experience relevant to dispersal. At the conclusion of the open field test, we scored the behavior of mice towards a novel object placed within the apparatus. We find that, between ~P60-80, male mice exhibit peaks in total distance travelled, risk taking (i.e., time spent in the center), and time spent interacting with a novel object in the open field. We are determining how changes in striatal DA signaling relate to these observations. A synthetic nanosensor-based infrared optical catecholamine sensor (nIRCat) allows us to compare spatiotemporal properties of evoked DA release across regions of the striatum (i.e., dorsolateral, dorsomedial (DMS), and ventral (VS)) in mice prior to (P30), during (P60), and after (P120) our observed behavioral peaks. When compared to P30 males, we find that P60 males have higher amplitudes of evoked DA release in the striatum. This suggests a potential mechanism by which developmental changes in DA signaling mediates a dispersal-related behavioral transition during adolescence.

Disclosures: G.S. Prounis: None. **L. Wilbrecht:** None.

Poster

703. Optical Methods: Applications

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 703.25/CC58

Topic: I.04. Physiological Methods

Support: NIH K99MH120053
NIH NS091230
NIH NS55104
NIH EB00790
NIH EB021018
NIH S10RR023401

Title: Two-photon microscopy imaging of partial pressure of oxygen (pO_2) in cortical tissue of awake mouse during breathing challenges

Authors: *I. ŞENCAN[1], K. KILIÇ[2], B. LI[1], B. FU[3], J. E. PORTER[3], T. ESIPOVA[4], M. DESJARDINS[5], M. A. YASEEN[1], D. BOAS[1,2], S. VINOGRADOV[4], A. DEVOR[1,5,6], S. SAKADŽIC;[1];
[1]Athinoula A. Martinos Ctr. for Biomed. Imaging, Dept. of Radiology, Massachusetts Gen. Hospital, Harvard Med. Sch., Charlestown, MA; [2]Departments of Biomed. and Electrical and

Computer Engin., Boston Univ. Neurophotonics Ctr., Boston, MA; [3]Athinoula A. Martinos Ctr. for Biomed. Imaging, Dept. of Radiology, Massachusetts Gen. Hosp., Charlestown, MA; [4]Departments of Biochem. and Biophysics, Univ. of Pennsylvania, Philadelphia, PA; [5]Dept. of Neurosciences, [6]Dept. of Radiology, Univ. of California San Diego, La Jolla, CA

Abstract: In this study, we aim to characterize tissue pO_2 in awake mice free from confounding effects of anesthesia on the animal physiology. We measured emission decays from the pO_2 probe (Oxyphor 2P; 75 kDa, ~3 µL, 30 µM) by using two-photon phosphorescence lifetime microscopy. The probe stays in the extracellular space once delivered into the tissue by direct injection to the site via a pressured glass micropipette, through a silicone-filled port in the chronic glass cranial window (Fig. 1b). For consecutive imaging of the microvasculature by the two-photon fluorescence microscopy, we labelled the blood plasma via retro-orbital injection of a dextran-conjugated Fluorescein isothiocyanate (FITC; 2 MDa, 0.2 mL, ~8.3 mg/mL). All injections were completed during brief isoflurane anesthesia, ~1 hr before imaging. At each cortical depth, we measured pO_2 over a grid of locations around arterioles, venules, and capillaries. We mapped the tissue pO_2 distribution and calculated the cerebral metabolic rate of oxygen in the whisker barrel cortex of awake mice at rest across different cortical layers under normal physiological conditions, hypercapnia, hypoxia, and hyperoxia. Our results will support efforts towards a better understanding of the oxygen transport in cortical tissue at microvascular scales and more quantitative interpretation of the blood oxygen level dependent functional magnetic resonance imaging (BOLD fMRI) signal.

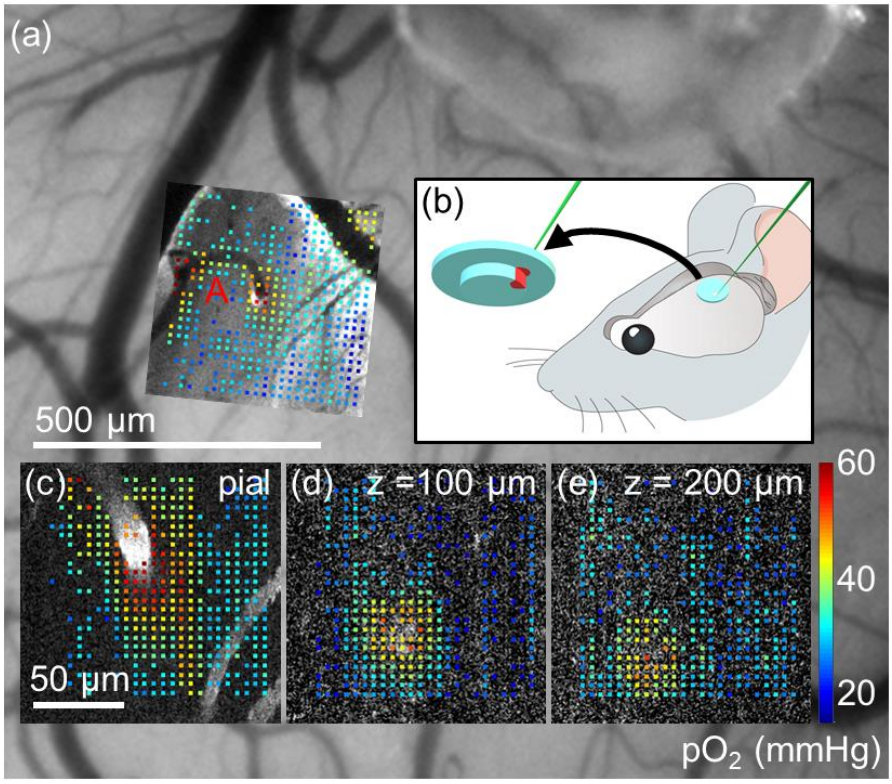


Figure 1. (a) Tissue pO_2 measurements in awake mouse. pO_2 values around a diving arteriole are

color-coded and overlaid over a bright field image of the pial surface. (b) Oxyphor 2P injected with the glass micropipette through a silicone-filled port in the chronic sealed cranial window. The inset shows the bottom of the glass window that is partially inserted through the cranial window. Silicone-filled port is highlighted red for better visibility. (c, d, and e) pO_2 measurements around the same diving arteriole marked in (a) overlaid over two-photon images of the FITC dextran-labeled plasma at the pial surface (c), and at cortical depths of 100 µm (d) and 200 µm (e).

Disclosures: I. Şencan: None. **K. Kiliç:** None. **B. Li:** None. **B. Fu:** None. **J.E. Porter:** None. **T. Esipova:** None. **M. Desjardins:** None. **M.A. Yaseen:** None. **D. Boas:** None. **S. Vinogradov:** None. **A. Devor:** None. **S. Sakadžic;:** None.

Poster

703. Optical Methods: Applications

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 703.26/CC59

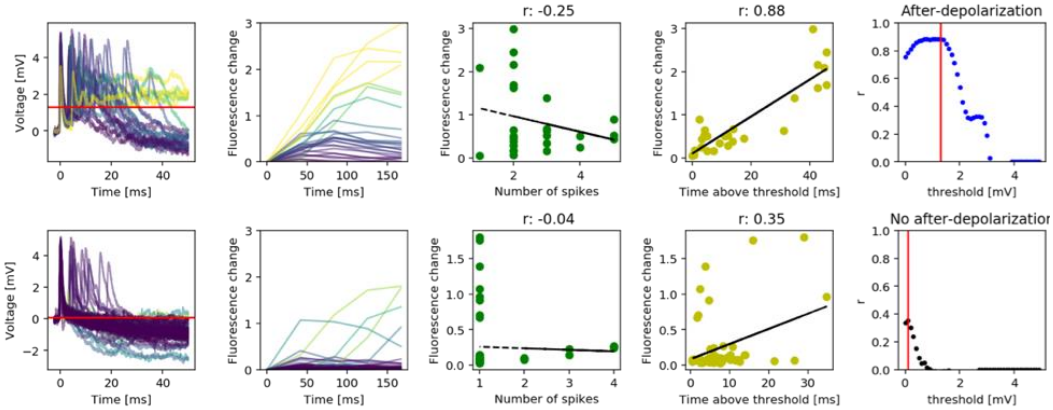
Topic: I.04. Physiological Methods

Title: Electrophysiological correlates of a non-stationary relationship between spikes and calcium

Authors: *P. LEDOCHOWITSCH, L. HUANG, G. OCKER, M. OLIVER, J. WATERS, H. ZENG, G. MURPHY, S. DE VRIES, M. BUICE;
Allen Inst. for Brain Sci., Seattle, WA

Abstract: Current attempts to infer the timing of action potentials from calcium-associated fluorescence (e.g. as measured via in-vivo two-photon microscopy) assume action potentials to be the only source of calcium in the neuron. Moreover, typically, the increase in calcium following a single action potential is modeled as stationary.
In this work, we present juxtacellular recordings paired with simultaneous *in vivo* two photon calcium imaging in transgenic mice, which show compelling violations of the above universal assumptions.
In 6/15 recordings from the Emx1-IRES-Cre;Camk2a-tTA;Ai93 line, but only in up to 3/19 in the other recorded line, Cux2-CreERT2;Camk2a-tTA;Ai93, significantly more of the variance in the fluorescence response could be explained by the presence and duration of after-depolarizations that followed spikes, than by the number of action potentials immediately preceding the fluorescence increases.
These observations indicate that, at least for some neurons, interpreting the magnitude of changes in calcium-associated fluorescence purely in terms of an instantaneous firing rate may be confounded by intracellular processes only weakly related to the cells' output spike train. We present a quantitative analysis of these effects and discuss plausible mechanisms.

The first row of the figure shows analysis of isolated and burst-like spiking events, which are followed by after-depolarizations of various duration for a single Emx1-IRES-Cre;Camk2a-tTA;Ai93 cell; the second row shows the same analysis but for spiking events without after-depolarizations.



Disclosures: **P. Ledochowitsch:** None. **L. Huang:** None. **G. Ocker:** None. **M. Oliver:** None. **J. Waters:** None. **H. Zeng:** None. **G. Murphy:** None. **S. de Vries:** None. **M. Buice:** None.

Poster

703. Optical Methods: Applications

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 703.27/CC60

Topic: I.04. Physiological Methods

Title: A validated GCaMP viral method for microendoscopic imaging in rat hippocampus CA1 during active behavior

Authors: ***S. GULATI**, D. CHENG, J. J. NASSI, A. M. STAMATAKIS;
Inscopix, Palo Alto, CA

Abstract: A large part of our understanding of the neurophysiological basis of sleep, memory, motivation and addiction has been derived from rodent experiments, particularly those involving rats. Studying behavior precisely paired with in-vivo cell specific neurological recordings is essential in deciphering how certain regions of the brain are involved in these behavioral attributes. One such tool that is extensively used to gather such information utilizes genetically encoded calcium indicators in combination with cell-specific viral-mediated delivery and one-photon imaging in freely behaving animals. Here we demonstrate an end-to-end solution to obtain stable neural recordings from hundreds of pyramidal neurons in rat CA1 region of

hippocampus using the Inscopix nVista3 miniature microscope paired with an active behavior responsive commutator. We utilized pre-diluted and validated ready-to-image virus to label the CA1 pyramidal neurons and studied their firing pattern while the animals actively explored an open field arena. Together these solutions will enable researchers to link behaviors to patterns of activity in the rat brain which will in turn lead to cutting-edge discoveries in neurophysiology and systems neuroscience.

Disclosures: **S. Gulati:** A. Employment/Salary (full or part-time):; Inscopix. **D. Cheng:** A. Employment/Salary (full or part-time):; Inscopix. **J.J. Nassi:** A. Employment/Salary (full or part-time):; Inscopix. **A.M. Stamatakis:** A. Employment/Salary (full or part-time):; Inscopix.

Poster

704. Biomarker and Drug Discovery: Neuropsychiatric Diseases

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 704.01/CC61

Topic: I.06. Computation/ Modeling/ and Simulation

Title: Engineering 3D neural tissues for drug screening

Authors: *A. N. VO, S. KUNDU, M. J. SONG, M. FERRER, M. E. BOUTIN;
Natl. Ctr. for Advancing Translational Sci., Rockville, MD

Abstract: In 2017, the opioid crisis in the U.S. was declared a public health emergency. To help combat this crisis, the 3D Tissue Bioprinting Laboratory at NCATS is supporting the NIH Helping End Addiction Long-Term (HEAL) Initiative by developing morphologically- and physiologically-relevant human 3D neural tissue models for the discovery of new treatments for pain and opioid addiction and overdose. Predictive *in vitro* 3D neural tissue model systems must contain functional mixtures of neurons and glial cells of the brain and mimic the native brain microenvironment. Our group is developing 3D biofabricated neural tissue models using human induced pluripotent stem cell (iPSC)-derived neuronal and astrocyte cells with macromolecular crowding (MMC) agents to induce extracellular matrix (ECM) production and deposition. Initial studies were performed in 2D monocultures to identify media which supports spontaneous neuronal activity in human iPSC-derived dopaminergic neurons and determine MMC agents which induce deposition of endogenous matrix by astrocytes. Among the tested media, neurons seeded in iCell Complete Maintenance Medium and transitioned to BrainPhys complete media on 2 days *in vitro* were found to have the most consistent spontaneous firing over a 28-day period. MMC optimization studies show that addition of Ficoll 70/400 crowding with ascorbic acid in astrocyte monoculture increased secretion and deposition of ECM proteins collagen I, collagen IV, and laminin. Ongoing studies include testing the optimal medium with MMC for co-culture of neurons and astrocytes in 3D and optimizing the hydrogel components for the

support of the 3D co-cultures. Future studies aim to utilize this 3D culture models to develop *in vivo*-relevant assays for HEAL-related experiments.

Disclosures: A.N. Vo: None. **S. Kundu:** None. **M.J. Song:** None. **M. Ferrer:** None. **M.E. Boutin:** None.

Poster

704. Biomarker and Drug Discovery: Neuropsychiatric Diseases

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 704.02/CC62

Topic: I.05. Biomarker and Drug Discovery

Support: AMED Grant iD3 Booster
KAKENHI (Glial assembly; 26117519)
KAKENHI (25430079)
KAKENHI (15K06790)
KAKENHI (16K07073)
KAKENHI (19K06916)
The Sakamoto Research Foundation of Psychiatric Diseases

Title: Discovery of novel antidepressant agents targeting protein kinases in oligodendrocytes

Authors: *S. MIYATA[1], S. SHIMIZU[1], Y. ISHINO[1], M. TOHYAMA[1,2];
[1]Kindai Univ/ Res. Ins Trad Asian Med., Osaka-Sayama, Japan; [2]Osaka Prefectural Hosp. Organization, Osaka, Japan

Abstract: Major depressive disorder (MDD) is thought to be a multifactorial disease susceptible to both environmental and genetic factors. Though the responsible genes and pathogenesis of MDD at the molecular level remain unclear. In the current study, we focused on the stress hypothesis. Hypothalamic-pituitary-adrenal axis, HPA axis, activation is one of the major stress-responsive reactions for the biological defense mechanism. In approximately 50% of patients with MDD, dysregulation of this negative feedback mechanism has been reported. However, the molecular pathway in the brain affected by the excess level of plasma glucocorticoids has not been well understood. Thus, we firstly developed an animal model of depression by exposing mice to chronic stress. These mice showed depression-like symptoms including chronically elevated plasma levels of corticosterone. We further found oligodendrocyte (OL)- specific activation of the protein kinase X cascade, increased expression of axon-myelin adhesion molecules, and elaboration of the OL arbor in the corpus callosum of chronically stressed mice. Next, we generated active protein kinase X transgenic mice to investigate the relationship between OL morphological changes and protein kinase X cascade activation in OL. These protein kinase X transgenic mice showed depression-like symptoms, but these transgenic mice

with repeated administration of inhibitor Y did not show these depression-like symptoms. Furthermore, our clinical and basic studies by diffusion tensor imaging in the anterior corpus callosum indicated that significantly lower fractional anisotropy values and axial diffusivity in patients with MDD and chronically stressed mice. This compromised white matter integrity were possibly related to axonal damage, and that specific white matter abnormalities might be closely associated with MDD onset. Thus, inhibition of protein kinase X cascade in OLs could provide us with new antidepressant therapy.

Disclosures: S. Miyata: None. **S. Shimizu:** None. **Y. Ishino:** None. **M. Tohyama:** None.

Poster

704. Biomarker and Drug Discovery: Neuropsychiatric Diseases

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 704.03/CC63

Topic: I.05. Biomarker and Drug Discovery

Support: Anonymus donor

Title: Isoform analysis of blood transcriptomic biomarkers for depression in human lymphocytes and hippocampal tissue

Authors: *S. L. WERT, E. REDEI;
Psychiatry and Behavioral Sci., Northwestern Univ. Feinberg Sch. of Med., Chicago, IL

Abstract: Access to brain tissue for psychiatric disorders is limited by the availability and quality of postmortem brain samples. Consequently, surrogate peripheral tissues, such as blood samples, have become common to employ. However, the extent to which transcriptomic changes from peripheral tissues can be used to represent or predict those of brain tissues is unknown. Additionally, the presence of transcript variants is known to differ between brain and blood, and therefore, it is important to identify what we measure in the blood as a surrogate for the brain. In the present study, we investigated previously identified blood transcriptomic markers for depression (Redei et al., 2014) for the expression of splice variants in human lymphocyte and hippocampal tissue. Expression for unique transcripts was measured by quantitative RT-PCR. Primers were designed to amplify specific isoforms. Transcript levels of *CD59*, *CADM1*, *KIAA1539*/*FAM214B*, were higher in the hippocampus in contrast to *ADCY3*, *DGKA*, *ATP11C*, *FAM46A* and *PSME1*, which had greater expression in lymphocytes. Although there were clear variations in isoform expression in both tissues, there were no extreme tissue-specific expression differences in these transcripts. Although *ASAH1* has 69 splice variants, there were no differences in transcript levels between hippocampus and lymphocytes. In contrast, large differences were found in the expression of the 13 splice variants of Ras association (RalGDS/AF-6) and pleckstrin homology domains 1 (*RAPH1*) within blood and hippocampus,

and compared to each other. The expression pattern of these differences clearly aligned to specific splice variants, and candidate mechanisms include the presence or absence of microRNA binding sites on the splice variants. Thus, isoform expression in the blood and brain is relatively homologous, but when it is not, tissue-specificity needs to be evaluated.

Disclosures: S.L. Wert: None. **E. Redei:** None.

Poster

704. Biomarker and Drug Discovery: Neuropsychiatric Diseases

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 704.04/CC64

Topic: I.05. Biomarker and Drug Discovery

Title: The pharmacological dichotomy of ketamine: *In vitro* assays to evaluate neuronal structure and EEG-like oscillations

Authors: I. BARBIERO[1], M. CUNNINGHAM[2], C. KILSTRUP-NIELSEN[1], ***M. BIANCHI**[3,2]; [1]Univ. of Insubria, Busto Arsizio, Italy; [2]Trinity Col. Dublin, Dublin, Ireland; [3]Ulysses Neurosci. Limited, Dublin, Ireland

Abstract: Ketamine (NMDA antagonist) is the only pharmacological therapy for treatment resistant depression (TRD) at sub-anaesthetic doses. However, ketamine is also used as an experimental pharmacological model for schizophrenia (SCZ) in the clinic due to its psychedelic effects. This pharmacological dichotomy is explored by pharmaceutical companies in order to develop new drugs for TRD and SCZ. Rapid *in vitro* assays are required to accelerate progression of compounds in the drug discovery phases. Here, we describe two *in vitro* assays to investigate effects of ketamine. 1) The antidepressant efficacy of ketamine is hypothesized to be linked to synaptic plasticity. We have explored effects of ketamine (0.3 and 1μM) on the structure of mouse hippocampal primary neuronal cultures at 24h and 72h post-exposure compared to vehicle (0.1% DMSO). Axonal length was analysed at DIV4 by staining with the axonal marker Tau1. Dendritic arborization was investigated at DIV10 by staining with the dendritic marker Map2. Spine maturation was analysed at DIV14 by staining PSD95 to visualize mature spines (PSD95-puncta). Quantitation was made by using ImageJ and FuJi software. The results showed no effects of ketamine on axonal length, while dendritic arborization was significantly increased at both concentrations at either 24h ($P<0.01, n\geq3$) or 72h ($P<0.05, n\geq3$) post-exposure compared to vehicle. PDS95-puncta were not changed by ketamine at both concentrations at 24h post-administration, while a significant increase ($P<0.05, n\geq3$) was observed at 72h at 1μM compared to vehicle. 2) Disruption in oscillatory EEG activity of gamma frequency is a biomarker of ketamine activity in the clinic. Rats were treated with ketamine (30 mg/kg) once a day for 5 days which is the standard pre-clinical protocol to model SCZ. The frontal section of the brain was then sliced isolate the anterior cingulate cortex (ACC). Slices

were transferred to an interface chamber and electrodes placed in the ACC in either deep or superficial layers. EEG-like activity including peak frequency, peak amplitude and area power were obtained from power spectra generated with Fourier analysis performed off-line using a 60s period every 10 minutes. The data showed that ketamine induced a significant ($P<0.05$) increase in peak frequency compared to vehicle indicating increase in speed of oscillatory activity compared to vehicle (0.9% NaCl). In contrast, ketamine did not induce changes in peak amplitudes or area powers. We have therefore developed *in vitro* assays which can be used by pharmaceutical companies for a first and rapid screening of ketamine-like compounds on synaptic plasticity and EEG-like oscillations.

Disclosures: **I. Barbiero:** A. Employment/Salary (full or part-time):; University of Insubria. **M. Cunningham:** A. Employment/Salary (full or part-time):; Trinity College Dublin. **C. Kilstrup-Nielsen:** A. Employment/Salary (full or part-time):; University of Insubria. **M. Bianchi:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ulysses Neuroscience Limited.

Poster

704. Biomarker and Drug Discovery: Neuropsychiatric Diseases

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 704.05/CC65

Topic: I.05. Biomarker and Drug Discovery

Support: NCBR Grant POIR.01.01.01-00-1021/15

Title: Safety assessment of esketamine administered via dry powder inhalation in animals and humans during preclinical toxicology and phase I clinical study

Authors: ***M. MATLOKA**[1], S. JANOWSKA[1], J. SIERZPUTOWSKA[1], K. JARUS-DZIEDZIC[2], J. PIECZYKOLAN[1], M. WIECZOREK[1];
[1]Celon Pharma S.A., Lomianki, Poland; [2]BioResearch Group Sp. z o.o., Kajetany, Poland

Abstract: Despite ketamine has been used as a medicine for over 50 years, there are only single reports on the safety of ketamine in animals and humans, in particular for other than parental administration routes. Esketamine inhaled as dry powder represents a new approach that may provide additional advantages over currently used administration routes. Here we present the safety profile of esketamine inhaled as dry powder assessed during preclinical and clinical studies. Preclinical safety has been assessed during safety pharmacology and toxicology studies. The animals were administered with esketamine as dry powder via inhalation. Wistar rats received doses up to 58.8 mg/kg during a single or 14-day administration study. Beagle dogs were exposed to doses up to 40.8 mg/kg during a single, 7 or 28-day toxicology studies. Safety pharmacology study assessed respiratory, cardiovascular and behavioural, neurological and

autonomic parameters. The clinical study consisted of an open label, two-part, single-ascending dose and multiple dose, randomized, double-blind, placebo controlled, ascending dose study with four administrations twice a week over 2 week period in healthy volunteers. Subjects received up to 48 mg of esketamine delivered by dry powder inhaler. Safety assessment included adverse events (AE) reporting, clinical laboratory tests, vital signs, physical examination, electrocardiography and psychoactive side effects. Most of the side effects observed during preclinical toxicology studies included slight to extreme incoordination, slight to extreme salivation, slight decreased activity, shaking, labored and/or slight increased respiration. Most of theses signs dissipated 1 hour post-exposure and were not observed following each dose occasion and not in every animal. All observations were not deemed toxicologically adverse since all signs were transient. Safety pharmacology study revealed no influence on respiratory or cardiovascular functions. Functional Observation Battery confirmed known anesthetic activity of esketamine. Administration of inhaled esketamine as dry-powder during clinical studies was generally safe and well tolerated with no serious AEs. The most common drug related AEs (mild to moderate intensity) were dizziness, a feeling of relaxation, numbness of the mouth and tongue, and hypertension. No discontinuation due to adverse effects was recorded. No abnormalities in laboratory tests or ECG were observed. The presented studies confirm that esketamine administered via dry powder inhalation is well tolerated and safe at doses intended to be used for efficacy studies in treatment-resistant and bipolar depression.

Disclosures: **M. Matloka:** A. Employment/Salary (full or part-time):; Celon Pharma S.A.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Celon Pharma S.A. **S. Janowska:** A. Employment/Salary (full or part-time):; Celon Pharma S.A. **J. Sierzputowska:** A. Employment/Salary (full or part-time):; Celon Pharma S.A. **K. Jarus-Dziedzic:** 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.; PI of Contracted Research. **J. Pieczykolan:** A. Employment/Salary (full or part-time):; Celon Pharma S.A. **M. Wieczorek:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Celon Pharma S.A..

Poster

704. Biomarker and Drug Discovery: Neuropsychiatric Diseases

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 704.06/CC66

Topic: I.05. Biomarker and Drug Discovery

Title: Resting-state functional MRI outperforms structural MRI in predicting transdiagnostic depression severity

Authors: *M. S. MELLEM, Y. LIU, H. GONZALEZ, M. E. KOLLADA, W. J. MARTIN, P. AHAMMAD;
Blackthorn Therapeut., San Francisco, CA

Abstract: Uncovering the biological basis of patient heterogeneity is a key to creating clinically-relevant biomarkers. Non-invasive imaging is enabling the visualization of the brain-to-symptom links underlying neurobehavioral disorders, but the technology is often too narrowly applied by only examining one aspect of biology (e.g., anatomical or functional MRI measures) or a single diagnostic group. Since symptoms such as depression span multiple neurobehavioral disorders, a more robust symptom biomarker could be better captured by examining transdiagnostic patient cohorts and utilizing multiple neuroimaging modalities. Here, we built a transdiagnostic multimodal MRI model that successfully identified biomarkers that can reliably predict clinician-rated depression severity across multiple neurobehavioral disorders. We utilized the Consortium for Neuropsychiatric Phenomics dataset, which includes resting-state functional MRI (rs-fMRI) and structural-MRI (sMRI) imaging measures from patients with schizophrenia, bipolar disorder, and attention deficit and hyperactivity disorder (n=142 total). Input features included preprocessed sMRI volume, surface, and thickness measures (270 features) and preprocessed rs-fMRI connectivity measures (34,716 features). Our outcome measure of depression was the clinician-rated 28-item total score from the Hamilton Rating Scale for Depression (HAMD). We used an importance-ranked forward selection procedure with Elastic Net regression and cross-validation for an efficient, data-driven feature selection approach to identify the most predictive features from these high-dimensional data. This data-driven approach yielded a highly predictive transdiagnostic model that explained 61% of variance of the HAMD total score. Moreover, the feature selection step of this machine learning procedure returned a subset of features that were predictive and highly interpretable. Of the rs-fMRI connectivity features, the Default Mode Network was the primary source, while other predictive features were widely distributed across various resting-state networks including the Fronto-parietal Task Control, Salience, Somatosensory/motor, Subcortical, Attention, and Sensory networks. Structural features did not contribute much to the predictive strength of this model, representing only about 1% of features found to be predictive. Thus, we created an algorithm to predict depression across multiple neurobehavioral disorders. The features important to this algorithm suggest that functional connectivity, rather than anatomy, provides a “depressive brain signature” which could be targeted for intervention.

Disclosures: **M.S. Mellem:** A. Employment/Salary (full or part-time):; BlackThorn Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BlackThorn Therapeutics. **Y. Liu:** A. Employment/Salary (full or part-time):; BlackThorn Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BlackThorn Therapeutics. **H. Gonzalez:** A. Employment/Salary (full or part-time):; BlackThorn Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BlackThorn Therapeutics. **M.E. Kollada:** A. Employment/Salary (full or part-time):; BlackThorn Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property

rights/patent holder, excluding diversified mutual funds); BlackThorn Therapeutics. **W.J. Martin:** A. Employment/Salary (full or part-time):; BlackThorn Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BlackThorn Therapeutics. **P. Ahammad:** A. Employment/Salary (full or part-time):; BlackThorn Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BlackThorn Therapeutics.

Poster

704. Biomarker and Drug Discovery: Neuropsychiatric Diseases

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 704.07/CC67

Topic: I.05. Biomarker and Drug Discovery

Support: NIH Grant R01 MH100068
Taylor Family Foundation for Chronic Disease

Title: Biomarker of neurofeedback response

Authors: M. RANCE[1], J. EILBOTT[3], S. A. KICHUK[2], W. N. KOLLER[1], D. SCHEINOST[1], P. GRUNER[2], C. J. PITTENGER[2], ***M. HAMPSON**[1];
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Abstract: To facilitate personalized medicine, we are interested in identifying biomarkers that predict response to our fMRI neurofeedback interventions. We have developed an intervention for obsessive-compulsive disorder (OCD) in which we train patients to control activity in a region of the ventral frontal cortex (Hampson et al, 2012). This intervention involves four scanning sessions per subject: two feedback scans, a pre-assessment scan and a post-assessment scan. In the assessment scans, we collect resting state data and measures of ability to control the target brain area in the absence of feedback. A yoked sham control group is used. In previous work, we tested the intervention in subjects with subclinical contamination anxiety. Results were promising in that neurofeedback subjects showed greater improvement in control over their contamination anxiety than sham subjects (10 neurofeedback and 10 sham subjects; Scheinost et al., 2013). Furthermore, we identified a region of the frontal pole in which global resting connectivity prior to neurofeedback training predicted response to the intervention in this subclinical study (Scheinost et al., 2014). We are now running a double-blind, randomized clinical trial of the same intervention in patients with OCD. The Y-BOCS (Yale-Brown Obsessive-Compulsive Symptom Scale) is our primary measure of symptom severity in the clinical population. About a year into this clinical trial, the 1.5T scanner we were using was decommissioned and we moved the protocol to a 3T system. Taking the data collected prior to

the scanner change (6 neurofeedback and 6 matched sham subjects), we examined whether the biomarker previously identified in the subclinical population also predicted neurofeedback response in this interim data from the clinical trial. Indeed, there was a significant correlation between pre-intervention global resting connectivity in the frontal pole (using an a-priori defined region based on the predictor we identified in the subclinical study) and symptom improvement in the neurofeedback group ($r=0.95$, $p<0.05$). There was no significant correlation between global connectivity in the frontal pole and symptom change in the yoked sham control group, consistent with the hypothesis that this biomarker of response is related to the mechanism of action of the active intervention and not a marker, for example, of an individual's susceptibility to placebo effects. We conclude that we have identified a biomarker of response to our neurofeedback intervention that is shared across subclinical and clinical populations.

Disclosures: M. Rance: None. **J. Eilbott:** None. **S.A. Kichuk:** None. **W.N. Koller:** None. **D. Scheinost:** None. **P. Gruner:** None. **C.J. Pittenger:** None. **M. Hampson:** None.

Poster

704. Biomarker and Drug Discovery: Neuropsychiatric Diseases

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 704.08/CC68

Topic: I.05. Biomarker and Drug Discovery

Support: NCBR Grant STRATEGMED2/268248/9/NCBR/2015

Title: Safety and pharmacokinetic study of phosphodiesterase 10A inhibitor (CPL500036) after a single dose in healthy volunteers

Authors: *S. JANOWSKA[1], K. JARUS-DZIEDZIC[2], J. SIERZPUTOWSKA[1], M. MATLOKA[1], M. WIECZOREK[1];
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Abstract: Background: Phosphodiesterase 10A (PDE10A) hydrolyses cyclic nucleotides and is highly expressed in striatal medium spiny neurons (MSNs). PDE10A inhibition may modulate the MSNs action in an efficient way. Therefore, PDE10A inhibitors may be used in the treatment of various types of psychosis. In the course of preclinical development CPL500036 proved to be effective in several animal models of psychotic and neuromotor disorders. The present study was intended to determine the safety and pharmacokinetic properties of CPL500036 after single oral administration in healthy volunteers. **Methods:** This was an open label, dose-escalation study with single oral administration of CPL500036 in healthy volunteers being in a fasted state. The study was performed in conventional '3+3 design', where MTD (maximum tolerated dose) is to be determined. 21 Caucasian male and female subjects were enrolled in 7 cohorts (n=3 per cohort). Volunteers received CPL500036 in doses ranging from 1 to 100 mg. Safety assessment

included adverse events (AE) reporting, clinical laboratory tests, vital signs, physical examination, electrocardiography. Blood samples for pharmacokinetic (PK) analysis were collected up to 72 hours after administration. Concentration analysis was evaluated by HPLC/MS/MS method. PK parameters were computed using a non-compartmental modelling approach. **Results:** Administration of CPL500036 was generally safe and well tolerated with no serious AE. The drug related AEs, of mild to moderate intensity, were drowsiness, sensation of heat, anxiety and difficulty speaking. Despite administration up to 100 mg of CPL500036, no dose limiting toxicities (DLT) was observed, therefore no MTD was determined. The CPL500036 exposure increased in a dose-dependent manner. The CPL500036 mean maximum plasma concentration (Cmax) values were in range of 13.76 - 284.96 ng/mL for cohort 1-7, respectively, and were recorded from 45-50 minutes (for the first two doses) to 3h (for the highest dose) after administration. The area under the curve of plasma concentration vs time (AUC0-72) for the first and the last cohort was 105.85 ng/mL*h and 9493.89 ng/mL*h, respectively. **Conclusion:** CPL500036 administration in all doses was safe and well tolerated by volunteers and resulted in few AE with mild to moderate severity. Pharmacokinetics of CPL500036 supports once daily dosing regimen. The obtain results justify further clinical development.

Disclosures: **S. Janowska:** A. Employment/Salary (full or part-time):; Celon Pharma S.A. **K. Jarus-Dziedzic:** 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.; PI of Contracted Research. **J. Sierzputowska:** A. Employment/Salary (full or part-time):; Celon Pharma S.A. **M. Matloka:** A. Employment/Salary (full or part-time):; Celon Pharma S.A.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Celon Pharma S.A. **M. Wieczorek:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Celon Pharma S.A..

Poster

704. Biomarker and Drug Discovery: Neuropsychiatric Diseases

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 704.09/CC69

Topic: I.05. Biomarker and Drug Discovery

Support: JSPS KAKENHI Grant 17K16381
JSPS KAKENHI Grant 18K07564

Title: Analysis of methylation and -141C Ins/Del polymorphisms of the dopamine receptor D2 gene in patients with schizophrenia

Authors: *Y. FUNAHASHI[1], Y. YOSHINO[3], K. YAMAZAKI[4], S. OCHI[2], J. IGA[5], S.-I. UENO[6];
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Abstract: The gene for dopamine receptor D2 (DRD2) is associated with schizophrenia (SCZ). Epigenetic changes may be related to SCZ pathology. The -141C Ins/Del polymorphism in DRD2 (rs1799732) is functional and associated with SCZ. Fifty SCZ patients and 50 control subjects were newly recruited and analyzed in addition to 50 previously reported SCZ samples and 50 previously reported control samples. Genomic DNA from peripheral leukocytes was analyzed. We replicated analysis of DNA methylation rates at seven CpG sites (CpG 1-1 to 1-7) and also analyzed five additional sites (CpG 2-1 to 2-5) in the upstream region of DRD2. We also performed genotyping of -141C Ins/Del and analyzed the effects of -141C Ins/Del on methylation of DRD2. Methylation rates were significantly lower in SCZ patients compared to control subjects, respectively. In control subjects, the methylation rates were significantly lower in individuals with the Ins/Ins genotype than in Del allele carriers. We replicated hypomethylation of the DRD2 promoter region in SCZ patients compared to age-matched control subjects. The -141C Ins/Del polymorphism affected the methylation rates in regions of DRD2. Hypomethylation and the -141C Ins/Del polymorphism of DRD2 may be biomarkers for SCZ.

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Poster

704. Biomarker and Drug Discovery: Neuropsychiatric Diseases

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Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 704.10/CC70

Topic: I.05. Biomarker and Drug Discovery

Support: Israel Science Foundation Grant 504/17

Title: EEG signal complexity as a computational bio-marker for schizophrenia

Authors: *E. J. WOLFSON[1], Y. LOEWENSTEIN[2], O. SHRIKI[3];
[1]Dept. of Brain and Cognitive Sci., BGU, Beer-Sheva, Israel; [2]Hebrew Univ., Jerusalem, Israel; [3]Ben-Gurion Univ., Beer-Sheva, Israel

Abstract: Schizophrenia (SCZ) is a severe disruption in cognition and emotion, affecting the most fundamental human functions: language, thought, perception, affect, and sense of self. It is

thought to be associated with alterations in the balance of excitation and inhibition, which lead to changes in the underlying network dynamics.
To identify potential biomarkers that could provide new insights and indicate altered neural dynamics, we applied multi-scale entropy (MSE) analysis, which quantifies signal complexity, along with conventional power spectrum analysis to resting-state MEG data from 54 SCZ patients and 98 healthy control subjects. To assess the feasibility of this analysis as a biomarker, we applied various machine learning classifiers, trained to differentiate between SCZ patients and control subjects.
The MSE method uses the concept of sample entropy to assess the level of temporal complexity of the measured signal across different time scales. Our analysis showed that sample entropy across specific time scales of SCZ patients is significantly higher than the sample entropy ascribed to controls. Specifically, a higher sample entropy is observed on 216 out of 273 channels and reaches a significance level of $p < 0.05$ on 114 channels, most of which are located at the center of the central, parietal and occipital lobes. The difference peaks between the frequencies 15 and 24 Hz.
To dissect the contributions of the amplitude and phase components to the entropy, we generated, for each subject, a phase-shuffled surrogate signal and applied to it the same MSE analysis. We found that in those channels in which a significant difference between the SCZ patients and controls was observed, this difference was dominated by the signal amplitude. Those channels also showed good agreement with the spectral analysis, in terms of both localization and quality of classification. Surprisingly, the phase shuffling exposed differences between the SCZ patients and control subjects in the areas in which the amplitude component (and also spectral analysis) did not show a significant difference between the two groups, mainly the frontal and temporal lobes.
These findings pave the way for new insights into the differences in the underlying neural dynamics of schizophrenia patients and may be useful as a diagnostic tool which goes beyond spectral features.

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Poster

704. Biomarker and Drug Discovery: Neuropsychiatric Diseases

Location: Hall A

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Program #/Poster #: 704.11/CC71

Topic: I.05. Biomarker and Drug Discovery

Support: National Research Foundation, South Africa, Innovation Award
University Research Committee, University of Cape Town, South Africa

Title: Thalamic neuroinflammation is associated with thalamo-cortical gating dysfunction in schizophrenia

Authors: *F. M. HOWELLS[1,2], H. S. TEMMINGH[1], J. H. HSIEH[1,2], D. J. STEIN[1,2,3]; [1]Psychiatry and Mental Hlth., Univ. of Cape Town, Cape Town, South Africa; [2]Neurosci. Institute, Univ. of Cape Town, Cape Town, South Africa; [3]Dept. of Psychiatry and Mental Health, Univ. of Cape Town, SU/UCT MRC Unit on Risk and Resilience in Mental Disorders, Cape Town, South Africa

Abstract: *Introduction:* Thalamo-cortical circuitry, as measured by delta/alpha electroencephalography (EEG) frequency activity has been suggested to delineate the following psychotic disorders: schizophrenia (SCZ), bipolar I disorder with a history of psychosis (BPD), and methamphetamine-induced psychotic disorder (MPD) (Howells et al., 2018). Recent literature suggests neuroinflammatory mechanisms may underlie in part the presentation of psychotic disorders. Proton magnetic resonance spectroscopy (^{1}H-MRS) is able to provide an *in vivo* measure of active neuroinflammation, i.e. increased *myo*-inositol (mI) with decreased n-acetyl-aspartate metabolite (NAA and NAA with NAAG) concentrations. The aim of the current study was to investigate whether ^{1}H-MRS markers of neuroinflammation (mI/NAA+NAAG) in the thalamus are associated with the pronounced delta/alpha cortical activity in SCZ, BPD and MPD. *Method:* This study included individuals with diagnosis of SCZ (n=17), BPD (n=22), MPD (n=23), and demographic-matched controls (CON, n=25). On the same day, between 09h00-11h00 participants underwent (1) EEG frequency record (electrodes: F_3,F_4,C_3,C_4,P_3,P_4) during resting conditions, eye open and eyes closed, and during a simple attention task and (2) proton magnetic resonance spectroscopy (^{1}H-MRS) of their left thalamus. Correlation analyses were performed as appropriate to determine relationships between delta/alpha frequency activity and mI/NAA+NAAG concentration, *a priori* setting Rho>±0.6 and p<0.01. *Results:* Only SCZ were found to hold significant positive relationships between delta/alpha frequency activity and left thalamic mI/NAA+NAAG concentrations. These relationships were apparent only during resting eyes closed condition, and apparent for bilateral frontal (F_3 and F_4), left central (C_3) and right parietal (P_4) electrodes. The remaining two electrodes (C_4 and P_3) showed positive relationships (Rho>±0.4 and p<0.5) but did not meet the *a priori* thresholds set. *Conclusions:* These findings are consistent with the hypothesis that neuroinflammatory processes play a role in dysfunctional thalamo-cortical connectivity in SCZ, but not in BPD and MPD. Further work is, however, needed to replicate and consolidate these findings.

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Poster

704. Biomarker and Drug Discovery: Neuropsychiatric Diseases

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 704.12/CC72

Topic: I.05. Biomarker and Drug Discovery

Title: SEP-363856, a novel psychotropic agent with a unique, non-D2 mechanism of action

Authors: *N. DEDIC[1], P. G. JONES[1], S. C. HOPKINS[1], R. LEW[1], T. HANANIA[2], U. C. CAMPBELL[1], K. S. KOBLAN[1];
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Abstract: For the past 50 years, the clinical efficacy of antipsychotic medications has relied on blockade of dopamine D_2 receptors. Drug development of non-D_2 compounds, seeking to avoid the limiting side effects of dopamine blockade, has failed to date to yield new medicines for patients. Here we report the discovery of SEP-363856 (SEP-856), a novel psychotropic agent with a unique mechanism of action. SEP-856 was discovered in a medicinal chemistry effort utilizing a high throughput, high content, mouse-behavior phenotyping platform known as SmartCube®, in combination with *in vitro* screening, aimed at developing non-D_2 (anti-target) compounds that could nevertheless retain efficacy across a variety of D_2-based animal models of schizophrenia. SEP-856 demonstrated broad efficacy in rodent models relating to positive- and negative symptoms of schizophrenia, including Phencyclidine (PCP)-induced hyperactivity, prepulse inhibition and PCP-induced deficits in social interaction. Autoradiography and positron emission tomography studies in rats and non-human primates demonstrated lack of D_2 receptor occupancy by SEP-856 at concentrations up to 200-fold greater than those observed to be behaviorally efficacious. In addition to its favorable pharmacokinetic properties and the absence of catalepsy, SEP-856's broad profile was further highlighted by its antidepressant activity in the mouse forced swim test and robust suppression of rapid eye movement sleep in the rat. Although, the mechanism of action has not been fully elucidated, *in vitro* and *in vivo* pharmacology data suggest that agonism at both 5-HT_{1A} receptors and trace amine-associated receptor 1 (TAAR1) are integral to its efficacy. This was further corroborated with electrophysiological slice recordings, demonstrating inhibition of dorsal raphe nucleus and ventral tegmental area neuronal firing via 5-HT_{1A} and TAAR1 receptors, respectively. Based on its unique mechanism of action and broad efficacy in preclinical animals models, SEP-856 was advanced into clinical development and represents a promising candidate for the treatment of schizophrenia and potentially other neuropsychiatric disorders.

Disclosures: **N. Dedic:** A. Employment/Salary (full or part-time):; Sunovion Pharmaceuticals Inc. **P.G. Jones:** A. Employment/Salary (full or part-time):; Sunovion Pharmaceuticals Inc. **S.C. Hopkins:** A. Employment/Salary (full or part-time):; Sunovion Pharmaceuticals Inc. **R. Lew:** A.

Employment/Salary (full or part-time):; Sunovion Pharmaceuticals Inc. **T. Hanania:** A. Employment/Salary (full or part-time):; Psychogenics Inc.. **U.C. Campbell:** None. **K.S. Koblan:** A. Employment/Salary (full or part-time):; Sunovion Pharmaceuticals Inc..

Poster

704. Biomarker and Drug Discovery: Neuropsychiatric Diseases

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Topic: I.05. Biomarker and Drug Discovery

Support: a Grants-in-Aid from the Japan Society for the Promotion of Science (18H02756)
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a Grants-in-Aid from the Japan Society for the Promotion of Science (18K07620)

Title: Abnormality in metabolism of docosahexaenoic acid-lysophosphatidic acid (DHA-LPA) in major depressive disorder and schizophrenia

Authors: *W. OMORI[1,2,3], K. KANO[4], K. HATTORI[5], N. KAJITANI[1], K. ITAGAKI[1,3], M. OKADA-TSUCHIOKA[1], H. ABE[1], A. MACHINO[2], A. INOUE[4], H. KUNUGI[5], J. AOKI[4], M. TAKEBAYASHI[1,6];
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Abstract: [Background]
Lysophosphatidic acid (LPA) is a phospholipid involved in various physiological processes such as inflammation in the central nervous system. LPA is synthesized from lysophosphatidylcholine (LPC) by lysophospholipase D (lyso-PLD), also known as autotaxin (ATX), and degraded by lipid phosphate phosphatases (LPPs). In addition, LPC and LPA have multiple molecular species. Both serum and cerebrospinal fluid (CSF) autotaxin levels are significantly lower in major depressive disorder (MDD) patients than in healthy controls (Itagaki et al., 2019). However, levels of multiple molecular species of LPA and LPC, and lyso-PLD activity in the CSF have not been measured in patients with major psychiatric disorders. Therefore, CSF levels of LPAs and related substances in patients with MDD and schizophrenia were examined in the current study.
[Method]
CSF was obtained from Japanese patients with MDD (n=26) and schizophrenia (n=27) and from

age- and gender-matched healthy controls (n=27). All participants underwent the Mini-International Neuropsychiatric Interview (M.I.N.I), Japanese version. For participants with MDD and schizophrenia, a diagnosis was made according to DSM-IV criteria on the basis of the M.I.N.I. Each level of LPAs and LPCs and lyso-PLD activity were measured by using liquid chromatography-tandem mass spectrometry (LC-MS/MS). LPP1 levels were quantified with ELISA. The ethics committee of the National Center of Neurology and Psychiatry and National Hospital Organization Kure Medical Center approved this study. All participants provided written informed consent.
[Results]
Between the three groups, there were no differences in levels of LPAs and LPCs, lyso-PLD activity, and LPP1 levels. However, the LPA/LPC ratio showed a significant reduction of 22:6 (docosahexaenoic acid; DHA) - LPA/LPC ratio in patients with MDD and schizophrenia. Additionally, a significant correlation between DHA-LPA levels and lyso-PLD activity was found in healthy controls, which was not observed in patients with either MDD or schizophrenia.
[Conclusion]
Turnover of DHA-LPC to DHA-LPA was specifically reduced in patients with either MDD or schizophrenia. The abnormal metabolism of DHA-LPA in CSF could explain reduction of DHA, known to have anti-inflammatory effects, in previous studies of postmortem brain with major psychiatric disorders, and might serve as a part of pathophysiology of the disorders.

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Poster

704. Biomarker and Drug Discovery: Neuropsychiatric Diseases

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Topic: I.05. Biomarker and Drug Discovery

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Title: Orphan GPCR ligands from ethnobotanical sources as novel drugs for mental disorders

Authors: *C. GALLO, G. POLETTI, R. ROJAS, A. VAISBERG;
Univ. Peruana Cayetano Heredia, Lima, Peru

Abstract: Traditional medicine knowledge is an important tool to direct the discovery of novel therapeutics that will eventually help to unravel biological processes behind the occurrence of mental disorders. We have compiled information on the traditional use of plants for the treatment of mental disorders in several Peruvian localities and geographical regions and currently have repository of ethanol extracts from 477 plant collections corresponding to 265 species from 87 different plant families. These plants have been used for centuries in traditional medicine for one or more of the following actions: antipsychotic, antidepressant, anxiolytic and/or sedative.
Working in collaboration with the NIMH Psychoactive Drug Screening Program, we have been able to identify plant extracts with potential antagonist activity for the orphan G-protein-coupled receptors (GPCRs) GPR4, GPR65 and GPR68; potential agonist and inverse agonist activity for GPR52, GPR68 and GPR88 and potential agonist activity for the orphan GPCRs MRGPRX1, MRGPRX2 and MRGPRX4.
These receptors belong to the rhodopsin (class A) family, which is the largest and extensively studied family of GPCRs; however, they are considered orphans because their endogenous ligands are yet putative or unknown. An additional challenge is that there is a lack of pharmacologically active compounds identified or developed for these targets.
Interestingly, all the studied orphan GPCRs have been shown to be expressed in the mammalian brain. Moreover, several of our extracts show activity for more than one of these receptors, which could mean the presence of shared binding domains or potential biological interactions between them in the biology of these disorders.
We are currently working on the isolation and characterization of the active molecules through bioassay-guided fractionation of the raw extracts.
GPCRs participate in diverse physiological functions and are promising targets for drug discovery. For this reason, elucidating the biological function of orphan receptors is compelling.

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Poster

704. Biomarker and Drug Discovery: Neuropsychiatric Diseases

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Program #/Poster #: 704.15/CC75

Topic: C.08. Ischemia

Support: NCSF Grant 31771221

Title: Resting-state EEG delta predicts neurofeedback treatment long-term response in nicotine addiction

Authors: J. BU, *X. ZHANG;
Univ. of Sci. & Technol. of China, Hefei, China

Abstract: Neurofeedback, as a novel cognitive neurostimulation technology, has been clinically employed in drug addiction over six decades. However, about 30% of participants fail to learn to self-regulate their brain activity during neurofeedback. Recently we developed a novel EEG neurofeedback protocol and found that it can impressively reduce cigarette consumption even at 4-month follow-up for smokers. However, obvious individual differences in long-term effects were observed. Therefore, it is critical to identify who will benefit at pre-neurofeedback. In current study, we examine whether resting-state EEG characteristics at pre-neurofeedback predict long-term effects and further explore the mechanism of the resting-state EEG predictor. With a randomized clinical trial (RCT), sixty nicotine-dependent participants were randomly assigned to the real-feedback group and the yoked-feedback group. They underwent two novel neurofeedback training sessions. At pre-neurofeedback and post-neurofeedback, participants underwent a 6 min resting EEG recording. At 4-month follow-up after neurofeedback training, the number of cigarettes smoked per day was assessed. First, the power of resting-state delta (1-3 Hz) at pre-neurofeedback strongly correlated with long-term effects in the real-feedback group ($r=0.70$, $p<0.001$). After control for all clinical variables and other EEG band power, the delta could also predict the long-term effects ($r=0.62$, $p<0.001$). The significant prediction was only observed in the realfeedback group, which suggested the delta represented a specific predictor of neurofeedback training. In addition, the strong correlation between pre-neurofeedback and post-neurofedback indicated the stability of the delta power ($r=0.69$, $p<0.001$). Moreover, the leave-one-out cross-validation procedure using machine learning methods revealed the relationship between the observed long-term effects and predicted effects by the delta power was strongly significant ($r=0.61$, $p<0.001$). Furthermore, previous studies have showed that late positive potential (LPP) was an indicator of addiction incubation effect. We found significant LPP appeared at 4-month follow-up. In addition, the delta predictor was significantly correlated with the LPP ($r=0.59$, $p<0.001$). Further, the EEG source analysis revealed that the delta was related with orbital frontal cortex which was also involved with incubation effect of addiction. With the RCT, we found resting-state delta power may represent a strong, stable and specific prognostic marker of neurofeedback effects, and the predictor may be linked to the addiction incubation effect.

Disclosures: J. Bu: None. **X. Zhang:** None.

Poster

704. Biomarker and Drug Discovery: Neuropsychiatric Diseases

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 704.16/CC76

Topic: I.05. Biomarker and Drug Discovery

Title: Stem cell-derived grinch neurons for high throughput screening and profiling

Authors: *R. HEILKER[1], S. TRAUB[2], D. BISCHOFF[3];
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Abstract: Human induced pluripotent stem (hiPS) cell-derived neurons promise to provide better model cells for drug discovery in the context of the central nervous system. Using GRowth factor-driven expansion and INhibition of NotCH (GRINCH) during maturation, sufficient numbers of hiPS cell-derived GRINCH neurons were generated to accommodate for the immense material needs of high-throughput screening (HTS). GRINCH cells displayed neuronal markers, and their functional activity could be demonstrated by electrophysiological recordings. The GRINCH neurons were employed as model cells to search for positive modulators of synaptic plasticity. Pharmacological characterization in GRINCH neurons paves the way for a new generation of predictive cell-based drug discovery and development.

Disclosures: R. Heilker: A. Employment/Salary (full or part-time):; Boehringer Ingelheim Pharma Gmbh & Co. KG. **S. Traub:** A. Employment/Salary (full or part-time):; Trenzyme GmbH. **D. Bischoff:** A. Employment/Salary (full or part-time):; Boehringer Ingelheim Pharma GmbH & Co. KG.

Poster

704. Biomarker and Drug Discovery: Neuropsychiatric Diseases

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 704.17/CC77

Topic: I.05. Biomarker and Drug Discovery

Support: NIH Grant MH107126

Title: Development of a PC12 cell-based assay for *in vitro* screening of catechol-O-methyltransferase inhibitors

Authors: *G. V. CARR[1,2], G. ZHANG[1], I. BUCHLER[1], M. DEPASQUALE[1], M. WORMALD[1,2], H. WEI[1,2], J. C. BARROW[1,2];
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Abstract: The male rat adrenal pheochromocytoma PC12 cell line can synthesize and release catecholamines (dopamine, epinephrine, and norepinephrine), and has been widely used as an *in vitro* model system in studies of neurotransmitter regulation. Catechol-*O*-methyltransferase (COMT) is involved in the inactivation of the catecholamine neurotransmitters and serves a critical role in regions of the brain with low expression of the dopamine transporter, such as the prefrontal cortex. In this study, we explored the feasibility of utilizing PC12 cells as a medium-

throughput drug screening platform. Our characterization data confirmed the presence of measurable tyrosine hydroxylase (TH), monoamine oxidase A (MAO-A), MAO-B, and COMT protein levels. Additionally, PC12 cells express the D1, D2, and D5 dopamine receptors. In agreement with previous studies of PC12 cells, no dopamine transporter protein was detected. Incubation of PC12 cells with tolcapone, a highly potent and selective COMT inhibitor, reduced the concentrations of dopamine metabolites 3-MT and HVA and increased concentrations of dopamine and DOPAC, another metabolite, in the cell culture medium. The effects of tolcapone in the PC12 assay were in agreement with *in vivo* measurements taken from the brain across species. Our novel COMT inhibitor, LIBD-3 produced qualitatively similar effects when compared to tolcapone. The relative changes in dopamine metabolites produced by LIBD-3 were slightly smaller than those produced by tolcapone, in line with the difference in potency measured in cell-free enzyme assays. Moreover, tolcapone and LIBD-3 incubation significantly potentiated the amount of dopamine released in response to high K^+-mediated depolarization, similar to the published results of *in vivo* microdialysis studies in rats. Together, our data support the view that PC12 cells represent a robust system that can serve as a bridge between cell-free enzyme assays and costly *in vivo* efficacy models in determining which COMT inhibitors should be advanced in a drug discovery setting.

Disclosures: G.V. Carr: None. **G. Zhang:** None. **I. Buchler:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent holder. **M. DePasquale:** None. **M. Wormald:** None. **H. Wei:** None. **J.C. Barrow:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent holder.

Poster

704. Biomarker and Drug Discovery: Neuropsychiatric Diseases

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 704.18/CC78

Topic: I.05. Biomarker and Drug Discovery

Title: Topographical patterns of brain function at the individual level: Informative and interpretable

Authors: *B. C. TABER-THOMAS;
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Abstract: Technological advances have allowed for the collection of large amounts of neuroimaging data, but relatively less progress has been made in developing analysis techniques that provide easily understandable and clinically useful information. This is partly due to the difficulty of reducing neuroimaging data to a format that is at the same time (i) human readable and (ii) information rich. A breakthrough is possible by leveraging the topography brain

organization to capture robust network phenomena in a simple, intuitive profile representing an individual's functional brain organization. The present analyses build on a recently developed topographical data reduction approach (Taber-Thomas et al., 2016; Deen et al., 2015) in order to extract individual patterns of brain organization. This analysis technique has revealed group differences in the topography of brain function; for example, children at risk for anxiety show a flattened pattern of salience network connectivity across the anterior cingulate cortex (Taber-Thomas et al., 2016). Here, topographical patterns of salience network connectivity are extracted at the individual level, providing a simple curve that represents an individual's topographical pattern of brain function or connectivity. Data previously analyzed at the group level and data culled from publicly available neuroimaging datasets are re-analyzed to reveal topographical patterns of brain function at the individual level. Insula connectivity is extracted for a series of regions of interest spanning the limbic system to provide a topographical pattern of salience network connectivity. Group analyses reveal the expected topographical pattern of insula connectivity: greater connectivity with dorsal and less connectivity with ventral anterior cingulate cortex. However, at the individual level significant variability in topography is observed. The reliability and utility of topographical patterns of brain function at the individual level will be discussed. In sum, a topographical data reduction approach has the potential to advance the discovery of neuroimaging biomarkers that are meaningful and interpretable at the individual level.

Disclosures: B.C. Taber-Thomas: None.

Poster

705. Virtual Brain Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 705.01/DD1

Topic: I.06. Computation/ Modeling/ and Simulation

Title: Parameter optimization in personalized Virtual Brain models using stochastic gradient descent

Authors: Z. WANG[1], K. SHEN[1], J. D. GRIFFITHS[1,2], *A. R. MCINTOSH[1];
[1]Baycrest Ctr., Toronto, ON, Canada; [2]Ctr. for Addiction and Mental Hlth., Toronto, ON, Canada

Abstract: In large-scale dynamic network modeling, a brute force search on model parameters is often used to optimize the fit between empirical and simulated functional connectivity (FC). Finding the optimal fit in such a search is dependent on the choice of search step and space. Fitting many parameters at once, such as considering connection parameters individually, can also become computationally expensive. Using tools implemented in machine learning may be a powerful way to estimate large sets of model parameters. Here we describe the integration of

stochastic gradient descent using TensorFlow, a machine learning library, with the generative model in TheVirtualBrain (TVB; thevirtualbrain.org). The advantage of using a framework like TensorFlow is the automatic computation of Jacobians which substantially improves the speed and tractability of optimization problems. Using data from the Human Connectome Project, we created personalized connectome-based models of 200 individuals. In each model, each node was represented by a neural mass model, coupled together according to the subject's structural connectome. The resultant model can be considered a type of recurrent neural network whose state weights can be trained. Noise served as the input to state weights. State-to-state weights were parameters of interest. Simulated resting-state BOLD-fMRI FC was computed in windowed increments of 15 time points and fit to corresponding windows of empirical FC using the stochastic gradient descent algorithm in TensorFlow (Adam). Fits were assessed using the Pearson correlation (r) between the simulated and empirical FC, and parameters were iteratively updated for each window. For each iteration, initial conditions for state variables were randomly selected. This was repeated 40-100x until the parameter estimates reached an asymptote and the average of parameters from the last 10 steps were kept. Fitting only three parameters - global coupling, noise and local gain - resulted in an average fit of r=0.45. By also fitting the interareal couplings (up to 83x83 additional parameters), the fits increased to an average of r=0.75. Our findings suggest that integrating machine learning methods into the generative model in TVB can be a powerful tool for large-scale network modeling efforts.

Disclosures: Z. Wang: None. **K. Shen:** None. **J.D. Griffiths:** None. **A.R. McIntosh:** None.

Poster

705. Virtual Brain Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 705.02/DD2

Topic: I.06. Computation/ Modeling/ and Simulation

Support: BAND2 grant from the Alzheimer's Association, Alzheimer's Research UK, The Michael J. Fox Foundation for Parkinson's Research and the Weston Brain Institute
BrightFocus Foundation

Title: Using personalized virtual brain models to reveal mechanisms of cognitive impairment in Parkinson's disease

Authors: *K. SHEN[1], Z. WANG[1], T. BROWN[1], D. SODUMS[2], A. R. MCINTOSH[1,3]; [1]Rotman Res. Institute, Baycrest, Toronto, ON, Canada; [2]Kunin-Lunenfeld Ctr. for Applied Res. & Evaluation, Baycrest, Toronto, ON, Canada; [3]Psychology, Univ. of Toronto, Toronto, ON, Canada

Abstract: Although Parkinson's disease (PD) is initially characterized by motor symptoms, >80% of patients develop dementia over the course of the disease. Using static neuroimaging profiles alone to develop biomarkers for PD-dementia is challenging because affected brain networks are also implicated in other dementias. Moreover, disease mechanisms occur at cellular/molecular scales and are undetectable with current noninvasive neuroimaging tools. We begin to address these challenges by integrating neuroimaging data with underlying cellular mechanisms via large-scale dynamic network models using TheVirtualBrain (TVB; thevirtualbrain.org) simulation platform. Personalized models of PD (N=70), prodromal forms of PD (N=13) and healthy controls (N=19) were created in TVB using each individual's structural connectome. The local dynamics of each brain region was modeled using a mean field model of coupled excitatory and inhibitory populations. Model parameters (global coupling, noise, & local coupling) were varied to optimize the fit between empirical and simulated resting-state functional connectivity. Good fits were obtained for all subject groups (mean: 0.38; range: 0.26-0.49). A multivariate analysis showed that increased global coupling and lower noise were related to better cognitive scores ($p < 0.01$). These findings suggest that disruptions to long-distance integration underlies cognitive impairment in PD. Our models are a solid first step towards the deliberate integration of neuroimaging data with computational modeling to elucidate the biophysical substrates of disease mechanisms in dementia.

Disclosures: K. Shen: None. **Z. Wang:** None. **T. Brown:** None. **D. Sodums:** None. **A.R. McIntosh:** None.

Poster

705. Virtual Brain Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 705.03/DD3

Topic: I.06. Computation/ Modeling/ and Simulation

Support: Human Brain Project SGA2

Title: Large scale modeling of the mouse brain dynamics

Authors: *L. KUSCH[1], S. PETKOSKI[2], V. K. JIRSA[3];
[1]Inst. de Neurosciences des Systèmes, Aix-Marseille Univ., Marseilles, France; [2]Inst. de Neurosciences des Systèmes, Aix-Marseille Univ., Marseille, France; [3]Inst. De Neurosciences Des Systemes UMR1106, Marseille, France

Abstract: Modeling the mouse whole-brain dynamics is viable using the paradigm of brain network models based on the structural connectivity of the mouse brain. This approach is implemented in the neuroinformatic platform The Virtual Brain (TVB) [1], where the tracing data from Allen Institute [2] can be combined with a range of neural mass models [3]. Another

common strategy is based on spiking neural networks and uses experimental data at the cellular level for the parameters, leading to bottom-up models such as the Blue Brain project. The former are better suited for study from dynamical systems viewpoint, while the complexity of the latter makes them more physiological plausible.
In this work we bridge the two approaches, by building a connectome based large-scale brain network model, where each region contains a population or a surface of spiking neurons, thus allowing a direct link to neuroimaging data, while increasing the biological realism. As a first step we use our modeling paradigm to analyze the impact of heterogeneous connectivity on the network synchronisation. For this, we reproduce earlier analysis of FitzHugh-Nagumo neurons on a torus[4], using adaptive exponential integrate and fire neurons. This is a more complex and realistic neuron model [5] and it is implemented with the Nest simulator [6] After this, we analyze the dynamics of the whole-brain model, and we compare the simulated activity with experimental results, with a focus on different metrics of functional connectivity. This allows us to link the results at the brain activity levels to the spiking neural networks, and to validate the model by using functional data. Hence, the new modelling approach allows bridging from neural mass model to spiking neural networks and using the advantages of the macro- and meso-scopic scales.
Reference:
[1]P. Sanz Leon et al., "The Virtual Brain: a simulator of primate brain network dynamics," Front. Neuroinform., vol. 7, 2013.
[2]S. W. Oh et al., "A mesoscale connectome of the mouse brain," Nature, vol. 508, no. 7495, pp. 207-214, Apr. 2014.
[3]F. Melozzi, M. M. Woodman, V. K. Jirsa, and C. Bernard, "The Virtual Mouse Brain: A Computational Neuroinformatics Platform to Study Whole Mouse Brain Dynamics," eNeuro, vol. 4, no. 3, p. ENEURO.0111-17.2017, May 2017.
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[5]J. Touboul and R. Brette, "Dynamics and bifurcations of the adaptive exponential integrate-and-fire model," Biol Cybern, vol. 99, no. 4-5, p. 319, Nov. 2008.
[6]Peyser, Alexander et al. (2017). NEST 2.14.0. Zenodo.

Disclosures: L. Kusch: None. **S. Petkoski:** None. **V.K. Jirsa:** None.

Poster

705. Virtual Brain Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 705.04/DD4

Topic: I.06. Computation/ Modeling/ and Simulation

Support: H2020 Research and Innovation Action grant 826421
H2020 Research and Innovation Action grant 650003
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ERC 683049
German Research Foundation CRC 1315
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Title: The Virtual Brain decodes molecular pathways by large-scale computational modeling in Alzheimer's disease

Authors: *L. STEFANOVSKI[1], P. TRIEBKORN[1], A. SPIEGLER[1], M.-A. DIAZ-CORTES[1,2], D. PERDIKIS[1], A. SOLODKIN[3], V. K. JIRSA[4], R. MCINTOSH[5], P. RITTER[1];
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Abstract: In this work, we demonstrate how computational multi-scale brain modeling links phenomena of different scales in Alzheimer's Disease (AD) and therefore identifies potential disease mechanisms leading the way to improved diagnostics and treatment. The Virtual Brain (TVB; thevirtualbrain.org) neuroinformatics platform allows standardized large-scale structural connectivity-based simulations of whole brain dynamics. As a novelty, we connect chemical compounds measured with positron emission tomography (PET) with neural function in TVB addressing the phenomenon of hyperexcitability in AD related to the protein amyloid beta (Abeta). We construct personalized virtual brains based on individual PET derived distributions of Abeta in patients with mild cognitive impairment and Alzheimer's Disease and in age-matched healthy controls using data from ADNI-3 data base (http://adni.lni.usc.edu). In the personalized virtual brains, individual Abeta burden modulates regional inhibition, leading to disinhibition and hyperexcitation with high Abeta loads. We analyze simulated regional neural activity, electroencephalograms (EEG) and compute functional connectivity. Known empirical alterations of EEG in patients with AD compared to HCs were reproduced by simulations. The virtual AD group showed slower frequencies in simulated local field potentials and EEG compared to MCI and HC groups. The heterogeneity of the Abeta load is crucial for the virtual EEG slowing which is absent for control models with homogeneous Abeta distributions. Slowing phenomena primarily affect the network hubs, independent of the spatial distribution of Abeta. Modeling the N-methyl-D-aspartate (NMDA) receptor antagonism of memantine in local population models, reveals potential functional reversibility of the observed large-scale alterations (reflected by EEG slowing) in virtual AD brains. Finally, we use modern machine learning techniques to demonstrates the ability of TVB to decode the empirical data and improve the diagnostic process in a clinically relevant way. When using the simulated data in addition to state-of-the art empirical multimodal datasets for machine learning classification, TVB leads to a significant improvement of accuracy. A preprint considering parts of this study can be found here: Stefanovski, L., P. Triebkorn, A. Spiegler, M.-A. Diaz-Cortes, A. Solodkin, V. Jirsa, R.

McIntosh and P. Ritter (2019). "Linking molecular pathways and large-scale computational modeling to assess candidate disease mechanisms and pharmacodynamics in Alzheimer's disease." bioRxiv: 600205.

Disclosures: **L. Stefanovski:** None. **P. Triebkorn:** None. **A. Spiegler:** None. **M. Diaz-Cortes:** None. **D. Perdikis:** None. **A. Solodkin:** None. **V.K. Jirsa:** None. **R. McIntosh:** None. **P. Ritter:** None.

Poster

705. Virtual Brain Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 705.05/DD5

Topic: I.06. Computation/ Modeling/ and Simulation

Support: Brain Network Recovery Group JSMF22002082
US-German Collaboration in Computational Neuroscience 01GQ1504A
Bernstein Focus State Dependencies of Learning 01GQ0971-5
Max-Planck Society Minerva Program
ERC Consolidator BrainModes 683049
BIH Johanna Quandt Professorship for Brain Simulation

Title: Music-induced emotions decoded by large-scale brain network modeling using the virtual brain

Authors: *J. COURTIOL[1,2], A. R. MCINTOSH[3,4], P. RITTER[1,2,5];
[1]Brain Simulation Section, Dept. of Neurol., Charité Universitätsmedizin Berlin, Berlin, Germany; [2]Bernstein Ctr. for Computat. Neurosci., Berlin, Germany; [3]Baycrest Ctr., North York, ON, Canada; [4]Dept. of Psychology, Univ. of Toronto, Toronto, ON, Canada; [5]Berlin Inst. of Hlth., Berlin, Germany

Abstract: Emotions are increasingly considered as complex nonlinear large-scale cortical-subcortical brain networks rather than one circumscribed regions. A valuable tool for the investigation of emotions and their neural correlates is through the lens of music, which has the potential to induce and convey strong emotions over time. Although recent neuroimaging studies on music-induced emotions have revealed important insights into how emotions change brain functions, the neural mechanisms underlying the emotional brain are still largely unknown. To shed light from a dynamical system's perspective, we propose a large-scale brain network model of emotions invoked by music-listening using subject-specific connectomes derived from diffusion tensor imaging (DTI), subject-specific EEG data, together with time-varying subject-specific ratings of arousal and valence over the course of music to simulate the fMRI activity. Using the neuroinformatics platform The Virtual Brain, we systematically carry out parameter

space explorations, fit and validate the brain model against the subject's empirical fMRI images.This new framework may guide future research on emotional processing and the development of music-based therapies for the treatment of neurological and psychiatric disorders, including neurodegenerative disease such as Alzheimer's disease, associated with dysfunctions in emotion brain networks.

Disclosures: J. Courtiol: None. **A.R. McIntosh:** None. **P. Ritter:** None.

Poster

705. Virtual Brain Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 705.06/DD6

Topic: I.06. Computation/ Modeling/ and Simulation

Support: BrightFocus Foundation
Human Brain Project (HBP)

Title: Mechanisms of functional disconnection in AD: Explorations with TheVirtualBrain

Authors: *A. SOLODKIN[1], C. M. ANDREYKA[2], M. MAPSTONE[3], S. CHEN[2], A. R. MCINTOSH[4], P. RITTER[5], M. J. BREAKSPEAR[6], V. K. JIRSA[7];
[1]Behavioral and Brain Sci., UT Dallas, Richardson, TX; [2]UC Irvine, Irvine, CA; [3]Neurol., Univ. of California, Irvine, Irvine, CA; [4]Baycrest Ctr., North York, ON, Canada; [5]Charite, Univ. Med. Berlin, Berlin, Germany; [6]Queensland Inst. of Med. Res., Herston, Australia; [7]Inst. De Neurosciences Des Systemes UMR1106, Marseille, France

Abstract: Objective:
TheVirtualBrain (TVB), is a multi-scale approach that uses empirical neuroimaging data to create brain's dynamic models cataloguing biophysical parameters producing empirical brain states. These biophysical parameters are invisible to brain imaging devices, thus TVB acts as a "computational microscope" that allows the inference of internal states and processes of the system. Using this unifying computational framework, this work focuses on the identification of basic mechanisms associated with changes in functional connectivity in aging and AD.
Methods:
We built dynamic network models of 77 subjects (16 AD, 35 aMCI and 16 cognitively normal (NC) and 10 cognitively supernormal (SNC)) using neuroimaging data from the Sydney Memory and Aging Study database (MAS). Each model was constrained by the individual's own large-scale 'connectome' derived from diffusion-weighted images. Models using the Stefanescu-Jirsa approach, focused on the systematic manipulation of the parameter "Global coupling (G)" to determine the value(s) associated with the simulation of regional oscillations in a 16-node limbic network. In addition, we determined the lowest value of G associated with oscillations (G

critical), the quality of oscillations and its association with the empirical rsfMRI.
Results:
Our results showed that: 1) G critical (Gc) differed among groups (from super normal to AD); 2) Compared to SNC, frequency of oscillations was higher in NC and aMCI and lower in AD; 3) brain dynamics in SNC and NC tended to operate at Gc but not in aMCI and AD; 4) G optimal (G value producing optimal simulations of rsfMRI) tended to be higher in aMCI and AD compared to healthy controls; 5) the larger G values showing oscillations correlated with stronger functional connectivity.
Interpretation:
The parameter Global coupling is a numerical correction that modifies globally, the gain of structural connections and can be thought as representing systemic effects of modulatory systems. In this context our results suggest a progressive decline on the efficiency of the system across groups (from SNC to AD) where NC and aMCI show an apparent compensatory behavior before the system shuts down in overt AD cases. These changes could be associated with deficiencies in adrenergic or cholinergic systems.
Our long-term goal with this work is by generating testable hypotheses, to develop multi-scale precision biomarkers with strong biophysical grounding that can serve as basis for personalized prognosis and/or therapeutic selection.

Disclosures: A. Solodkin: None. **C.M. Andreyka:** None. **S. Chen:** None. **A.R. McIntosh:** None. **P. Ritter:** None. **M.J. Breakspear:** None. **V.K. Jirsa:** None. **M. Mapstone:** None.

Poster

705. Virtual Brain Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 705.07/DD7

Topic: I.06. Computation/ Modeling/ and Simulation

Support: Human Brain Project No.785907

Title: Validation workflow of the region-specific models: Frequentist vs Bayesian methods

Authors: *H. E. WANG, M. HASHEMI, V. K. JIRSA;
Aix Marseille Univ, INSERM, INS, Inst. Neurosci Syst, Marseille, France

Abstract: Brain regions differ between each other with respect to cell types and distributions, receptors, neuromodulators, transcriptomes, synaptic densities, multiscale and nested connectomes as well as morphological gradients across the cortex. This variability translates into a dynamic repertoire of cell populations, microcircuits and networks, accessible via invasive and non- invasive brain imaging and physiological methods, for instance as expressed in the region-specific physiological patterns in iEEG. Now the scientists start to map the regional data features

upon the multiscale regions models to simulate the functional rhythms. In our study, we are interested in the functional validation of multiscale brain models against empirical data. We design the model validation workflow which outputs quantitatively the veracity of models (model evidence) and infer mechanisms underlying the emergence of the large repertoire of brain states (model inversion). To do so, we first design examples to benchmark the capability of two branches of parameter inference methods: frequentist and Bayesian approaches. Both frequentist and Bayesian methods are used for identification of the optimal parameters on the region-specific models. We use for frequentist approaches local search gradient-based methods (such as LBFGS algorithm) and global search gradient free (evolutionary algorithm from artificial intelligence); and for Bayesian methods, we use Markov Chain Monte Carlo both on gradient-free (such as Metropolis-Hasting algorithm) and gradient-based (such as Hamiltonian Monte-Carlo algorithm), as well as variational inference methods (such as Stein variational gradient scent and automatic variational inference). For systematic comparison of these approaches, we operationalize variation of priors in application to an instructive toy model composed of network nodes and low-dimensional dynamic systems. The priors are differently specified over the nodes based on the experimental anatomical and/or functional data. Using model evidence measured by different information criteria and the standard error metrices, we evaluate these methods on both synthetic datasets with defined ground truth and experimental datasets with their own data features. In this work, we demonstrate the trade-off between different used methods. We also show the conditions when the variational inference methods and MCMC converge to the similar results.

Disclosures: **H.E. Wang:** None. **M. Hashemi:** None. **V.K. Jirsa:** None.

Poster

705. Virtual Brain Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 705.08/DD8

Topic: I.06. Computation/ Modeling/ and Simulation

Support: NSERC Grant RGPIN-2018-04457
NIH DP2 MH119735

Title: Revealing the evolution of brain dynamics in response to emotional music using topological data analysis

Authors: M. SAGGAR[1], ***S. E. FABER**[2], S. SHAKIL[3], A. R. MCINTOSH[4];
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Abstract: Emotional responses to music are personal. Here, we estimated personal reactivity to music. Participants rated their response to music while we collected EEG. The goal was to map subjective experience with the manifolds of the EEG to uncover neurophysiological signatures of the evolving dynamics of emotional reactivity in response to music. Data were collected from 14 adults (5 males). Subjects completed a questionnaire of music listening habits and training, and the Barcelona Musical Reward Questionnaire (BMRQ). EEG data were acquired using a 76 channel BioSemi system and processed with BrainStorm. Forty excerpts (each approximately 40s) from Western art music from various eras were selected. As subjects listened to a piece, they moved a cursor across a rating map to indicate their level of arousal and valence.
To extract the shape or manifold of the evolution of neuronal dynamics in response to music, we applied the Topological Data Analysis (TDA) based Mapper algorithm (Saggar et al. 2018) on concatenated source-localized EEG data across all pieces for each individual. Each node in the Mapper-generated graph represents whole-brain cortical activity at one or more time points during the experiment. Nodes connected in the graph represent a high-degree of similarity between cortical activity at those time points. Mapper-derived shape graphs for each participant were annotated using the piece that the individual was listening to at each time point and the modularity of each graph was computed. High modularity indicates well-separated neurodynamical representation across compositions (Figure 1A-B). Graph modularity was positively related to BMRQ measures and musical habits/training. Our results suggest that participants who give higher importance to music show more segregated brain dynamics during music perception.

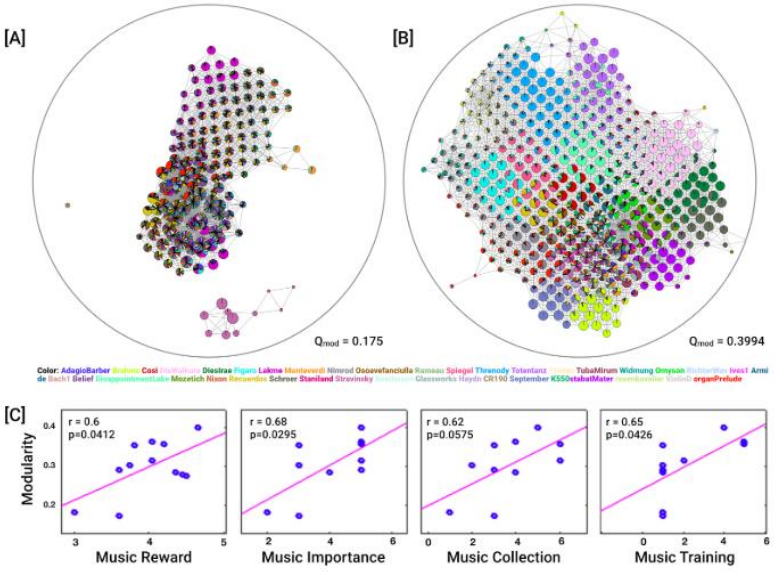

Figure 1: [A-B] Manifolds (or shape graphs) extracted from source-localized EEG data using TDA-based Mapper approach. The graphs are colored (annotated) by music-piece. Graphs from two participants are shown here - [A] participant with the lowest modularity and [B] with the highest modularity. [C]

Disclosures: **M. Saggar:** None. **S.E. Faber:** None. **S. Shakil:** None. **A.R. McIntosh:** None.

Poster

705. Virtual Brain Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 705.09/DD9

Topic: I.06. Computation/ Modeling/ and Simulation

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ERC 683049
German Research Foundation CRC 1315 & 936
RI 2073/6-1
Berlin Institute of Health & Foundation Charité
Johanna Quandt Excellence Initiative
Alzheimer's Disease Neuroimaging Initiative (ADNI)

Title: The virtual brain improves machine-learning-driven classification of Alzheimer's disease

Authors: *P. TRIEBKORN[1], L. STEFANOVSKI[1], A. SPIEGLER[1], M. DIAZ-CORTES[1], D. PERDIKIS[1], A. SOLODKIN[2], V. K. JIRSA[3], A. R. MCINTOSH[4], P. RITTER[1];
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Abstract: Central to this article is The Virtual Brain (TVB; thevirtualbrain.org) neuroinformatics platform. TVB allows standardized large-scale structural connectivity (SC)-based models for simulating whole brain dynamics. In a former study, we demonstrated how the systematic implementation of pathogenetic candidate mechanisms in TVB reveals their systems effects in human virtual brains (1). Here, we will demonstrate how individual models can explain mechanistically inter-subject variability of functional activity and cognitive performance and therefore can serve as mechanistic biomarkers. Using machine learning, we demonstrate the superiority of mechanistic model derived biomarkers compared to imaging derived markers for the classification of individual patients. For the Alzheimers Disease (AD) group simulations of brain models that were personalized using individual beta-amyloid PET data, yielded slower frequencies in neural activity and EEG, global graph theoretic disconnection and less efficient functional network structure compared to healthy controls (HC) and individuals with mild cognitive impairment (MCI). The combination of model-derived 'virtual' biomarkers with an empirical state-of-the-art multi-modal dataset (Abeta and Tau-PET, MRI volumetry) significantly outperformed the usage of empirical data alone. This effect was stable across a wide range of tested classification methods and corrections in feature space. Our results hold the potential to lead in future to clinically relevant benefits not only in the diagnosis of AD patients

but also for the identification of mechanistic targets for therapeutic interventions.
References:(1) Stefanovski, L., P. Triebkorn, A. Spiegler, M.-A. Diaz-Cortes, A. Solodkin, V. Jirsa, R. McIntosh and P. Ritter (2019). "Linking molecular pathways and large-scale computational modeling to assess candidate disease mechanisms and pharmacodynamics in Alzheimer's disease." bioRxiv: 600205.

Disclosures: P. Triebkorn: None. **L. Stefanovski:** None. **A. Spiegler:** None. **M. Diaz-Cortes:** None. **D. Perdikis:** None. **A. Solodkin:** None. **V.K. Jirsa:** None. **A.R. McIntosh:** None. **P. Ritter:** None.

Poster

705. Virtual Brain Models

Location: Hall A

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Topic: I.06. Computation/ Modeling/ and Simulation

Support: NIH/NIBIB (P41-EB018783)
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Title: Simulating large-scale cortical function and resulting behavior

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Abstract: Neuroscience is often referred to as “data-rich, but theory-poor.” While there are useful biophysical models of individual or small groups of neurons, these models cannot readily explain the large-scale function of the brain or its resultant behavior. Some functional-anatomical models (such as the thalamo-cortical system producing movements) are useful for making general predictions about specific behaviors, but do not make specific predictions about the underlying neural signal dynamics. In our ongoing work, we seek to define general principles of brain function, to implement them in a simulator, and to use simulations of brain signal dynamics to infer behavior.
Our cortical simulator is based on five principles that govern signal dynamics and their translation into behavior: they are 1) excitatory and rhythmic inhibitory input to the cortex; 2)

phase selectivity of cortical output; 3) task-relevant pre-stimulus alpha suppression; 4) event-related de-/synchronization; and 5) propagation delay between cortices. We validated our cortical simulator by comparing its output to behavioral results presented in the literature. Specifically, we implement simple auditory and visual reaction-time tasks within our cortical simulator. To do this, we modeled task-related cortical networks using a series of cortical patches, each of which implemented the same five principles described above. Using this simulation, we replicated the well-described effects of alpha power, phase, and frequency on cortical excitability and behavior; and the effects of stimulus intensity, duration, contrast, modality and congruency on behavior. We varied these parameters and used the cortical simulator to infer the neural signal dynamics at each cortical node as well as the resultant behavioral output.
The results show that, despite its current simplicity, the output of our cortical simulator is in substantial congruence to physiological and behavioral results of studies that investigated similar stimulus-response tasks. Specifically, alpha power and phase reduced cortical excitability and behavioral response rate, whereas higher intensity/contrast, congruent and multi-modal stimuli decreased reaction time and increased response rate. In summary, the results of our ongoing study show that five simple and general principles of cortical function can accurately model a variety of brain signal dynamics and different behaviors.

Disclosures: H. Cho: None. **G. Schalk:** None.

Poster

705. Virtual Brain Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 705.11/DD11

Topic: I.08. Methods to Modulate Neural Activity

Support: Canadian Institutes of Health Research (CIHR) Foundation Grant FDN-143209
Brain Canada Neurophotonics Platform
Canadian Partnership for Stroke Recovery

Title: Short latency (~100 ms) markerless video tracking of body parts in mice using deep neural networks

Authors: *B. J. FORYS, D. XIAO, P. GUPTA, J. D. BOYD, T. H. MURPHY;
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Abstract: Real-time, markerless tracking of animal movement would open up the possibility of manipulating motor feedback, allowing detailed explorations of the neural basis for behavioral control. However, there is currently no robust real-time tracking system that allows for tracking of specific body part movement (as opposed to whole-body movement) based on one's own datasets. To address this need, we present a method that leverages DeepLabCut (Mathis et al.,

2018) - a robust yet flexible movement-tracking framework - for real-time tracking of body part movements in mice. To demonstrate our method's real-world efficacy, we present DeepCutRealTime. We stream footage of a head-fixed mouse to a computer running DeepLabCut, which estimates the pose and location of the mouse's paws in each frame. To test the response latency of the system, we then use GPIO to trigger an LED when the mouse's running movements exceed a pre-defined threshold. Across all of our trials (n = 37) with n = 3 male mice (who were between 2-4 months of age), we found that our system can track movement at a frame rate of M = 30.30 Hz, SD = 0.53 Hz, with a mean time delay between movement initiation and the LED flash of M = 93.44 ms, SD = 8.79 ms. These results represent critical progress towards building a real-time tracking framework for individual body parts that can provide feedback to the subject based on analysis of this movement. Our exploratory study suggests a robust yet easy-to-implement method for real-time movement tracking that can be easily integrated with other methods such as optogenetic stimulation and wide-field brain imaging, allowing us to better understand the links between cognition and action at a more granular level than before. This real-time movement tracking framework could also be used to provide closed-loop feedback directly to the brain based on specific behaviours.

Disclosures: B.J. Forys: None. **D. Xiao:** None. **P. Gupta:** None. **J.D. Boyd:** None. **T.H. Murphy:** None.

Poster

706. Analytical Computational Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 706.01/DD12

Topic: I.06. Computation/ Modeling/ and Simulation

Title: Why does ICA-decomposed EEG sometimes show deep dipoles?

Authors: *M. M. MIYAKOSHI[1], S. MAKEIG[2];
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Abstract: Independent component (IC) analysis (ICA) has been used for scalp-recorded EEG preprocessings. For IC source localization, a common practice is to fit a single equivalent current dipole to IC scalp maps. A problem of deep dipoles has been known; dipoles are localized deeper than cortices, which is physiologically implausible. Interestingly, the deep dipoles usually show well-defined event-related potential (ERP). We hypothesized that these deep dipoles have a systematic cause that has not been investigated yet. The alternative hypothesis is that the deep dipoles are noise due to localization errors. To investigate this issue, we performed a study. The 32-ch EEG data recorded from 24 healthy young adults during visual discrimination task (faces and objects) with 600-700 trials were used (all conditions merged). Offline, the EEG data were

preprocessed using EEGLAB to filter the data, artifact rejection using artifact subspace reconstruction, ICA, and dipole fitting using Fieldtrip functions. In doing so, 1) the default EEGLAB's unit system was changed from A to nA (x10^9) and from mm to m (x10^-3) to calculate dipole moment, for which peak amplitudes of the absolute ERP (0 to 1 sec window) of each IC was calculated to be multiplied with the IC scalp maps, then 2) EEGLAB plugin ICLabel was used to identify brain components (criterion > 0.70); 3) probabilistic anatomical labels were assigned using Talailach daemon (confusion sphere 20 mm) to classify ICs into three classes; basal/limbic, cortical, and outside the brain (criterion > 0.50). The outside-the-brain ICs were excluded; 4) The brain ICs were compared between cortical vs. basal/limbic groups for dipole moments and equivalent patch size that was computed by using estimate of 100 nAm per 4 cm^2. The results showed that 249 ICs were identified to be cortical and 21 ICs basal/limbic, the latter were contributed by 17/24 participants. The mean dipole moments were 196 (312) vs. 26 (31) nAm, and the mean equivalent patch sizes 7.8 (12.5) vs. 1.1 (1.3) cm^2 for basal/limbic and cortical ICs, respectively. As typical dipole moment for averaged sensory evoked response being about 100 nAm, and the estimated minimum active patch size to produce scalp-measureable single-trial EEG being 6.5 cm^2, the obtained values are confirmed to be in a valid range. We concluded that there is clear tendency of the deep dipoles toward larger dipole moment/patch size, indicating systematic influence rather than random process. Moreover, this tendency was also found in the cortical ICs. We speculate that ICA may identify a temporally independent synchronous patches that are much larger than we have conventionally thought.

Disclosures: M.M. Miyakoshi: None. **S. Makeig:** None.

Poster

706. Analytical Computational Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 706.02/DD13

Topic: I.06. Computation/ Modeling/ and Simulation

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NSF Graduate Fellowship Research Program

Title: State space oscillator models with priors on frequency

Authors: *A. M. BECK[1], H. SOULAT[2], E. P. STEPHEN[2], P. L. PURDON[3];
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Abstract: Oscillatory neuronal activity reflects the functional coupling of brain networks and can be measured with local field potentials, or in the aggregate at the scalp with electroencephalogram (EEG). Many well-established oscillatory patterns have been characterized in response to tasks or states of arousal. These patterns are often composed of multiple oscillations, such as slow waves and spindles during sleep, slow oscillations and alpha waves during anesthesia, or harmonic series representing nonlinear oscillations such as mu-rhythms. In some scenarios, the data analysis problem focuses on determining whether or not an oscillation is present; in others, the problem focuses on separating component oscillations so that their distinct features or interactions may be studied, revealing new information (Cole & Voytek Cell 2017).

State space models have been developed to identify oscillations with varying frequencies and estimate their instantaneous phase (Matsuda & Komaki Neural Comp. Feb 2017). These models significantly improve the estimation of the oscillatory signals, and may provide a means to distinguish oscillations from broadband "1/f" noise (Beck et al. IEEE EMBC 2018). A major advantage of this approach is that inferences about underlying oscillations or waveforms can be made based on model parameters estimated from the data with the expectation maximization algorithm. However, this parameter estimation is also one of the most challenging aspects of this approach. Models with multiple oscillations may not always converge, particularly in low signal-to-noise scenarios, and are highly dependent upon parameter initialization. We will describe novel methods for parameter estimation in state space oscillatory models and apply model selection procedures to help identify the presence or absence of oscillations, including the contribution of nonlinear terms. We follow an empirical Bayes approach and define prior probability distributions on the state space model parameters, and evaluate methods of model selection to account for the large number of estimated states. These improvements increase the accuracy of the model and signal estimates, while maintaining a simple initialization procedure to enable practical application in neuroscience data analysis.

Disclosures: A.M. Beck: None. **H. Soulat:** None. **E.P. Stephen:** None. **P.L. Purdon:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inventor on patents pending on brain monitoring technologies assigned to Massachusetts General Hospital, Inventor on a patent assigned to Massachusetts General Hospital and licensed non-exclusively to Masimo Corporation, Co-Founder of PASCALL Systems, Inc., a start-up company developing closed-loop physiological control systems.

Poster

706. Analytical Computational Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 706.03/DD14

Topic: I.06. Computation/ Modeling/ and Simulation

Support: IITP grant funded by the Korea government (No. 2017-0-00451)
NRF of Korea (2018R1A2B2005687)

Title: Feasibility study on super resolution using deep convolutional neural networks; auditory ERP data

Authors: *M. KWON, S. C. JUN;
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Abstract: Super-resolution (SR) is a technique that enhances data quality from low-resolution (LR) to high-resolution (HR) with data-driven approach in image processing, which requires to solve underdetermined inverse problems. Recently, deep convolutional neural network (CNN) has been applied to develop SR-techniques. Also, audio processing has applied SR-techniques to increase sampling rate of audio signals. In a conceptual manner, we may adopt them to improve EEG spatial resolution. EEG has relatively high temporal resolutions that is easy to do real-time monitoring, however, it has poor spatial resolution of a few fractions of centimeter. Poor spatial resolution may yield incorrect source localization, thus high-density EEG system is required at a quite tremendous expense. For comfortability and efficiency of EEG system, it is necessary to measure brain activity with as small number of sensors, keeping high quality signals. Therefore, we proposed CNN model to enhance the spatial resolutions from LR to HR using auditory evoked potential (AEP) EEG data.
EEG data was collected from 64 channels for brain activity. Beep sound was given to subject for each trial. A total of 1,000 trials were done and inter-stimulus-interval was randomly between 1,000 and 1,500 ms. The data was band-pass filtered with 1 - 50 Hz; noise components and bad trials were rejected. After preprocessing, we generated low resolution data as choosing 32 (2x), 16 (4x), 8 (8x), 4 (16x) channels. Remaining channels were interpolated with neighboring sensors. Our proposed CNN model are similar to autoencoder; He initializer, Adam optimizer and linear activation function was used. We used 80 % of trials for training and 20 % of trials for testing.
SR data estimated by CNN showed the clear ERP patterns for all kinds of up-sampling rates (2x, 4x, 8x, 16x) and almost channels; N1, P2 amplitudes resembled HR patterns more than LR patterns on cento-parietal channels, which are representative channels of ERP signal. However, latencies of N1, P2 were not that significantly different for SR, HR, and LR. Frontal lobe with

many noisy components and temporal lobe containing high frequency signal yielded higher errors in SR than those in LR. In source imaging, even original data (HR) showed two sources on right/left temporal regions, LR data yielded the incorrectly located source on left hemisphere, while SR data likely yielded sources correctly located.
Our proposed deep neural networks come up with a possibility for improving EEG spatial resolutions from even far small number of sensors.
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Disclosures: M. Kwon: None. **S.C. Jun:** None.

Poster

706. Analytical Computational Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 706.04/DD15

Topic: I.06. Computation/ Modeling/ and Simulation

Title: Forward and inverse modeling between local field potential and intracranial macroelectrodes for neuroprosthetic applications

Authors: *Y.-J. CHANG[1], J. M. CARMENA[3,4], S. R. SANTACRUZ[1,2];
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Abstract: Local field potential (LFP) is pre-synaptic activity of hundreds of neurons typically recorded using microelectrodes, and is a signal type commonly used for both neuroscientific studies and therapeutic applications. Although this signal is rich and has high signal-to-noise ratio (SNR), it requires the most invasive method of acquiring neural activity. In this work, we consider how LFP data can be estimated using signals recorded from intracranial macroelectrodes (ICME). Both LFP and ICME signals are recorded simultaneously in awake behaving rhesus macaques. LFP data is recorded from one hemisphere, whereas ICME signals are acquired across both hemispheres. We develop an ICME / LFP inverse model to investigate the signal translation between these two measurements. NonLinear Principal Component Analysis (NLPCA) is employed to reduce the complexity of computation. The forward model is then derived from an electro-physiological perspective to capture the dynamics of the neural signals. To represent nonlinear approximations, a NeuroBondGraph (NBG) approach is introduced to model both the system dynamics and nonlinearities in a more efficient way. The inverse solution is then established by integrating with the de-mapping part of NLPCA. Here we demonstrate the applicability of this technique to the experimental data, and address both accuracy and stability of the inverse models used to estimate LFP from ICME recorded data. The

inverse solution produced with this methodology could significantly improve the performance of LFP-based closed-loop neuroprosthetic applications without increasing the LFP channel count.

Disclosures: **Y. Chang:** None. **J.M. Carmena:** None. **S.R. Santacruz:** None.

Poster

706. Analytical Computational Models

Location: Hall A

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Program #/Poster #: 706.05/DD16

Topic: I.06. Computation/ Modeling/ and Simulation

Support: 1R24MH116922-01

Title: Extending the NWB:N neurophysiology data standard: Methods and applications

Authors: ***O. RUEBEL**[1], A. TRITT[1], B. DICHTER[2], R. LY[2], M. DOUGHERTY[2], V. BARATHAM[3], T. J. DAVIDSON[4], L. NG[5], L. M. FRANK[6], K. BOUCHARD[7];
[1]Computat. Res. Div., [2]Lawrence Berkeley Natl. Lab., Berkeley, CA; [3]UC Berkeley, Berkeley, CA; [4]HHMI/UCSF, San Francisco, CA; [5]Allen Inst. for Brain Sci., Seattle, CA; [6]Dept. of Physiol., UC San Francisco, San Francisco, CA; [7]Biol. Systems and Engin., LBNL/UCB, Berkeley, CA

Abstract: The Neurodata Without Borders: Neurophysiology (NWB:N) data standard provides neuroscientists with a common standard to share, archive, use, and analyze neurophysiology data. NWB:N supports a large range of neurophysiology data, including from intracellular and extracellular electrophysiology and optical physiology experiments, as well as tracking and stimulus data. The NWB:N data standard is defined via a formal specification language and organizes data in a modular collection of neurodata types that can be reused via inheritance and composition. This approach allows users to create extensions to NWB:N in a formal and backward compatible way. Extension are central to enabling the neurophysiology community to adopt and curate NWB:N, support the integration of new data types and use cases, and definition of canonical data organizations for data analysis and management.
We present the Neuro Data Extensions Catalog (NDXC), a novel online resource for sharing, deploying, and validating NWB:N extensions. NDXC provides a web-archive and associated tools to enable users to easily create, search, review, access, and install extensions. NDXC enables the neurophysiology community to share and maintain extensions, curate NWB:N, and collaborate to create new standards for emerging use cases. As part of the NDXC, we are also developing a formal review process for inclusion of extensions into the core NWB:N format so that NWB:N can adapt to the evolving neuroscience needs.
We demonstrate the application of extensions in practice for integrating new data types and interfacing with data analysis and management tools. We present the simulation output extension

to support storage of continuous data from compartments of simulated cells and compartment metadata. Another key application of extensions is to define a rigid organization of neurodata types and refinement of required fields for standardized experiments, analysis pipelines, and tools. We demonstrate the application of extensions to standardize the organization of experiments and for integration of NWB:N with analysis tools (e.g, Brainstorm).

Disclosures: O. Ruebel: None. **A. Tritt:** None. **B. Dichter:** None. **R. Ly:** None. **M. Dougherty:** None. **V. Baratham:** None. **T.J. Davidson:** None. **L. Ng:** None. **L.M. Frank:** None. **K. Bouchard:** None.

Poster

706. Analytical Computational Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 706.06/DD17

Topic: I.06. Computation/ Modeling/ and Simulation

Support: NIH DP2 MH119735
NIH R00 MH104605

Title: Implementing evolutionary optimization to model resting state functional connectivity

Authors: K. MAILE[1], R. MIIKKULAINEN[1], ***M. SAGGAR**[2];
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Abstract: Computational models are crucial in understanding brain function. One particularly interested class of models is designed to replicate known brain structures using structural connectivity (SC) measured with diffusion spectrum imaging, and the behavior that emerges is then compared to empirical functional connectivity (FC), measured using functional magnetic resonance imaging. As the models become more accurate and more complex with more parameters, they can explain more of the observed phenomena, and may eventually be used for diagnosis and design of treatments of brain disorders. However, those parameters need to be carefully optimized for the models to work best, which becomes intractable to do manually or with traditional computational techniques like gradient descent as the models grow. Evolutionary computation techniques use adaptation over generations in nature as inspiration to optimize functions that are otherwise difficult and have succeeded in solving optimizations in similarly difficult search spaces (Miikkulainen, 2019). In this work, the Covariance Matrix Adaptation Evolutionary Strategy (CMA-ES) was configured to optimize continuous parameters of a large-scale biophysical network model that stimulates neural activity from structural connectivity of 66 cortical parcellations and computes FC (Deco et al., 2013). Empirical SC and FC data were collected and aggregated from 24 right-handed healthy young volunteers (Deco et al., 2013). The

application of CMA-ES on this data resulted in a significantly better fit to empirical FC data than manually selected parameters in all four trials run of the CMA-ES algorithm so far. The best parameter set from the best trial run generates a functional connectivity matrix with a correlation of 0.5205 +- 0.0102 with empirical FC, compared to the previous best set of manually selected parameters that yield a correlation of 0.4647 +- 0.0114. This work provides a basis for utilizing evolutionary computation to optimize neural activity models. Statistically significant improvement has already been achieved with a relatively simple approach. To further increase the optimization potential, this approach will be combined with other evolutionary computation techniques to optimize other parameters, and these techniques will be scaled up to more detailed and patient-specific SC and FC data and more complex computational models. Optimizing neural activity models will further our understanding of the human brain and bring the field of neurology closer to personalized medicine.

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Poster

706. Analytical Computational Models

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Topic: I.06. Computation/ Modeling/ and Simulation

Support: NSF #1458840
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NSF #1730655

Title: The neuroscience gateway: Enabling large scale modeling and data processing in neuroscience on supercomputers

Authors: *A. M. MAJUMDAR[1], S. SIVAGNANAM[2], K. YOSHIMOTO[1], N. T. CARNEVALE[3];
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Abstract: We review the origin and evolution of the Neuroscience Gateway (NSG; http://www.nsgportal.org) providing access to high performance computing (HPC) resources for neuroscientists. When it first becameavailable to users in 2013, NSG's design goal was to provide neuroscientists free and easy access to simulation software installed on HPC hardware for their increasingly complex models of biological neurons, neural circuits, and systems. More recently we have expanded it to also serve cognitive and experimental neuroscientists facing

large scale data analysis problems (e.g. fMRI processing, connectome pipelines). It is also being used for educational purposes in neuroscience courses and workshops. The diverse and growing set of modeling and data analysis tools currently available via NSG includes BluePyOpt (from the European Human Brain Project), Brian,CARLsim, DynaSim, EEGLAB, Freesurfer, Human Neocortical Neurosolver (HNN), Large Scale Neural Modeling Simulator, MATLAB, MOOSE, NEST, NetPyNE, NEURON, Octave, PGENESIS, PyNN, Python, R, TensorFlow, and The Virtual Brain Personalized Multimodal Connectome Pipeline.These can be accessed either through a web portal or programmatically through a RESTful API. NSG allows a wide range of use cases: individual users with NSG accounts can work directly with individual tools, or with packaged pipelines, or configure their own pipelines; users of communityprojects that take advantage of NSG's RESTful API (e.g. OpenSourceBrain) can employ HPC resources via NSG without having to leave their familiar working environment or even obtain their own NSG accounts; software developers can use NSG for dissemination of their projects, e.g. BluePyOpt, CARLSim, DynaSim, EEGLAB, HNN. NSG is being used by neuroscienceresearchers, educators, and students at institutions and laboratories around the world, and its user base is currently is about 900 and still growing. Based on increasing demand and usage, we have successfully obtained progressively larger allocations of HPC resources through the competitivepeer review process of the Extreme Science and Engineering Discovery Environment (XSEDE) program. Developing and operating the NSG has given us a unique opportunity to understand the diverse HPC needs of neuroscientists and explore associated issues and needs forcollaboration, data sharing/management and various forms of computing. Supported by NSF 1458840 (SS, KY, AM), NIH #1R01EB023297-01A1 (SS, KY, AM) and NSF 1458495 (NTC).

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Poster

706. Analytical Computational Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 706.08/DD19

Topic: I.06. Computation/ Modeling/ and Simulation

Support: Helmholtz Portfolio Theme “Supercomputing and Modeling for the Human Brain”
European Union's Horizon 2020 research and innovation programme under grant agreement No 720270 (HBP SGA1) and No 785907 (HBP SGA2)
Juelich-Aachen Research Alliance (JARA-CSD) Graduate Student Support

Title: Learning-to-learn and learning-to-optimize for spiking neuronal networks and high-throughput hyperparameter search on hpc

Authors: A. YEGENOGLU[1], S. DIAZ-PIER[1], A. SUBRAMONEY[2], W. KLIJN[1], W. MAASS[2], G. VISCONTI[3], M. HERTY[3], ***A. PEYSER**[1];
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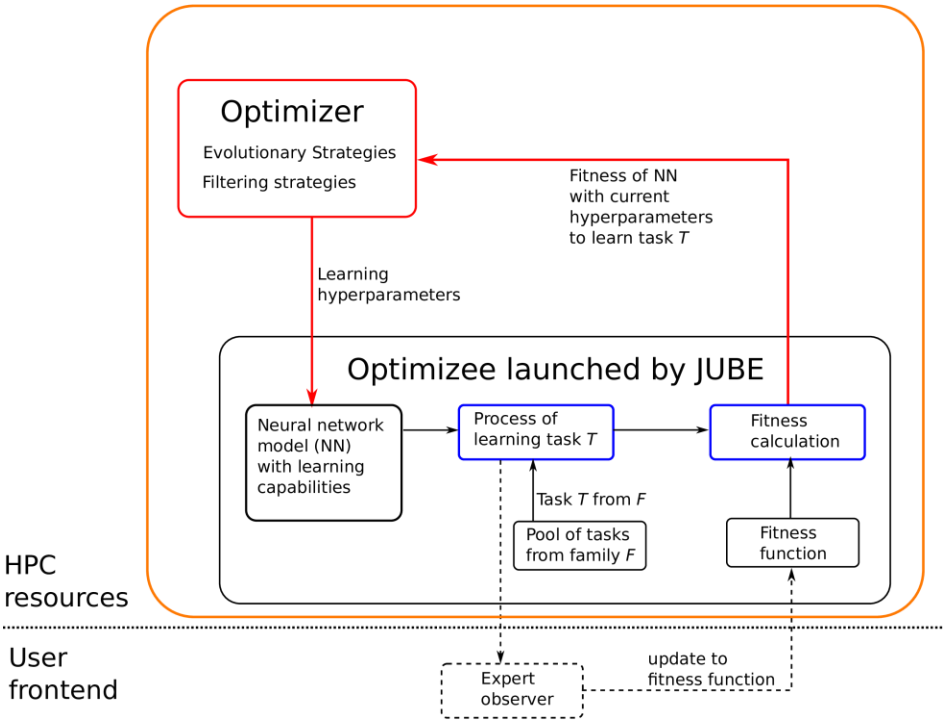
Abstract: The simulation of biological neural networks (BNN) is essential to neuroscience. The complexity of the brain's structure and activity combined with the practical limits of in-vivo measurements have led to the development of computational models which allow us to decompose, analyze and understand its elements and their interactions.
Impressive progress has recently been made in non-spiking but brain-like learning capabilities in ANNs [1, 3]. A substantial part of this progress arises from computing-intense learning-to-learn (L2L) [2, 4, 5] or meta-learning methods. L2L is a specific algorithm for acquiring constraints to improve learning performance. L2L can be decomposed into an optimizee program (such as a Kalman filter) which learns specific tasks and an optimizer algorithm which searches for generalized hyperparameters for the optimizee. The optimizer learns to improve the optimizee's performance over distinct tasks as measured by a fitness function (Fig 1).
We have developed an implementation of L2L on High Performance Computing (HPC) [6] for hyperparameter optimization of spiking BNNs as well as hyperparameter search for general neuroscientific analytics. This tool takes advantage of large-scale parallelization by deploying an ensemble of optimizees to understand and analyze mathematical models of BNNs. Improved performance for structural plasticity has been found in NEST simulations comparing several techniques including gradient descent, cross entropy, and evolutionary strategies.



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Poster

706. Analytical Computational Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 706.09/DD20

Topic: I.06. Computation/ Modeling/ and Simulation

Support: NIH Grant 1OT3OD025348-01

Title: o^2S^2Parc - the simulation platform for all computational modeling in the NIH SPARC initiative (PNS neuromodulation & impact on organ physiology)

Authors: *E. NEUFELD[1], N. CHAVANNES[1], A. M. CASSARA[1], B. LLOYD[1], P. CRESPO-VALERO[1], M. GUIDON[1], O. MAIZ[1], I. PASCUAL[1], S. ANDEREGG[1], N. KUSTER[2], W. KAINZ[3];
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Abstract: Advances in neuro-engineering have opened up new avenues for ‘electroceuticals’ devices that affect organ function through neuromodulation. The NIH SPARC initiative was established to “transform the understanding of nerve-organ interactions” and “advance the neuromodulation field towards precise disease treatment”. A key component of SPARC is a freely accessible online platform (o^2S^2PARC) to support modeling-related activities. o^2S^2PARC is designed to allow studying the interaction of physical stimuli with the human body and its physiology via multi-physics/-scale simulations. It is an open-source framework to create, host, connect, and execute computational models, as well as solvers for anatomical model-centred multi-physics simulations. At the core of o^2S^2PARC are detailed, human and animal models, which are functionalized with dynamic nerve models and serve as integration centres for

computational (tissue/organs/⋯) models and measurement data and as context for physical modeling. Multiple o^2S^2PARC prototypes (front/back-end, communication, and compute services) were realized to compare technologies and identify pitfalls. A full-stack system production-version of the platform has been implemented and deployed in the cloud. It involves a (i) front-end built on the qooxdoo framework, (ii) Python-based web-server, (iii) scalable network of computational services deployed inside Dockers, (iv) director to orchestrate the services/interact with the web server. Critical solvers (e.g., for coupled electromagnetic-neuronal dynamics modeling) were developed, validated, and successfully applied to study a range of therapeutic applications. Anatomical phantoms were extensively functionalized with peripheral nerves based on high-resolution cryosection images these nerve trajectories are associated with dynamic electrophysiology models (sensory/motor MRG models). Selected models from SPARC teams (cardiac physiology & regulation, compound action potential prediction, enteric nervous system) can now be executed within containerized services. The evaluated technologies demonstrate that the ambitious vision of o^2S^2PARC is feasible. It is an important contribution towards open and extendable simulation platforms for electroceuticals/ neuroprosthetics research.

Disclosures: **E. Neufeld:** None. **N. Chavannes:** None. **A.M. Cassara:** None. **B. Lloyd:** None. **P. Crespo-Valero:** None. **M. Guidon:** None. **O. Maiz:** None. **I. Pascual:** None. **S. Anderegg:** None. **N. Kuster:** None. **W. Kainz:** None.

Poster

706. Analytical Computational Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 706.10/DD21

Topic: I.06. Computation/ Modeling/ and Simulation

Support: European Union Horizon 2020 Framework Programme for Research and Innovation Grant Agreement No. 720270 (Human Brain Project SGA1)
European Union Horizon 2020 Framework Programme for Research and Innovation Grant Agreement No. 785907 (Human Brain Project SGA2)

Title: Scientific validation of data-driven neuroscience models despite complexity and sparse data

Authors: P. E. GARCIA-RODRIGUEZ, L. SHARMA, S. APPUKUTTAN, *A. P. DAVISON;
ICN, Paris-Saclay Inst. of Neurosci., Ctr. Nationale De La Recherche Scientifique (CNRS), Gif sur Yvette, France

Abstract: Computational simulations are a valuable tool to gain insight into brain function, from the sub-cellular to the network scale. However, before a model can be used in research or medical applications, an assessment of its performance is required, including a validation with respect to experimental data. Validating a model concerns its generalization/predictive power, i.e. its ability to replicate observations obtained in experimental scenarios other than those used in constructing the model. To that end, a prediction error can be calculated to quantify the model's performance by the match between model prediction and experimental observation. Model validation implies scientific challenges such as intensive data searching or meta-analysis, reconciling conflicting findings, and deciding the weighting of different validations. The application of traditional statistical hypothesis testing, to judge the relevance of the discrepancy between experiment and model, requires the specification of a probability distribution for the reference data. However, many studies report too few observations to accurately determine the statistical description needed. Such sparse experimental data also presents a serious handicap to accurately estimate prediction errors using bootstrap or cross-validation methods.
An alternative to hypothesis testing in model assessment is model selection, where different alternatives are compared to choose the most appropriate model. Models often differ in terms of complexity, and prediction errors are known to follow a non-monotonic curve, showing a minimum at intermediate complexity (Hastie et al. 2001). This behavior is related to the bias-variance trade off and the well known under- and over-fitting compromise. It is caused by the opposite trends of these two quantities that determine the prediction error. Finally, each model can be assigned a score defined as the relative prediction error with respect to the uncertainty level present in the data and in the model.
We are attempting to address the above challenges by developing test suites that automate comparison between different models, and allow tracking the performance of a model over time as it is refined. In these test suites, model and test definitions use the SciUnit interface (Gerkin & Omar, 2014), which supports model-agnostic validation suites by decoupling test and models. MorphoUnit is for validating morphologically-detailed cell models according to neurite features. eFELUnit is designed to validate the biophysical behavior of single cell models. BasalUnit and CerebUnit provide validation tests specific to the basal ganglia and cerebellum respectively.

Disclosures: P.E. Garcia-Rodriguez: None. **L. Sharma:** None. **S. Appukuttan:** None. **A.P. Davison:** None.

Poster

706. Analytical Computational Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 706.11/DD22

Topic: I.06. Computation/ Modeling/ and Simulation

Support: NRF-2017M3C7A1049051

Title: Dynamic causal modeling toolbox for multimodal electrophysiological data

Authors: *J. KANG[1,4], J. EO[2], H.-J. PARK[2,4,3];
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Abstract: In general, since both mechanisms of the generating observation signals and neural activities are complex, and computational modeling is essential to understand brain activities. To overcome these difficulties, recently, we developed an analytical scheme of electrophysiology data of the voltage sensitive dye imaging (VSDI) and calcium imaging (CaI) adopting the dynamic causal modeling (DCM) method. In the present study, we present a novel analytical scheme for the multimodal electrorheology data analysis, named multimodal electrophysiology data. We connected VSDI-DCM and CaI-DCM scheme by sharing the neural activity, and named it multimodal electrophysiological data-DCM (med-DCM). Since the CaI signals are usually recorded with high-spatial and low-temporal resolutions, and the VSDI with shows low-spatial and high-temporal resolutions, in the med-DCM modeling, we utilized these signals to extract neural state parameters properly.
To describe both of CaI and VSDI signals, we construct a hierarchical neural state model. Specifically, in the CaI data analysis, neural state model directly converted to the CaI signals. However, the VSDI signals from one region were estimated from multiple neural populations. Thus, spatially a region of the VSDI model can contain multiple regions of the CaI model. We optimized the DCM parameters in three steps. Firstly, DCM parameters were estimated for the CaI signals which give us high spatial information. Secondly, the parameters were fitted for the VSDI signals which contain better temporal information. Then, finally, we optimized all DCM parameters simultaneously for both signals.
In the present study, to validate the novel system, we simulated multimodal data of the CaI and VSDI based on the DCM results of the hippocampus VSDI signals. Our results suggested that the multimodal data can increase the accuracy of the model inference, and provide an entire analytic scheme for the multimodal mesoscale electrophysiological data with DCM. The present multimodal data analytic scheme could be extended and applied to the various mesoscale electrophysiological data. We also developed graphic user interfaces for these simulations and model inference calculations.

Disclosures: **J. Kang:** None. **J. Eo:** None. **H. Park:** None.

Poster

706. Analytical Computational Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 706.12/DD23

Topic: I.06. Computation/ Modeling/ and Simulation

Support: Samsung Scholarship

Title: Efficient robust spectral analysis of spike data

Authors: *A. H. SONG[1], P. L. PURDON[5], E. N. BROWN[2,6,3,7,4], D. BA[8];
[1]Electrical Engin. and Computer Sci., [2]Brain and Cognitive Sci., [3]Picower Inst. for Learning and Memory, [4]Inst. for Med. Engin. and Sci., MIT, Cambridge, MA; [5]Anesthesia, Critical Care, and Pain Mgmt., Massachusetts Gen. Hosp., Charlestown, MA; [6]Anesthesia, Critical Care, and Pain Mgmt., [7]Neurol., Massachusetts Gen. Hosp., Boston, MA; [8]Sch. of Engin. and Applied Sci., Harvard Univ., Cambridge, MA

Abstract: The current practice of spectral analysis of spike data involves direct application of the Fourier transform to the data, which is problematic for two reasons: 1) The binary nature of the data makes the spectral content diffuse across all frequencies, and 2) the spectral estimates overfit the data and often are not interpretable. We introduce a model-based framework for spectral analysis of binary data, where a latent harmonic process is assumed to be driving the spikes. We cast the latent process estimation problem within an Empirical Bayes framework, in which the posterior distribution of the states given the spikes is maximized. Specifically, we use a group sparsity prior which emphasizes the dominant oscillatory components and simultaneously tracks the temporal dynamics within these components. To this end, we develop a statistical and computational approach rooted in Minorization-Maximization (MM) algorithm and Kalman filter/smoother, that is more efficient than existing model-based approaches [1]. We apply the framework to data collected from electrocorticography (ECoG) of human patients under propofol general anesthesia, and for which the slow oscillation (0.1~0.5Hz) is believed to strongly modulate the ensemble of spikes [2]. The algorithm successfully identifies the slow frequency bands as the dominant process modulating the spikes when the patient is unconscious. Furthermore, it is able to detect the change point of the underlying brain states when the patient loses consciousness, in an unsupervised manner. Overall, this framework offers a principled approach for analyzing the dominant oscillatory content of the binary data, capable of tracking the dynamics over the duration of the entire recording.
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[2] Laura Lewis et al., Rapid fragmentation of neuronal networks at the onset of propofol-induced unconsciousness. \textit{PNAS}, 2012

Disclosures: A.H. Song: None. **P.L. Purdon:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); PASACALL. **E.N. Brown:** A. Employment/Salary (full or part-time):; MGH/MIT. 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.; R01 GM104948, P01GM118269. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); PASACALL. **D. Ba:** None.

Poster

706. Analytical Computational Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 706.13/DD24

Topic: I.06. Computation/ Modeling/ and Simulation

Support: Whitehall Foundation (2017-12-73)
NSF Grant 1736028

Title: Evaluating spectral estimation methods for time-resolved measurement of aperiodic activity

Authors: *T. FARNAN, T. DONOGHUE, B. VOYTEK;
Cognitive Sci., UC San Diego, La Jolla, CA

Abstract: Electrophysiological neural time series, when considered as frequency representations, exhibit both periodic (oscillatory) components, as well as an aperiodic, 1/f-like, component wherein power exponentially decreases as frequency increases. This aperiodic component can be measured as $1/f^{\chi}$, whereby the χ value is equivalent to the slope of the power spectrum in log-log space.Prior work measuring aperiodic activity in neural time series has shown that it is a dynamic property. Aperiodic activity “flattens” with age, is a robust marker of sleep-wake or anesthetization status, and can vary in a trial-by-trial manner with cognitive and perceptual demands. Past measurements of aperiodic activity have relied on relatively long time windows, with coarse temporal resolution. However, short-time, sliding-window Fourier analyses—and other similar approaches—should permit a time-resolved aperiodic analysis. In this project, we extend a previously described method for parameterizing neural power spectra, which estimates both periodic and aperiodic components from frequency representations of neural data (Haller et al, 2018). Using this method, we examine short-time, sliding window analyses and develop a procedure for accurate, time-resolved aperiodic estimates. Our experiments use simulated neural time series that are either statistically representative or real electrophysiology. This allows us to simulate a range of dynamic variations in both aperiodic and periodic components. Given these ground truth neural time series, we implement existing spectral estimation methods to generate a suite of power spectra that represent frequency content across time. Specifically, we explore short-time Fourier transforms, wavelet transforms, and multi-taper approaches and assess their performance across a range of settings. We then evaluate the accuracy of our method’s aperiodic property reconstruction by stepping across the suite of generated spectra, internal method settings, and additional processing steps such as spectral smoothing. We report a comprehensive analysis on these time-resolved power spectra estimation procedures and provide benchmarks for ideal approaches given different constraints of the data, such as sampling rate, recording modality, and fitting range. Finally, we demonstrate these

approaches on a series of real datasets of local field potential (LFP) and electrocorticography (ECoG) data, and show how aperiodic properties change over time in real data.

Disclosures: **T. Farnan:** None. **T. Donoghue:** None. **B. Voytek:** None.

Poster

706. Analytical Computational Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 706.14/DD25

Topic: I.06. Computation/ Modeling/ and Simulation

Title: Statistical accuracy of fMRI retinotopic mapping in patients with altered neurovascular function: Sequential vs random stimulus presentation

Authors: *G. PATIL[1], C. L. SCHNEIDER[2,4,5], B. SAHIN[6], B. Z. MAHON[4,6,3,7];
[2]Brain and Cognitive Sci., [3]Ctr. for Visual Sci., [1]Univ. of Rochester, Rochester, NY;
[4]Psychology, Carnegie Mellon Univ., Pittsburgh, PA; [5]Univ. of Rochester Sch. of Med. and Dent., Rochester, NY; [6]Neurol., [7]Neurosurg., Univ. of Rochester Med. Ctr., Rochester, NY

Abstract: Functional Magnetic Resonance Imaging (fMRI) measures neural activity indirectly by monitoring local changes in blood oxygenation and blood flow. Researchers have used fMRI to understand the role of neuroplasticity in functional recovery after brain injury; however, the altered patterns of cerebral blood flow that occur, for instance, in stroke patients, may affect the analysis and interpretation of fMRI data. We hypothesized that a random presentation sequence will lead to less systematic bias in the fMRI analysis than a sequential (or stereotyped) presentation sequence when the hemodynamic response is delayed. We used computational modeling to determine how the accuracy and precision of retinotopic mapping is affected by altered hemodynamic responses for both general linear modeling (GLM) and population receptive field mapping (pRF). Hemodynamic response functions (HRFs) for both analyses were modeled using a 2-gamma function with a time-to- peak (TTP) varying between -3 and 9 repetition times (TRs) from stimulus onset. We found that the GLM analysis was more robust to an altered hemodynamic response when the stimuli were presented in a random sequence rather than an ordered sequence. Sequential stimulus presentation sequences led to systematic errors that were not present with a random presentation sequence. There were, however, limitations to the random presentation sequence: if the TTP was delayed by greater than +/- 1 TR the sensitivity and specificity of the analysis greatly deteriorated (window of resilience = +/- 1 TR). Prolonging the stimulus duration to 10 TRs led to no difference in accuracy between the ordered and random presentation sequence and the window of resilience increased to -3/+5 TRs for both presentation paradigms. The pRF results showed that the window of resilience was no different between sequential and randomized data: +/- 1 TR for polar angle and 0 TRs for both eccentricity and receptive field size. These results highlight the importance of tailoring

experimental designs to altered hemodynamic responses, and point to the need for subject- and voxel-specific hemodynamic response functions when analyzing fMRI data in patient populations with neurovascular abnormalities.

Disclosures: **G. Patil:** A. Employment/Salary (full or part-time):; University of Rochester. **C.L. Schneider:** A. Employment/Salary (full or part-time):; University of Rochester School of Medicine and Dentistry, Carnegie Mellon University. **B. Sahin:** A. Employment/Salary (full or part-time):; 4.University of Rochester Medical Center. **B.Z. Mahon:** A. Employment/Salary (full or part-time):; Carnegie Mellon University.

Poster

706. Analytical Computational Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 706.15/DD26

Topic: I.06. Computation/ Modeling/ and Simulation

Support: DoD Grant W81XWH-15-2-0032

Title: Cyclicity vs. similarity measures for fMRI resting state time series analysis

Authors: I. T. ABRAHAM[1], S. SHAHSAVARANI[3], B. ZIMMERMAN[4], Y. M. BARYSHNIKOV[1], *F. T. HUSAIN[2];
[1]ECE, [2]Neuroscience, Speech and Hearing Sci., Univ. of Illinois at Urbana-Champaign, Champaign, IL; [4]Neurosci. Program, [3]Univ. of Illinois At Urbana-Champaign, Urbana, IL

Abstract: The present study is a comparison of novel type of analysis based on cyclicity with traditional fMRI resting state functional connectivity measures. Cyclicity analysis captures pairwise relations between multiple time series by generating translation and reparametrization invariant features amenable to matrix analysis methods. The resting state fMRI time series demonstrate cyclic patterns that may not be periodic, indicating an underlying self-sustained cycling among processes in different regions of the brain. Such cyclic interactions remain indiscernible to correlation-based methods, which formulate functional interactivity by measuring the similarity among time series. Contrary to correlation-based features, those generated by cyclicity analysis can provide information germane to the cyclic ordering among time series, as a measure of functional interactivity. In this study, we compared the stability and robustness of cyclicity analysis with (1) zero-lag correlation, (2) lagged cross-correlation, and (3) dynamic time warping analyses. To do so, we obtained and analyzed fMRI data from patients with tinnitus (N=49) and healthy controls (N=29) in two visits held one week apart, using a 3T Siemens Prisma magnet. The dataset consisted of four 10-minute resting state EPI scans per subject. Both cyclicity and correlation-based analyses resulted in more stable feature matrices across two scan visits compared with dynamic time warping analysis in patients and controls.

However, the degree of this stability depends on preprocessing choices including global signal regression and filtering specifications. In general, global signal regression was in favor of cyclicity and correlation-based analyses. Whereas filtering was detrimental to cyclicity analysis, it increased the stability of correlation-based analyses. Dynamic time warping analysis, while more robust to the choice of preprocessing steps, was found it to be less stable over the week. No single analysis method was found to have distinct advantage in classifying patient and control populations when used in traditional techniques such as discriminant analyses and support vector machines. Due to the fact that cyclicity and correlation methods capture different aspects of functional interactivity, current efforts are targeted towards on developing methods accounting for both cyclic ordering and similarity between time series. Future work will investigate dynamic functional interactivity focusing on these features as they evolve through the duration of the scan.

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Poster

706. Analytical Computational Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 706.16/DD27

Topic: I.06. Computation/ Modeling/ and Simulation

Support: NSF DMS award #1714094
HFSP RGP0019/2018

Title: A new method for large-scale neuronal simulation

Authors: N. WANG[1], *D. B. FORGER[2];
[1]Univ. of Michigan, Ann Arbor, MI; [2]Mathematics, Bioinformatics and Data Sci., Univ. of Michigan, Ann Arbor, MI

Abstract: With many large-scale datasets being collected, much recent effort has focused on developing computational tools which can simulate large regions of the brain. In addition to a large number of neurons, other complications in developing these tools include accurately representing the synaptic, paracrine or other signaling that occurs between neurons, and accounting for the fact that neurons are intrinsically noisy. A common approach to these problems is to use neural mass models, which treat neurons probabilistically. However, these models are based on a mean-field approximation of population density and a one-or-two-dimension simplification of neuron dynamics such as the Theta model. Consequently, these methods do not allow detailed dynamics for neurons at the level of individual ionic conductance. An alternative approach is simulating a network of individual noisy neurons. But such a

simulation for a large brain region is computationally intensive. Here, we present a numerical scheme, based on a novel asymmetric particle method, for simulating coupled noisy neuronal populations with a detailed (Hodgkin-Huxley type) description of ionic channel conductances. We find very accurate agreement with a direct simulation of neuronal networks over a range of noise and coupling levels, which is achieved at a fraction of the computational cost. Our method is versatile in that it can be easily applied to other Hodgkin-Huxley type models with minimal modification. This technique could lead to new computational approaches that can be integrated with the new large-scale neuronal datasets currently being collected.

Disclosures: D.B. Forger: None. **N. Wang:** None.

Poster

706. Analytical Computational Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 706.17/DD28

Topic: I.06. Computation/ Modeling/ and Simulation

Title: Discovery of dynamic functional connectivity of cortical networks by learning fast correlation sequences in large-scale neural activity data

Authors: *C. GRABER, *R. LOH, Y. VLASOV, A. SCHWING;
Univ. of Illinois, Urbana, IL

Abstract: What can we learn about the functional organization of cortical microcircuits from large-scale recordings of neural activity? Most of the current efforts are focused on decoding multidimensional manifolds by various implicit methods [1-4] of dimensionality reduction to reconstruct the behavior. A key component, however, to furthering our understanding of organization of cortical networks is the ability to extract time-dependent functional connectivity and to establish the dynamics of the cortical information flow. To obtain interpretable results for neural activity dynamics, we develop a method which explicitly models correlations across space and time between all recorded neurons in the network. This approach is based on Neural Relational Inference [5], a variational autoencoder-based model where the latent variables represent connections between output variables, i.e. dynamics of neurons spiking. This approach not only explicitly models the functional connections between neurons, but also capture the dynamics of their change over time. Furthermore, this formulation allows for the use of arbitrarily expressive models, unlike previous approaches such as [2] which are restricted to generalized linear models. We experiment on neural spiking data obtained from the primary somatosensory cortex of a mouse while performing a whisker-guided navigation task. On this data, we show that our approach not only performs well in reconstruction, but also explicitly models the connections between neurons across cortical layers in the barrel cortex and how they change during various phases of experimental trials. Correlation of dynamic network

connectivity with whisker-guided navigation behavior can shed light on specific dynamic organization of columnar microcircuits and reveal stages of tactile information flow during perceptual decision making. [1] C. Pandarinath, et al, Nature methods 15, 805(2018)[2] S. Linderman, et al., NIPS (2016) [3] A. Williams, et al., Neuron, 1099.e8. 98.6 (2018) [4] E. Mackevicius, et al., eLife 8, e38471 (2019) [5] T. Kipf, et al. ICML (2018)

Disclosures: **C. Graber:** None. **R. Loh:** None. **Y. Vlasov:** None. **A. Schwing:** None.

Poster

706. Analytical Computational Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 706.18/DD29

Topic: I.06. Computation/ Modeling/ and Simulation

Support: NIH Grant 5 R01 DA035484-03
NIH Grant 5 R01 MH076136-10

Title: Multilevel principal component regression for brain imaging

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Abstract: Multivariate modeling of brain imaging data, or multivoxel pattern analysis (MVPA), captures useful brain representations of theoretically constructs and clinically meaningful outcomes. Here we present an MVPA technique to take into account hierarchical structure in brain imaging data (e.g. subjects or imaging sites). We extend principal component regression (PCR) by substituting mixed effect regression for ordinary least squares and multilevel component analysis for principal component analysis. Finally, we incorporate Bayesian optimization to select principal components to retain at each level of the model. Resultant models yield separate MVPA maps for predicting outcome variance within and between subjects. We compare MLPCR and PCR model performances according to variance explained in out of sample observations using nested cross validation in two datasets and three tasks. We show MLPCR has similar sensitivity and specificity in all cases (table I). In dataset 1 (n = 86, 4542 single trial images) models trained to predict subjective thermal pain intensity ratings or subjective sound intensity ratings successfully predict corresponding out of sample ratings. However, models trained to predict pain do worse than an intercept only model in predicting sound intensity ratings and vice versa, indicating specificity. Similar results were obtained in the second dataset (n = 32, 2939 single trials) comparing thermal pain rating and nonpainful thermal

rating tasks. MLPCR shows comparable performance to PCR, but has several advantages over established MVPA methods. First, MLPCR provides greater model transparency by segregating different levels of pattern representation across hierarchical levels of an experimental design. This allows greater insight into obtained representations, for instance by identifying subject or site effects. Second, MLPCR reduces experimenter degrees of freedom by creating a framework within which common analytic design decisions can be automated (e.g. mean centering subjects). Further work is needed to evaluate MLPCA performance in the case of unbalanced designs and heteroskedastic noise, scenarios where mixed effects regression models have distinct advantages over more naïve models.

Out of sample variance explained

	MLPCR pain trained dataset1	PCR pain trained dataset 1	MLPCR sound trained dataset 1	PCR sound trained dataset 1	MLPCR pain trained dataset2	PCR pain trained dataset 2	MLPCR thermal trained dataset 2	PCR thermal trained dataset 2
pain test data	0.128	0.176	-0.514	-0.35	0.127	0.145	-0.286	-0.299
sound test data	-0.33	-0.93	0.103	0.43				
thermal test data					0.007	0	0.039	0.039

1 - mse(pred) / var(obs), nested cross validation, negative values indicate mse(pred) > var(obs)

Disclosures: **B. Petre:** None. **C. Woo:** None. **E. Losin:** None. **H. Eisenbarth:** None. **T.D. Wager:** None.

Poster

706. Analytical Computational Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 706.19/DD30

Topic: I.06. Computation/ Modeling/ and Simulation

Support: NIH Grant R01 GM104948
NIH Grant P01GM118269

Title: *In silico* modeling of temporally interfering electric fields for deep brain stimulation

Authors: *I. DALLA BETTA[1,2], A. M. CASSARA[3], E. S. BOYDEN[2], E. N. BROWN[2,4,5], F. J. FLORES[4,5];

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Abstract: The use of electric fields to manipulate neural activity and function has been common practice in research and the clinic for several decades. Non-invasive techniques, such as transcranial direct current stimulation (tDCS) and transcranial alternate current stimulation (tACS), and invasive techniques such as deep brain stimulation (DBS) have a variety of uses in the treatment of psychiatric and neurological disorders. Recently, the discovery that temporally interfering (TI) electric fields can achieve a finer focus of neural stimulation has combined the non-invasive quality of tACS with the localized stimulation obtained with DBS. However, to position the focus of TI within the brain, it is necessary to consider several parameters such as current intensity, tissue properties, electrode position, and others. In this study, we assessed the distribution of electric fields and maximal TI in a laminar head model and a realistic mouse model and studied the effects of current intensity, electrode size, and electrode position geometry. To solve Maxwell's equations, we used the finite element method under an electro ohmic quasi-static regime with Dirichlet boundary conditions. We found that the focus and depth of maximal TI is directly proportional to the size of the return electrodes, and inversely proportional to the angle between source and return electrodes and to the distance between the source electrodes. Also, increase in current intensity increases the strength of the maximal TI but not its focus or its depth. The focus provided by TI is always better than that provided by the same tACS configuration. Our *in silico* study provides a systematic assessment of the relevant parameters to optimize TI and can guide future *in vivo* studies seeking to achieve neural stimulation of deep brain regions.

Disclosures: I. Dalla Betta: None. **A.M. Cassara:** None. **E.S. Boyden:** A. Employment/Salary (full or part-time):; MIT. **E.N. Brown:** A. Employment/Salary (full or part-time):; MG and MIT. 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: R01 GM104948 (to E.N.B.) and P01GM118269 (to E.N.B.); the Department of Anesthesia, Critical Care and Pain Medicine, MGH, & the Picower Institute for Learning and Memory, MIT. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); MGH has licensed IP for EEG monitoring developed by E.N.B. to Masimo. E.N.B. holds interest in PASCALL, a start-up company developing EEG-based anesthetic state control systems for anesthesiology. **F.J. Flores:** A. Employment/Salary (full or part-time):; MGH.

Poster

706. Analytical Computational Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 706.20/DD31

Topic: I.06. Computation/ Modeling/ and Simulation

Support: NIH Grant U01-NS103569-01
NIH Grant R01-NS094206
NIH Grant P50-NS098573
NIH Grant R01-NS081118

Title: Temporally-rotating and orientation-selective electric fields enable finer control of axonal activation with deep brain stimulation applications

Authors: *S. S. SANG[1,2], L. LEHTO[2], J. SLOPSEMA[1], L. WU[2], S. MAMGIA[2], S. MICHAELI[2], M. D. JOHNSON[1];
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Abstract: Introduction: The therapeutic benefits of deep brain stimulation (DBS) strongly depend on the electrode configuration and stimulation pulse patterns. Commercial DBS probes have a limited number of electrodes that in turn limit the flexibility to which electric fields can be steered and sculpted within the brain. Here, we demonstrate in computational models that with high-density electrode arrays one can achieve (1) more efficient axonal activation with temporally rotating electric fields, and (2) unidirectionally propagating action potentials using spatial ambulation of electric fields over time. **Approach:** Computational models consisted of a finite element model of a high-density electrode array coupled with biophysical multi-compartment myelinated axon models that were distributed across a broad range of orientations relative to the electrode array. Stimulation thresholds for axonal activation were investigated in the context of sinusoidal waveforms applied with varying phase offsets across multiple electrodes. The degree to which unidirectionally propagating action potentials and action potential block could be elicited was investigated in terms of the spatial electric field gradient over time along the shank surface. **Main results:** Narrow aperture rotating electric fields using three or more electrodes were found to have lower stimulation thresholds than monopolar configurations and bipolar configurations across a broad range of axon orientations. Unidirectionally propagating action potentials from 2um diameter myelinated axons could be elicited in close proximity to the electrode array within 150 um using linearly increasing stimulation amplitudes along the surface of the high-density electrode array. This method could also be used to block the propagation of action potentials along an axon. **Significance:** These results suggest that higher density electrode arrays using novel temporally rotating electric fields and orientation-selective electric fields can enable finer scale manipulation of axonal activation over traditional approaches to electrical stimulation within the brain.

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Poster

706. Analytical Computational Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 706.21/DD32

Topic: I.06. Computation/ Modeling/ and Simulation

Support: NSF Grant IIS160811
GAANN Fellowship Grant P200A150316

Title: Canvas: A computational neuroscience Matlab design tool for large scale synthetic nervous systems

Authors: *F. R. YOUNG[1], A. J. HUNT[2], R. D. QUINN[1];
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Abstract: Animals demonstrate the complex environmental interactions roboticists seek to emulate with machines. The coupled nature of the nervous system's form and function indicates that its composition is crucial to task-level flexibility. The enviable benchmark set by this neural tractability has lead to the development of control systems modeled after the nervous system. Development of "synthetic nervous systems (SNSs)" serves the dual purpose of a robotic control platform and a modeling tool for computational neuroscience.
By decomposing the nervous system into functional subunits, it has been shown that established neural functionality can be replicated in an accessible, hierarchical nature. Specifically, functional subunits associated with rhythmic oscillations called central pattern generators (CPGs) have been used to implement locomotor control in simulation. Once the system architecture has been established, optimization techniques are used to tune individual neuron parameters and coordinate motion.
The complex nature of SNSs makes their implementation computationally expensive. While some methods already exist for the design and optimization of relatively small neural systems, we are unaware of an existing tool for the creation of large-scale SNSs. This work presents a Matlab modeling tool capable of rapid design and deployment of SNSs to ease their creation while implementing fundamentals developed on the subject.
This tool, called Canvas, features a graphical user interface (GUI) wherein a user is able to develop their own large-scale SNSs. Users are able to define system geometry for their specific task with the capability of exporting and importing neural designs. Canvas allows users to define synaptic and neuron parameters for each node in the simulation individually. Additionally, functional subunits can be easily created with the appropriate calcuated parameters allowing users to quickly perform algebraic combinations of neural signals.
This tool currently offloads simulation results into an open source program called Animatlab.

Animatlab is a simulation environment used to simultaneously integrate neural control with physiological motor manipulation. While Animatlab is a useful tool for implementing neuromechanical control, it lacks the functionality for creating large-scale neural systems. Canvas allows users to automatically generate an Animatlab project file for rapid deployment of SNS designs for neural simulations. With this tool, it will become possible to generate large-scale SNSs for the control of complex neuromechanical simulations, aiding both the robotics and biology communities.

Disclosures: F.R. Young: None. **A.J. Hunt:** None. **R.D. Quinn:** None.

Poster

706. Analytical Computational Models

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 706.22/DD33

Topic: I.06. Computation/ Modeling/ and Simulation

Support: This project has received funding from the European Union's Horizon 2020 Research and Innovation Programme under Grant Agreement No. 720270 (HBP SGA1) and 785907 (HBP SGA2)

Title: EBRAINS fair data service: A novel infrastructure for making neuroscience data findable, accessible, interoperable, and reuseable

Authors: *K. A. ANDERSSON[1], C. H. BLIXHAVN[1], H. KLEVEN[1], U. SCHLEGEL[1], O. SCHMIDT[2], M. A. PUCHADES[1], A. P. DAVISON[3], T. DICKSCHEID[4], T. B. LEERGAARD[1], J. G. BJAALIE[1];
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Abstract: There is a growing need for sharing of research data and computational models to address the reproducibility and transparency challenges that are currently manifested across all scientific disciplines. In addition, an increasing number of researchers are recognising the benefits of sharing research data to obtain greater exposure of their research and to access shared data assets for re-analysis and re-use in new combinations. Today, several general data repositories are offering opportunities for researchers to share research data and models. However, many of these repositories lack the necessary stewardship and standards for making the research data and models Findable, Accessible, Interoperable and Reusable (FAIR), in accordance with the FAIR principles (Wilkinson et al., Scientific Data 3:160018, 2016). To address these challenges, the Human Brain Project (HBP) is developing a new research infrastructure, EBRAINS FAIR data service, providing tools, workflows and curation services

tailored for integration and sharing of heterogeneous, multimodal neuroscience data and computational models. Curation includes also verification of relevant permissions and adherence to regulations and ethical standards. Data are stored at HPC centers, close to compute resources, made citable through DOIs, and tagged with a Creative Commons copyright license, chosen by the data provider. Data sharing through EBRAINS is one of several services delivered by the EBRAINS infrastructure, developed by the HBP. We demonstrate currently available services and provide examples showing the added values of sharing data through the new infrastructure.

Disclosures: **K.A. Andersson:** None. **C.H. Blixhavn:** None. **H. Kleven:** None. **U. Schlegel:** None. **O. Schmidt:** None. **M.A. Puchades:** None. **A.P. Davison:** None. **T. Dickscheid:** None. **T.B. Leergaard:** None. **J.G. Bjaalie:** None.

Poster

706. Analytical Computational Models

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Program #/Poster #: 706.23/DD34

Topic: I.06. Computation/ Modeling/ and Simulation

Support: This project has received funding from the European Union's Horizon 2020 Research and Innovation Programme under Grant Agreement No. 720270 (HBP SGA1) and 785907 (HBP SGA2).

Title: Find and explore rodent brain data using 3D atlases in the new EBRAINS infrastructure

Authors: *C. H. BLIXHAVN, K. A. ANDERSSON, H. KLEVEN, U. SCHLEGEL, M. A. PUCHADES, J. G. BJAALIE, T. B. LEERGAARD;
Inst. of Basic Med. Sci., Univ. of Oslo, Oslo, Norway

Abstract: The neuroscience community steadily produces a richness of multi-scale and multi-modal data, but so far these data are difficult to find, access and reuse. By comparison, Google Earth allows us to find and view different sites, services and information of interest, connected to specific locations in geographic maps. Following a similar logic, the new EBRAINS infrastructure makes use of three-dimensional brain atlases to provide anatomical context for different research data, allowing users to find and reuse selected data of interest to solve new questions. With the interactive EBRAINS platform, users can navigate and combine datasets in atlas viewers. The shared datasets are linked to collections of tools and workflows that can utilise the anatomical atlas information for further analyses of data. We here present workflows used to localise anatomical positions in different types of neuroscience data. We exemplify the added value of presenting, navigating and analysing spatially relevant data within an atlas framework. The Human Brain Project now invites the community to use the new research infrastructure to share, find and use open access research data.

Disclosures: **C.H. Blixhavn:** None. **K.A. Andersson:** None. **H. Kleven:** None. **U. Schlegel:** None. **M.A. Puchades:** None. **J.G. Bjaalie:** None. **T.B. Leergaard:** None.

Poster

707. Data Analysis: Neuronal Networks

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 707.01/DD35

Topic: I.07. Data Analysis and Statistics

Support: NIH 1 U24 RR021992
NIH 1 U24 RR025736-01
NIH R01EB020407
NIH P20GM103472
NIH P30GM122734
NSF 1539067

Title: Using filter bank to estimate functional connectivity in both low and high frequencies: Application to schizophrenia

Authors: *A. FAGHIRI, E. DAMARAJU, V. CALHOUN;
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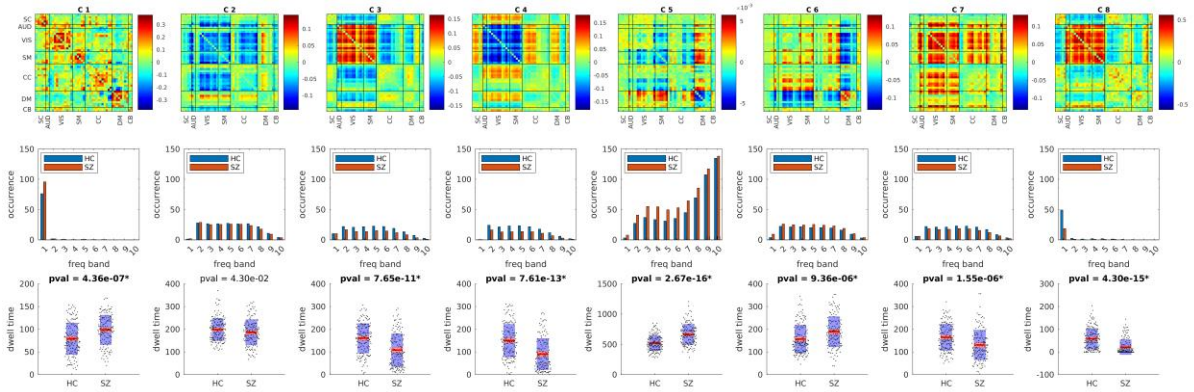
Abstract: Dynamic functional network connectivity (dFNC) among different parts of the brain can be estimated using sliding window Pearson correlation (SWPC). Selecting a window size is required for SWPC where using a very short window size increases standard error while faster changes in connectivity can go undetected if we use long window sizes. Here, we propose a new method inspired by SWPC that uses filter bank to estimate dFNC in all frequency bands.SWPC is essentially two systems in series. In the first system, two time series are demeaned and multiplied (Pearson correlation part). The output is then filtered using a low pass filter in the second system (the sliding window). Here, we use a filter bank covering the whole frequency space instead of the second system.We analyzed an fMRI dataset including healthy controls (HC, n = 163) and schizophrenia patients (SZ, n = 151). First, group independent component analysis is used to decompose the data into 100 spatial maps and their time series. Next, 48 components were selected and grouped into 8 functional domains. We designed 10 filters to divide 0 - 0.25 Hz (TR=2s) space into equal band passes and used them to estimate dFNC matrix. Finally, we clustered all dFNC values into 8 clusters (Figure 1 first row). The number of occurrence of each cluster for each frequency band (Figure 1 second row) and the amount of time each subject stayed in each state (dwell time) was compared between HC and SZ (Figure 1 third row). States 1 and 8 occur mainly in the lowest frequency band. HC stay more in cluster 8 while SZ stay more in cluster 1 suggesting that SZ and HC subjects have different static connectivities. In addition, we have some clusters that almost never occur in low frequency band (cluster 2 and 4).

Note that these are high frequency states which are not visible in SWPC results.To summarize, this approach enables us to estimate high frequency states not detected using SWPC and allows us to differentiate between low and high frequency states. In addition, we were able to detect some cluster pairs that have opposite patterns which we speculate subjects oscillate between them.



Disclosures: **A. Faghiri:** None. **E. Damaraju:** None. **V. Calhoun:** None.

Poster

707. Data Analysis: Neuronal Networks

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 707.02/DD36

Topic: I.07. Data Analysis and Statistics

Support: This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 777364. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA

Title: The EQIPD framework for rigour in the design, conduct and analysis of biomedical experiments

Authors: *J. VOLLERT[1], E. SCHENKER[2], M. R. MACLEOD[3], A. BESPALOV[4], H. WUERBEL[5], M. C. MICHEL[6], U. K. DIRNAGL[7], H. POTSCHKA[8], K. E. WEVER[9], T. STECKLER[10], T. VAN DE CASTEELE[11], B. M. ALTEVOGT[12], G. RIEDEL[13], A. S. C. RICE[1]; [1]Imperial Col. London, London, United Kingdom; [2]Inst. de Recherches, Servier, Croissy-sur-Seine, France; [3]Univ. of Edinburgh, Edinburgh, United Kingdom; [4]Partnership for Assessment and Accreditation of Scientific Practice, Heidelberg, Germany; [5]Univ. of Bern, Bern, Switzerland; [6]Johannes-Gutenberg-Universität, Mainz, Germany; [7]Charite Universitätsmedizin Berlin, Berlin, Germany; [8]Ludwig-Maximilians- Univ., Munich, Germany; [9]Radboud Univ.

Med. Ctr., Nijmegen, Netherlands; [10]Johnson & Johnson PRD, B-2340 Beerse, Belgium; [11]Janssen Pharmaceutica NV, Beerse, Belgium; [12]Pfizer Inc, Silver Spring, MD; [13]Univ. Aberdeen, Aberdeen, United Kingdom

Abstract: Within the last years, there has been growing awareness of the negative repercussions of unstandardized planning, conduct and reporting of preclinical research. Several initiatives have set the aim of increasing validity and reliability in reporting of studies and publications. While these overlap significantly, they differ in detail, and show variance in generalizability or specific challenges for a single field. Additionally, reporting guidelines do not cover planning and conduct of studies, which face a similar situation. Consequently, it is hard for researchers to decide which guidelines to follow, especially at the stage of planning future studies.Aim of the EQIPD (European Quality in Preclinical Data) framework was to unify current suggestions, find a basis in evidence behind their rationale, and prospectively test the newly set framework for feasibility in multi-center animal experiments.
In a first step, in a systematic review of guidelines, a systematic search yielded 13,863 results, in which 62 publications fit to the inclusion criteria. From these, a list of 58 unique items were extracted, and in a two-round Delphi process with a subsequent consensus meeting, 33 of these items were included in the final framework. This framework was constructed into five major domains.
DOMAIN 1: Exploratory vs. confirmatory research: Answer the following question: Is your experiment testing a predefined scientific hypothesis which is statistically testable (confirmatory research) or is it exploring a space of interesting options to generate hypotheses (exploratory research)?
DOMAIN 2: Pre-planning and standard operating procedures (SOPs): Prespecify, document and standardize all methods and analyses before the experiment.
DOMAIN 3: Statistics: Think about which form of aggregate measures are meaningful for your data and choose appropriate statistical methods, and plan your sample size accordingly.
DOMAIN 4: Randomization and blinding: Randomize and blind your processes to avoid the introduction of confounding and systematic error.
DOMAIN 5: Documentation: Not all bias can be avoided, but most can be uncovered: use full and comprehensive documentation.
The EQIPD framework is currently prospectively tested for feasibility and blind spots in a multi-center animal study, which will further inform the final version. In parallel, a literature search is conducted to identify the provenance of diligence - the evidence for an impact of the proposed items, and the history of their application. While, for the moment, the framework is being developed around animal work, its applicability to in vitro studies will also be assessed.

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Poster

707. Data Analysis: Neuronal Networks

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 707.03/DD37

Topic: I.07. Data Analysis and Statistics

Title: Automatic diagnosis of epilepsy using current source estimate with a deep neural network

Authors: *N. URA[1], T. YANAGISAWA[2], R. FUKUMA[3], T. HARADA[4], S. YAMAMOTO[3], J. AOE[5], H. KISHIMA[2];
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Abstract: Introduction: Epilepsy is one of the most common neurological disorders in the world. Magnetoencephalography (MEG) is an important examination for the diagnosis of epilepsy, but seizures are identified by epileptologists who read extensive MEGs, which is time-consuming and requires experience. Developing a practical and reliable intelligent diagnosis algorithm would be of great significance. We explored the feasibility of using automatic interpretation of MEG signals by a deep neural network to diagnose epileptic patients. **Method :** We used MEG signals and MRI images from 80 epileptic patients and 80 healthy subjects, recorded at Osaka University Hospital. The MEG system was a 160-channel whole-head MEG equipped with a coaxial-type gradiometer housed in a magnetically shielded room (MEGvision NEO; RICHO Electric Corporation, Kanazawa, Japan). During MEG measurements, subjects were in a supine position with the head centered in the gantry. Participants were instructed to close their eyes and, not move their head. MEG signals recorded in one session (either 240s or 300s) during which the subject was awake. Sampling frequency was 2k Hz, with the high-pass filter at 0.1 Hz. We aligned the head image and estimated the current source estimation from the magnetic field signal through spatial filtering processing using MEG signals and the MRI images. The source estimation data was divided into 800-ms segments, which were used as input for a convolutional neural network (CNN), called MNet, to classify epilepsy patients and health volunteers using 10-fold cross-validation. MNet was designed to extract global features of 160 channels of segment data. To compare the MNet classification accuracy, we studied the accuracies for the same combination of subjects using a support vector machine (SVM). **Result :** The classification accuracy using MNet was 81.07%, which was higher than the study using an SVM with source estimate data. **Conclusion :** The trained MNet succeeded in differentiating subjects with neurological disease from healthy subjects using big data from MEG signals. This is the first study to classify such subjects using current source estimation data from magnetic field signals. Using deep learning with big datasets will improve the diagnosis of neurological disease.

Disclosures: **N. Ura:** None. **T. Yanagisawa:** None. **R. Fukuma:** None. **T. Harada:** None. **S. Yamamoto:** None. **J. Aoe:** None. **H. Kishima:** None.

Poster

707. Data Analysis: Neuronal Networks

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 707.04/DD38

Topic: I.07. Data Analysis and Statistics

Title: CA2 area detection from hippocampal microscope images using deep learning

Authors: *H. OJIMA[1], S. MORINAGA[1], T. ISHIKAWA[2], M. YASUI[2], S. AKIZUKI[1], M. HAMADA[1], T. KURODA[1];
[1]Integrated Design Engin., Keio Univ., Yokohama, Japan; [2]Pharmacol., Keio Univ., Tokyo, Japan

Abstract: The Cornu Ammonis area in the hippocampus divides into three subregions, including the CA1, CA2, and CA3. Anatomical and functional properties of each subregion have been extensively studied; however, it has been difficult to identify the anatomical area of each subregion. Molecular markers provide a powerful tool to assess anatomical area of the subregions, on the other hand, additional time-consuming techniques, such as preparation of transgenic animals or post-hoc immunostaining, are necessary. The aim of our research is the creation of an alternative method to assess anatomical area of the CA2 subregion from hippocampal microscope images by deep learning, which is a time efficient computational machine learning approach. As an initial step towards creating such a system, we utilized a modified version of a convolutional neural network architecture for medical image segmentation called U-Net, to assess the CA2 subregion from a microscope transmitted-light images of the mice hippocampus. The output of our system is a confidence heatmap and a maximum confidence coordinate, which provides the CA2 location in the hippocampal CA2 area. This proposed system was trained by a dataset which consists of 220 transmitted-light images and manually labeled CA2 region masks created from fluorescent images. We tested the system on another dataset which consists of 12 images. All images were obtained from PFA-fixed horizontal hippocampal slices from adult (9-11 weeks) C57BL/6J mice. Based on the probability that the maximum confidence coordinate exists in the CA2 area, the proposed system achieved the detection accuracy of 100% on the test dataset. This work will provide biologists with efficient and accurate tools to assess the CA2 subregion, improving the efficiency of studies in the area.

Disclosures: **H. Ojima:** None. **S. Morinaga:** None. **T. Ishikawa:** None. **M. Yasui:** None. **S. Akizuki:** None. **M. Hamada:** None. **T. Kuroda:** None.

Poster

707. Data Analysis: Neuronal Networks

Location: Hall A

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Program #/Poster #: 707.05/DD39

Topic: I.07. Data Analysis and Statistics

Support: ARC Grant DP170102263
ARC Grant DP180100636

Title: Model-based decoupling of evoked and spontaneous neural activity in calcium imaging data

Authors: *M. A. TRIPLETT, Z. PUJIC, B. SUN, L. AVITAN, G. J. GOODHILL;
Queensland Brain Inst., Univ. of Queensland, St Lucia, Australia

Abstract: The pattern of neural activity evoked by a stimulus can be substantially affected by ongoing spontaneous activity. In calcium imaging data this spontaneous activity often appears highly structured, and may reflect parallel encoding of non-sensory variables, mechanisms for circuit development, or other internal state factors that regulate sensory-guided behaviour. Accurately studying the interplay between stimulus-evoked and spontaneous activity therefore requires the ability to reliably separate these two components. However, this is challenging as the internal factors that give rise to spontaneous activity typically cannot be directly observed or measured.
To address this problem we developed a latent variable model that decouples the components of calcium imaging data due to evoked activity from those driven by structured spontaneous activity. We use Bayesian methods to fit the model to data and identify low dimensional structure underlying spontaneous activity that proceeds unimpeded during stimulus presentation. Our model also fits a simple linear receptive field, ensuring that the estimated stimulus tuning properties already account for the variability that this ongoing spontaneous activity introduces. After validating the model on surrogate data we then apply it to data from zebrafish tectum and mammalian cortex. By analysing the variance that the evoked and spontaneous components contribute to neural activity, the model allows us to characterise how neurons are differentially driven by external stimuli, latent internal factors, and their interaction.

Disclosures: M.A. Triplett: None. **Z. Pujic:** None. **B. Sun:** None. **L. Avitan:** None. **G.J. Goodhill:** None.

Poster

707. Data Analysis: Neuronal Networks

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 707.06/DD40

Topic: I.07. Data Analysis and Statistics

Support: NIH Award T32EB019944
AFOSR Grant FA9550-17-1-0387

Title: Time-varying monitoring of dynamic neural connectivity using calcium imaging

Authors: *C. RENTERIA, Y.-Z. LIU, S. A. BOPPART;
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Abstract: Recent advances in optical imaging technologies and connectome research have rapidly increased the volume and complexity of imaging data, and the need to comprehensively understand the network properties of the brain. This complexity is furthered by the many metrics used to identify connection strength, causing uncertainty about appropriate metric selection. One limitation of these metrics is the inability to track dynamic connectivity changes. Current techniques also do not provide directionality of signal propagation, and consequently provide limited information about information transfer in neural systems. We propose a time-varying, time-frequency approach for analysis to overcome these weaknesses. For these studies, hippocampi were isolated from P2-P3 mice expressing GCaMP6 (C57BL/6J-Tg(Thy1-GCaMP6s)GP4.12Dkim/J, Jackson Lab) and cultured. Cultures were optically excited and imaged with a commercial Zeiss microscope (Axio Observer.D1) at 22.7 Hz using a Zeiss CCD camera (Axiocam 503 mono) for 10 minutes, followed by perfusion of 10, 25, and 100 μM glutamate to monitor chemically-induced changes. Cell culture media (NbActiv4) was used as a control. For analysis, somas were identified by manual selection, and the ΔF/F calculated for all cells from their fluorescence. A ten-second, windowed Pearson's correlation coefficient was used to analyze dynamic connectivity. The prominent frequency of these signals was quantified by averaging the signals from all cells over time, calculating the Welch's power spectrum, and identifying the maximum frequency. The wavelet transform was also implemented to monitor the frequency content over time. Wavelet coherence was used to monitor the coherence and phase between cellular signals at the prominent frequency. Spike-sorting was implemented by thresholding for signals larger than two standard deviations above the mean, and peak-identification of the calcium transients was used to determine the firing properties of individual cells, and the network. Our results demonstrate a strong agreement between the time-varying correlation and coherence approaches for monitoring network connectivity, and consequently support that the two give complimentary information. The phase from the wavelet analysis

provides information regarding information flow, demonstrating an ability to resolve directionality of signal propagation alongside the connectivity metrics. This combined approach for analyzing neural signals and connectivity could provide new information about the network structure of neural circuits and the brain, not just for optical imaging, but for other functional brain imaging techniques.

Disclosures: C. Renteria: None. **Y. Liu:** None. **S.A. Boppart:** None.

Poster

707. Data Analysis: Neuronal Networks

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 707.07/DD41

Topic: I.07. Data Analysis and Statistics

Title: *In-vitro* structural neurotoxicity testing using deep convolutional neural networks

Authors: *M. MADDAH[1], K. LOEWKE[1], H. TRUONG[2], H. YU[2];
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Abstract: The incidence of neurological disorders is increasing around the world. There is a need for more advanced tools that can be used to screen large sets of compounds for potential neurotoxicity. Human induced pluripotent stem cell (iPSC)-derived neurons are emerging as widely-used cell models in toxicity testing. To fully leverage their potential, the development of robust and accurate assays is of the utmost importance. We present a novel tool, PhenoTox, which uses deep convolutional neural networks to capture subtle and complex compound-induced structural changes in cell-based models, such as iPSC-derived neurons. The input to PhenoTox is a collection of microscopy images captured and grouped at multiple doses and time-points for the drug of interest and a control set for each time point where no drug is applied. PhenoTox performs a series of 2-class neural network trainings comparing the test conditions to the controls and generates a classification accuracy for each training. The final output is a heatmap of the z-factors across all test conditions, depicting the doses and timepoints at which structural changes have happened and how strongly they differ from controls. Here, we present the results of our first experiments applying PhenoTox for evaluating drug-induced structural toxicity using iPSC-derived Gaba neurons. Cells from Cellular Dynamics were cultured on a 384-well plate. A panel of 7 compounds, 5 with known neurotoxicity profiles and 2 proprietary compounds, were applied at 10 different concentrations (with highest concentration of 50uM and 1:3 serial dilution) with 3 replicates each for 48 hours. Cells were fixed and stained with Beta III Tubulin and Hoechst and fluorescence microscopy images were collected at 9 locations per well. PhenoTox detected dose-dependent structural changes for all 5 known drugs, while no changes were detected for the two proprietary compounds. Structural changes detected by PhenoTox were more pronounced for the Beta III Tubulin marker compared to Hoechst as expected. EC50

values derived from PhenoTox were compared to EC50 values calculated from a commercial neurite-length assay. The concentrations nearest to EC50 matched exactly for Vincristine, Brefeldin A, FCCP, and Tunicamycin. For Staurosporine, PhenoTox was more sensitive than the neurite-length assay, showing half-maximal response 3 concentrations sooner (6.29nM vs. 360nM). For the 2 proprietary compounds, PhenoTox and the neurite-length assay showed EC50 greater than max concentration. These results are the first demonstration of PhenoTox in successfully capturing of dose-dependent structural changes on a panel of drugs with known neurotoxicity profiles.

Disclosures: **M. Maddah:** A. Employment/Salary (full or part-time):; Dana Solutions. **K. Loewke:** A. Employment/Salary (full or part-time):; Dana Solutions. **H. Truong:** A. Employment/Salary (full or part-time):; Gilead. **H. Yu:** A. Employment/Salary (full or part-time):; Gilead.

Poster

707. Data Analysis: Neuronal Networks

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 707.08/DD42

Topic: I.07. Data Analysis and Statistics

Title: Brainwide coactivation patterns revealed by multi-site electrophysiological recording and resting state fMRI in awake rodents

Authors: *Q. ZHANG, N. ZHANG;
Biomed. Engin., The Pennsylvania State Univ., State College, PA

Abstract: How populational neuronal firing in a local brain region relates to brain-wide network patterns is still an intriguing question. This issue has been thwarted by insufficient electrophysiological samplings from all neuronal populations and the challenge of simultaneous measurement from a large number of neurons across distributed regions during fMRI scanning. Here we analyzed the spiking rate data recorded using neuropixel probes across multiple brain regions with hundreds of neurons in each area when the animal was in darkness, and correlated the co-firing patterns derived from the electrophysiology data to resting state fMRI (rsfMRI) data acquired in separate animals. We found two cell types in the caudoputamen were coupled to other regions (thalamus, V1, motor cortex) in a distinct manner. Specifically, MSN's response was anticorrelated with the populational activity in the thalamus, whereas FSI's activity was positively correlated with the thalamus spiking. The co-firing patterns across multiple regions including caudoputamen, thalamus, V1 and motor cortex also well corresponded to the co-activation patterns in the rsfMRI data. We will confirm this result through simultaneous electrophysiological and fMRI recordings in awake rats.

Disclosures: **Q. Zhang:** None. **N. Zhang:** None.

Poster

707. Data Analysis: Neuronal Networks

Location: Hall A

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Program #/Poster #: 707.09/DD43

Topic: I.07. Data Analysis and Statistics

Support: DP160104368
DP160104316

Title: Spatial temporal organisation properties of neural oscillations in primate cerebral cortex

Authors: *X. LONG[1,2], S. G. SOLOMON[3,5], P. R. MARTIN[2,3,4], P. GONG[1,2];
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Abstract: Neural oscillations emerging from cortical circuits exhibit oscillatory bands covering frequencies from a few tenths to hundreds Hz. These oscillations have been widely observed in the cortex, but their spatial and temporal organisation properties remain unclear. In this study, we adapt concepts and methods from turbulence physics to analyse neural oscillations in local field potential (LFP) activity recorded from the extrastriate visual cortex of marmosets. We find that rather than being sustained, regular oscillations, neural oscillations at all frequency bands exhibit intermittent, bursting properties with varying peak frequencies and that these bursts are organised as spatially localized, propagating patterns. We further demonstrate that the higher the frequency bands, the smaller the averaged size of the propagating patterns and that the averaged sizes of these patterns scale as a power function of their frequencies with an exponent of -1.2. Such a scaling behaviour of the propagating patterns is invariant across different recordings. In addition, we find that there exist rich interactions of these propagating patterns across temporal scales.

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Poster

707. Data Analysis: Neuronal Networks

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 707.10/DD44

Topic: I.07. Data Analysis and Statistics

Title: Detection and characterization of gamma bursts in LFP signals

Authors: *Z. CHEN[1], F. FENG[2], D. B. HEADLEY[3], D. K. C. HO[1], D. PARE[4], S. S. NAIR[1]; [1]Electrical & Computer Engin., Univ. of Missouri Columbia, Columbia, MO; [2]Electrical & Computer Engin., Univ. of Missouri-Columbia, Columbia, MO; [3]Rutgers, The State Univ. of New Jersey, Newark, NJ; [4]Rutgers Univ. Newark, Newark, NJ

Abstract: Gamma oscillations (30-80 Hz) are expressed in many brain regions, where they are reflected in signals arising from the electroencephalogram (EEG) and local field potential (LFP). However, the accuracy of gamma burst detection and estimation is diluted by unrelated spontaneous activities and background noise. To overcome this, we developed a robust technique for the detection of gamma bursts in an LFP signal and subsequent estimation of burst frequency and duration. We tested the method on three types of artificial LFP signals: (i) those constructed by adding synthetic bursts at several frequencies to noise generated using the $1/f^{\alpha}$ characteristic; (ii) same as the previous case but with noise generated using the power density spectrum recorded *in vivo* from BL of freely behaving rodents; and (iii) LFP recorded in a large scale computational model of rodent BL.
Noise in neural signals is generally modeled with a $1/f^{\alpha}$ characteristic (pink noise) in the power spectrum where α ranges from 1.5 to 4. We considered the problem of detecting gamma bursts in the presence of such noise using the three LFP signal types presented above. The proposed detector exploits the pink noise characteristics and reduces noise using a linear predictor before bandpass filtering and energy detection. Since the gamma bursts vary in width continually, it is difficult to determine a suitable window size to determine short-term energy. Hence we adopted a Hilbert transform approach and appropriate thresholds to detect gamma bursts. The performance of this algorithm was evaluated as a function of whether linear prediction was used, characteristics of our filtering, and the threshold set for detection. Once detected, we characterized their amplitude, duration, frequency of individual detected gamma bursts, and overall burst properties such as their rate. The ROC curves of detection provided insights into performance with different burst characteristics such as amplitude and duration. For example, detection rate exceeded 50% with burst amplitudes higher than 0.4 of the noise amplitude and duration longer than 30 ms. Furthermore, an investigation of false positives in the synthetic LFP signal (case (i) above) revealed that most, ~95%, come from true bursts with high amplitude, and frequencies <10 Hz from the filter band edges, rather than from pure noise. This suggests that many false positives are actually bursts close to the filter band. However, these false positive bursts tend to have lower Hilbert transform amplitude and longer durations than the true positive bursts.

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Poster

707. Data Analysis: Neuronal Networks

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Support: NSERC Discovery Grant 356153-2013
Frank LeBlanc Chair in Spinal Cord Injury Research
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Parkinson Alberta Graduate Studentship

Title: Whole-brain cell count analysis: Crowd-sourcing manual cell counting

Authors: *L. H. KIM[1,4], L. MOLINA[4], Z. H. T. KISS[2,4], P. J. WHELAN[3,1,4];
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Abstract: Amazon's Mechanical Turk (MTurk) service is being used to crowd-source annotations at a relatively low cost and high speed across a variety of research settings, including in neuroscience. With the increasing use of data-intensive whole-brain imaging techniques, we tested the feasibility of using this crowd-sourcing platform to expedite cell counting. A C57BL/6 mouse brain was cleared using the iDISCO method with immunohistochemistry for presence of tyrosine hydroxylase expression (a marker for dopaminergic cells). The cleared brain was imaged using the LaVision BioTec Ultramicroscope II Light Sheet Microscope (2X objective with 4X optical zoom, 640 nm laser) with ethyl cinnamate-mediated refractive index matching. Images were obtained in the coronal plane of the brain with Z-step of 15 microns. The image tiles were stitched using Fiji and colour-encoded maximum intensity, 90 µm Z-projections, were produced. These images were resized to have a width of 7680 pixels while maintaining the aspect ratio and exported to JPG format with 90% quality to reduce the download time on the client side of the MTurk platform. We compared the performance of MTurk annotations under three different instructions (A, B, and C) against two expert counters using one mouse brain. These instructions varied in terms of the breadth, complexity, quality, and effort required for the task per image. Each image was annotated by at least ten unique MTurk workers. To discourage premature, incomplete submissions, they had to annotate 1-3 cell hidden sites serving as positive controls. All images and counting annotations were imported into the WholeBrain Software and registered with the Allen Brain mouse atlas. Based on the results obtained by three different instructions, we found the changes in the following variables to improve their reliability: i) simplicity of the task (less effort and time spent per image), ii) quality of instruction with troubleshooting tips and, iii) real-time validation of annotation accuracy using positive and

negative controls. Further improvements could be made by incorporating a short-training period and optimizing the images to minimize dense cellular areas and overlapping expressions.

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Poster

707. Data Analysis: Neuronal Networks

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 707.12/DD46

Topic: I.07. Data Analysis and Statistics

Support: VA RR&D RX002783

Title: A novel deep learning framework for automated lesion segmentation of structural MRI data

Authors: *I. PAPPAS[1], H. HECTOR[2], K. HAWS[3], B. CURRAN[4], A. S. KAYSER[2], M. D'ESPOSITO[1];
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Abstract: In MRI studies of patients with neuropathology (e.g. stroke, trauma), it is critical that the full extent of the brain lesion is identified. Typically, segmentation of the lesion from the areas without pathology is performed manually by one, sometimes two, experts who outline the area of damage slice-by-slice using different types of MRI scans (e.g. T1-weighted, T2-weighted, Flair). This process is time-consuming, prone to human error and likely not reliable. Deep learning techniques have recently emerged as state-of-the-art approaches to supervised learning in large, complex datasets (Krizhevsky, Sutskever, Hinton, 2012). Deep learning refers to the use of multi-layered neural networks that extract a hierarchy of features from raw input images. Despite their widespread prevalence in identifying features in 2D image datasets, deep-learning approaches have not been applied to automated lesion segmentation of 3D MRI scans. We implemented a deep learning network, which uses MRI T1 images as inputs and outputs a lesion segmentation prediction. Our approach implements a neural network that consists of two parts: (1) First a 3D-UNet network that consists of an analysis pathway including a series of 3D convolution and max pooling operations on the T1 image, and a synthesis pathway including a series of 3D up-convolution operations on the downsampled image (Çiçek et al., 2016). (2) In turn, the output feature maps are inserted into a second 3D convolutional pipeline. This pipeline employs a dual pathway architecture that processes input maps at multiple scales simultaneously: one pathway processes high-resolution samples with a series of 3D convolutions, while a second pathway processes low-resolution samples (Kamnitsas et al. 2017). The two parts thereby extract

multi-scale features of the input image and, eventually, output a segmentation mask representing the lesion. Using consensus human expert predictions as the current standard and training our deep learning network on 59 T1-weighted MRI scans from stroke patients, we produced the following results: training data mean accuracy (0.9544), sensitivity (0.9017), specificity (0.9011), and Dice coefficient (0.9014), demonstrating a very high level of accuracy in lesion segmentation. Moreover, we note that performance of our deep learning network will improve as it incorporates a large number of MRI scans from patients with brain lesions. We propose that this automated approach is a more reliable, more accurate method for brain lesion segmentation, as compared to widely used user-defined approaches.

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Poster

707. Data Analysis: Neuronal Networks

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Program #/Poster #: 707.13/DD47

Topic: I.07. Data Analysis and Statistics

Support: NIH Grant R01EB026936

Title: Calcium imaging analysis with graph filtered temporal dictionary learning

Authors: A. S. CHARLES[1], N. CERMAK[2], J. SCHILLER[3], ***G. MISHNE**[4];
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Abstract: Optical calcium imaging is a versatile imaging modality that permits the recording of neural activity, including deep neural populations as well as single dendrites and spines using two-photon microscopy. Calcium imaging analysis relies on extracting the temporal fluorescence fluctuations of each component (e.g., spines, cell bodies or dendrites) from the full video. Traditional segmentation methods used spatial information to extract regions of interest (ROIs), and then projected the data onto the ROIs to calculate the time-traces. Current methods rely on strong a-priori spatial and temporal regularization to isolate each component, which can bias time-trace estimation and restrict applicability across imaging scales.
We reverse the modeling and instead aim to minimize the spatial inference, while focusing on finding the set of temporal traces present in the data. We reframe the problem in a dictionary learning setting, where the dictionary contains the time-traces and the sparse coefficient are spatial maps. To learn the dictionary of time-traces, we introduce constraints to implicitly infer the number of components and suppress their redundancy, while ensuring stable convergence. To learn the spatial maps, we propose a new sparse coding solution, ReWeighted l1 Graph Filtering

(RWL1-GF), which adapts Reweighted l1 spatial filtering to a graph-based filter. The filter incorporates non-local spatial information, thus handling both components with compact spatial support such as cell-bodies, in addition to far ranging spatial components such as dendrites. We demonstrate on synthetic and real calcium imaging data at different scales (population and dendritic imaging) that our solution has advantages regarding initialization, implicitly inferring number of neurons and simultaneously detecting different neuronal types. We compare our method to a current state-of-the-art algorithm, Suite2p, on the publicly available Neurofinder dataset. The flexible spatial constraints allows our model to isolate both disconnected portions of the same neuron and small components otherwise over-shadowed by stronger components. This latter case is important as such configurations can cause scientifically-misleading false transients. For densely labeled dendritic data (GCaMP6f signals recorded at 30 Hz from tuft dendrites of M1 layer 5 pyramidal tract neurons), our method isolates dozens of individual spines and dendrites.

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Poster

707. Data Analysis: Neuronal Networks

Location: Hall A

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Program #/Poster #: 707.14/DD48

Topic: I.07. Data Analysis and Statistics

Title: Low-dimensional global dynamics and underlying network architectures in the *Caenorhabditis elegans* dynome

Authors: *R. S. MCGEE[1], E. SHLIZERMAN[2];
[1]Biol., [2]Applied Mathematics, Univ. of Washington, Seattle, WA

Abstract: Neurosensory networks integrate information from environmental signals to encode internal representations of prevailing conditions and direct corresponding behavior. A thorough understanding of sensory integration requires a framework that relates the physical connections that route signals with the collective neural dynamics that process and encode information. The nematode *Caenorhabditis elegans* is an attractive model system for studying the interplay of neural connectivity and dynamics, given that its stereotypic nervous system is comprised of only 302 sensory, motor, and interneurons with well-characterized electrophysical connections. We combine the known connectome structure with a physiologically appropriate neuron model to simulate the dynamics of the entire *C. elegans* network in response to stimuli. Through systematic stimulation of all neurons in the network, we find that the space of the whole-network dynamics is low-dimensional, with 6 dimensions capturing 95% of induced network activity. We show that these low-dimensional dynamics have a large number of unique attractors, which can be classified into functional groups corresponding to neural states and motor behaviors.

Furthermore, we assess the sensitivity of the observed dynamics to the particular network architecture by comparing the dimensionality and attractor characteristics of the wild-type *C. elegans* network to those of systematically perturbed networks. This work contributes to a foundational understanding of how connectivity and dynamics combine to generate complex functionality, and informs how evolved network architectures shape global network dynamics.

Disclosures: R.S. McGee: None. **E. Shlizerman:** None.

Poster

707. Data Analysis: Neuronal Networks

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Topic: I.07. Data Analysis and Statistics

Support: NSFC Grant 81671106
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Title: Automated cell segmentation for *in vivo* two-photon Ca^{2+} imaging data using deformable convolutional networks

Authors: *X. LIAO[1], J. GUAN[2], X. LI[1], Z. ZHAO[2], S. LIANG[2], L. LUO[2], H. JIA[3], X. CHEN[2]; [1]Ctr. for Neurointelligence, Chongqing Univ., Chongqing, China; [2]Brain Res. Ctr., Third Military Med. Univ., Chongqing, China; [3]Brain Res. Instrument Innovation Ctr., Suzhou Inst. of Biomed. Engin. and Technology, Chinese Acad. of Sci., Suzhou, China

Abstract: Two-photon Ca^{2+} imaging has been widely used in tracking brain activity *in vivo* with cellular resolution and high-throughput properties. However, the advances in technology have also led to a deluge of imaging data, making data analysis an extremely challenging task. In the analysis pipeline for Ca^{2+} imaging data, separating individual cells from the background is the basis for the extraction of neuronal activity information, and it is also the most time-consuming work by manual annotation. To address this issue, we aim to develop computational approaches that can facilitate the automated and efficient segmentation of neurons in Ca^{2+} imaging data. In this study, we developed an efficient method based on a deep convolutional neural network with transfer learning to perform cell detection and segmentation. We integrated deformable convolution within the network and hence enhanced the segmentation power by adapting to the variability of cell morphologies. We tested this approach on *in vivo* two-photon Ca^{2+} imaging datasets obtained from mouse cortical neurons with differently sized view fields, and particularly for the imaging cells labelled by a variety of chemical and genetically encoded Ca^{2+} indicators. Through testing, we demonstrate that the algorithm can efficiently detect and segment cells labeled by different indicators and achieve excellent results with minimal training data. In

addition, we show that this approach exhibits superior performance for cell detection and segmentation compared with the existing published tools. Therefore, the proposed method in our study can be used to process Ca^{2+} imaging data automatically and efficiently, and it will be a useful tool for *in vivo* brain activity mapping.

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Poster

707. Data Analysis: Neuronal Networks

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Program #/Poster #: 707.16/DD50

Topic: I.07. Data Analysis and Statistics

Support: Department of Defense Epilepsy Research Program

Title: Homeostatic plasticity supports cortical activity enhancement as a novel treatment for post traumatic epilepsy

Authors: *A. C. MOORE[1,2], J. WANG[3], W. XIONG[1,2], X. JIN[2,1];
[1]Indiana Univ. Sch. of Med., Indianapolis, IN; [2]Stark Neurosci. Res. Inst., Indianapolis, IN; [3]Indiana Univ., Indianapolis, IN

Abstract: INTRODUCTION: Traumatic brain injury (TBI) can cause post-traumatic epilepsy (PTE), a condition characterized by chronic seizures caused by aberrant hyperexcitability. Homeostatic plasticity is a self-tuning phenomenon where neurons adjust their intrinsic properties and synaptic transmission in response to an imposed increase or decrease in activity. It could induce a compensatory response to TBI-induced cell death and loss of activity and lead to PTE. If true, enhancing activity could suppress this compensatory response. In a partially isolated neocortex (undercut) model of PTE, we tested the hypotheses that homeostatic plasticity contributes to PTE and that enhancing activity will control PTE by suppressing homeostatic plasticity.
METHODS: Adult Thy1-GCaMP6 transgenic mice received undercut injury and activity of cortical pyramidal neurons were imaged with *in vivo* two-photon microscopy at baseline, day 1, and weeks 1-4. Correlation analyses were used to quantify changes in functional network connectivity and network topology, modeled by path length, betweenness centrality, and clustering coefficient. To treat PTE, undercut Thy1-Channelrhodopsin-2 transgenic mice received either daily intraperitoneal injection of D-cycloserine (DCS), a partial NMDAR agonist, or optogenetic stimulation on days 30-40 after undercut. Then continuous wireless EEG and video recordings were used to monitor spontaneous seizure activity for two weeks, and seizure susceptibility was measured using a pentylenetetrazol (PTZ) test.

RESULTS: *In vivo* 2-photon imaging showed acute decrease in the proportion of active neurons in the network at day 1, followed by progressive increase from week 1 - week 4 ($F(5,38 = 9.22$, $p<0.01$). Peak area followed the same trend ($F(5,38 = 8.12$, $p<0.01$), higher at week 3 compared to baseline ($p<0.01$). The trend was observed for synchronization ($F(5,38 = 19.19$, $p<0.01$), with more synchronized neurons at week 3 and 4 compared to baseline ($p<0.01$). Centrality ($F(5,46 = 12.51$, $p<0.01$) and clustering ($F(5,68 = 207.63$, $p<0.000001$) showed the same trend, with higher centrality at week 4 ($p<0.01$) and higher clustering coefficients at week 3 ($p<0.01$) compared to baseline. EEG data showed that both DCS ($p<0.01$) and LED ($p<0.01$) groups had fewer spontaneous seizures per day compared to undercut. In the PTZ test, seizure latencies to first observed seizure in both DCS ($p<0.05$) and LED ($p=0.0189$) groups were longer compared to undercut.
CONCLUSIONS: Taken together, these data suggest that undercut brain injury induced homeostatic plasticity regulation and that chronic activity enhancement reduced spontaneous seizures and seizure susceptibility.

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Poster

707. Data Analysis: Neuronal Networks

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MEYS CR LO1212
MEYS CR LH15047
KONTAKT II
FNUSA-ICRC CZ.1.05/ 1.1.00/02.0123.

Title: Deep learning for seizure forecasting in canines with epilepsy

Authors: *P. NEJEDLY, V. KREMEN, V. SLADKY, M. NASSERI, H. GURAGAIN, P. KLIMES, J. CIMBALNIK, Y. VARATHARAJAH, B. BRINKMANN, G. WORRELL; Mayo Clin., Rochester, MN

Abstract: This research introduces a fully automated, subject-specific deep-learning convolutional neural network (CNN) system for forecasting seizures using ambulatory intracranial EEG (iEEG). The system was trained and tested on 75 seizures collected over 1608 days (~38500 hours) of continuous data from 4 canines with naturally occurring epilepsy. The trained CNN models were tested in pseudo-prospective mode in all canines, and were compared

to Monte Carlo simulations using a Poisson random predictor with equal time in warning to evaluate seizure forecasting performance. The results show the CNN models forecasted seizures at rates significantly above chance in all 4 dogs ($p<0.01$, with mean 0.79 sensitivity and 18% time in warning).
The deep learning method presented here surpassed the performance of previously reported methods using computationally expensive features with standard machine learning methods like logistic regression and support vector machine classifiers. In order to show that the method can be deployed in real-time and work with implantable neurostimulation (INS) integrated with hand-held devices with limited CPU execution, we deployed the trained models on the Mayo Epilepsy Patient Assistant Device (EPAD) (Kremen V. et al. 2018). The Mayo EPAD is a tablet computer with a software application that acquires iEEG data streaming from an INS and runs a custom suite of algorithms including seizure detection and seizure forecasting. The average processing time for 30-seconds of 16 channels iEEG sampled at 400 Hz was 80 msec. The running model utilized ~120 MB of RAM. This demonstrates that our CNN model using continuous iEEG as input can be deployed on a commercial tablet computer, and provide online near real-time predictions for patients.
The seizure forecasting framework presented here reliably identified preictal periods associated with increased seizure probability and with performance exceeding previously reported approaches when tested on the same datasets. Notably, the identified pre-ictal states are generally not detectable by trained epileptologists when visually reviewing the iEEG. We demonstrated the feasibility of using our approach on a tablet computer, and in future work will apply the proposed system in prospective trials clinical trials.

Disclosures: **P. Nejedly:** None. **V. Kremen:** None. **V. Sladky:** None. **M. Nasseri:** None. **H. Guragain:** None. **P. Klimes:** None. **J. Cimbalnik:** None. **Y. Varatharajah:** None. **B. Brinkmann:** None. **G. Worrell:** None.

Poster

707. Data Analysis: Neuronal Networks

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 707.18/DD52

Topic: I.07. Data Analysis and Statistics

Support: NRF 2017R1C1B5017593
National Program for Excellence in Software at Handong Global University 2017-0-00130

Title: A novel method for multi-frequency components of a single channel in brain state classification

Authors: *D. GWON[1], M. AHN[2];
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Abstract: In general, more channels are likely to have rich information which is beneficial for classifying different brain states. However multiple channels may not be available in practical situation. In particularly, only one to two electrodes may be sufficient for deep brain stimulation in treating diseases (e.g. Parkinson'sdisease patients). Usually power spectral density (PSD) is popularly adopted as representative feature in neural signal processing. However recent studies have highlighted the importance of cross-frequency coupling in brain function. In this study, we introduce a novel method to reflect the both information in generating discriminative features of brain states from the limited number of channel. In the proposed method, covariance matrix is composed of low frequency and envelop of high frequency components from a single channel signal. Then covariance matrices of two brain states are used in generalized Eigen-value problem to obtain the spectral filter which maximizes the difference between two states. Finally the variances of the projected components by chosen spectral filters represent the discriminative feature set. The method was tested with electroencephalogram (EEG) from 52 healthy subjects; each subject conducted 100 motor imagery trials for left and right hand respectively. We calculated the classification accuracy from a single channel (e.g. C4) over 14 subjects showing themeaningful performance (70% or above) in common spatial pattern method with 64 channels. Accuracies were calculated through three different methods. First, PSDs were estimated at intervals of 8Hz from 4 to 100 Hz and used as feature vector. The second and third methods employed low frequency (4 to 40Hz / 4Hz step) and high frequency (30 to 100Hz / 5Hz step) components. In the second method (CFC_W), the covariance matrix was estimated from combined signal of low and high frequency components, and spectral filters were obtained. Meanwhile each covariance matrix was obtained per each component, and spectral filter was also estimated separately in the third method (CFC_S). We fixed the size of feature vector to 12 for fair comparison, and linear discriminant analysis was used for classification. The final mean accuracy was obtained from 30 estimates through cross validation technique. As a result, the accuracy were 63.64% (PSD), 66.70% (CFC_W) and 68.94% (CFC_S) respectively. Statistical test (Wilcoxon signed rank test) revealed that using multi-frequency information, especially CFC_S, outperforms than conventional PSD method by showing $p = 0.0203$. We conclude that our proposed method will contribute to brain state classification in a single channel data.

Disclosures: D. Gwon: None. **M. Ahn:** None.

Poster

707. Data Analysis: Neuronal Networks

Location: Hall A

Time: Wednesday, October 23, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 707.19/DD53

Topic: I.07. Data Analysis and Statistics

Support: NSF Award 1807216
NIH Award 1U19NS10746401

Title: A statistical approach to the dynamic analysis of synchronous spiking in neuronal ensembles

Authors: *S. MUKHERJEE[1], K. M. O'NEILL[2], B. L. FIRESTEIN[4], W. LOSERT[3,2], B. BABADI[1];
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Abstract: Neuronal synchrony in circuits is well-documented to occur across many areas of the brain and is closely linked to memory and learning. Characterizing synchrony has largely consisted of correlational analyses of smoothed spike trains, but more recent work has utilized likelihood models of spike train data. Existing likelihood methods use either of the two following approaches. The first approach uses spiking statistics from repeated trials to capture dynamics in synchronous spiking. The second uses spiking statistics from a single trial to fit a static multinomial Generalized Linear Model (mGLM) that characterizes the rates of all possible higher-order interactions.
While the former approach can capture dynamics in synchrony, it is developed for settings where multiple repeated trials are available and assumed to be identical. Furthermore, limiting assumptions on the relevant higher-order interactions are required to solve the problem tractably in practice. Conversely, the latter approach can characterize all higher-order interactions in a single trial but assumes that the underlying model is static and lacks an accompanying statistical framework.
To address these limitations, we propose an algorithm that dynamically identifies synchrony of any order based on spiking statistics of a single trial. Adapting recent theoretical results related to Adaptive Granger Causality (AGC) analysis, we also provide a precise statistical inference framework for dynamically quantifying the significance of synchronous activity in an ensemble of spiking neurons. In simulation studies, we demonstrate the utility of our algorithm in tracking synchronous behavior of an ensemble with statistical confidence. Applying our algorithm to microelectrode array data from general anesthesia and *in vitro* hippocampal cell cultures reveals unique information about the function of the underlying networks.

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Poster

707. Data Analysis: Neuronal Networks

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Program #/Poster #: 707.20/DD54

Topic: I.07. Data Analysis and Statistics

Support: NSF Grant 1831962

Title: Using machine learning techniques and ground-based analogs of inflight stress to assess effects of space exploration on brain function

Authors: *H. YOON[1], A. KHAN[2], L. D. SANFORD[3], L. L. WELLMAN[3], B. L. WILLIAMS[3], R. A. BRITTEN[4];
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Abstract: Potential neurocognitive impairments and associated neural structural alterations are a great concern for any deep space mission, especially the planned mission to Mars where astronauts may spend several hundred days on the planet before returning to Earth. While the effects of inflight stress, radiation and microgravity on central nervous system function in prolonged missions have been examined, their mechanisms are largely unknown. The aim of this study was to use depth electrodes and multichannel data acquisition systems to assess how neural network activity is altered during exposure to ground-based models of space-flight stressors. Neurophysiological signals from various regions in the rat brain were recorded and collected signals were preprocessed to remove artifacts using Independent Component Analysis (ICA). By applying Hilbert transform to the signals, directionality and time lag of local field potentials were identified. An unsupervised machine learning algorithm will be introduced that can analyze brain function and the impact of space-related stressors without requiring or incorporating prior knowledge of underlying brain activity patterns.

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Poster

707. Data Analysis: Neuronal Networks

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Topic: I.07. Data Analysis and Statistics

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Title: Determining the number of states in dynamic functional network connectivity using cluster validity indexes

Authors: *M. S. SALMAN[1], V. M. VERGARA[1], A. ABROL[2], V. CALHOUN[1];
[1]The Mind Res. Network, Albuquerque, NM; [2]Dept. of Psychology, Georgia State Univ., Atlanta, GA

Abstract: Background: The functional network connectivity (FNC) in the human brain demonstrate temporally dynamic behavior. The reoccurring patterns of temporal activity, or states, can be identified using clustering analysis. Due to the high dimensionality and noisy nature of the dynamic FNC (dFNC), it is difficult to determine the number of clusters or states in the data.
Methods: In this work we examine the use of several clustering validity indexes (CVIs) for determining the number of states. The Davies-Bouldin index (Davies & Bouldin, 1979), McClain-Rao index (McClain & Rao, 1975) and Ray-Turi index (Ray & Turi, 1999) are based on the ratio of within-cluster and between-cluster distances among the data points and the cluster centroids, whereas the SD index is based on the scattering (S) within clusters and the dispersion (D) between clusters (Halkidi et al., 2001). The number of clusters in a certain dataset for which it results in the minimum index value for any of these, indicates the optimal number of states in the dataset. The subjects for the current experiment have been previously used to study the replication of time-varying connectivity patterns (Abrol et al., 2017). 7000 subjects were divided into 28 equal age-matched folds. The dFNC was estimated for each subject using the averaging sliding window correlation (ASWC) method and for five different window lengths between 10-50 seconds (Vergara et al., 2019). Finally, the CVIs were estimated from the dFNC data of each fold.
Results: Fig. 1(A) shows the mean of the CVI values computed across 28 groups for number of clusters (K) between 3 and 8 and for different sliding window sizes. All subfigures indicate minimum CVI values for K=4. Fig. 1(B) presents a bar plot of the number of times each index estimated a K between 3 and 8 as optimal. Fig. 1(C) depicts the average dFNC in 4 different states as surface maps. The results clearly indicate the presence of 4 states in the data.
Conclusion: We demonstrate that the above indexes deliver a unique discrete response to provide robust automated selection of the number of states in dFNC analysis.

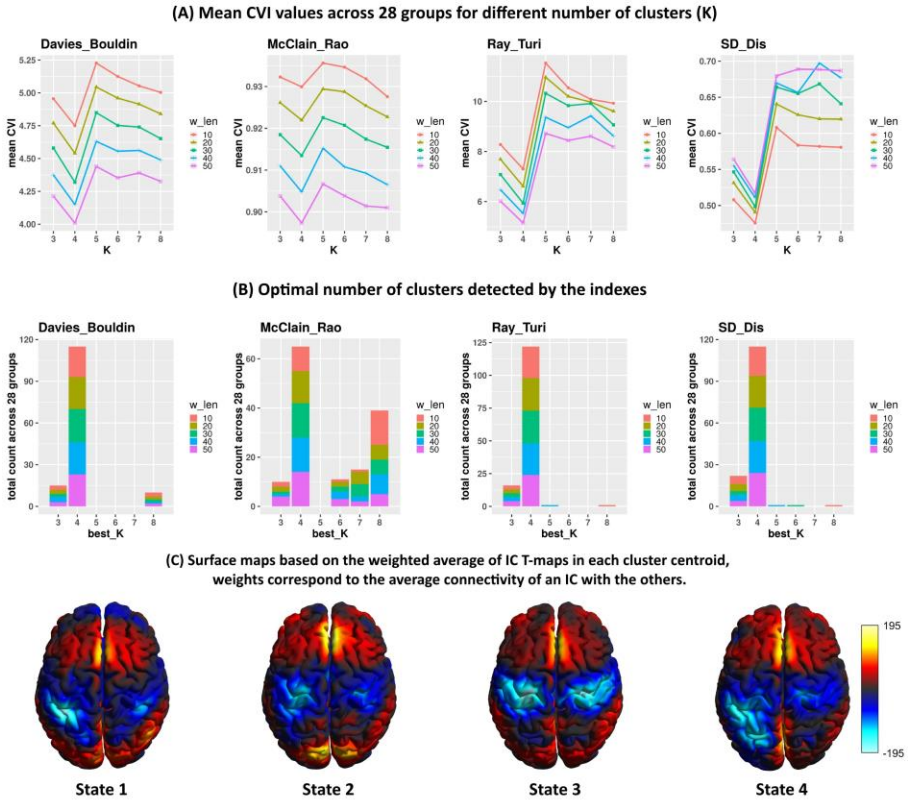

Fig 1. Indexes demonstrating robustness in determining the number of states in averaging sliding window correlation (ASWC) dynamic functional network connectivity (dFNC) data across 7000 subjects divided into 28 groups

Disclosures: M.S. Salman: None. **V.M. Vergara:** None. **A. Abrol:** None. **V. Calhoun:** None.

Poster

707. Data Analysis: Neuronal Networks

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Program #/Poster #: 707.22/DD56

Topic: I.07. Data Analysis and Statistics

Support: National Science Foundation NCS 1835364

Title: Deep learning to extract single-trial trajectories from two-photon calcium imaging

Authors: *R. TANDON[1], H. GRIER[2], M. T. KAUFMAN[2], C. PANDARINATH[1,3];
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Abstract: Activity can be monitored from vast numbers of neurons with two-photon (2P) calcium imaging. However, a tradeoff with this technique is that sampling larger volumes in space permits less frequent sampling of each neuron in time. This is a critical limitation: it is vital to sample different cortical layers and areas, since they perform different processing, yet activity changes on fast time scales. A potential solution comes from findings that activity in cortical circuits changes in coordinated ways across neurons. If activity of a given neuron can be inferred from activity of spatially-distant neurons, then reducing the sampling frequency for each neuron should be possible with minimal loss. Here, we tested whether modeling the low-dimensional dynamics of a neural population, using a subset of neurons, could enable recovering activity in other neurons. We used a publicly available 2P dataset from mouse Anterior Lateral Motor cortex (ALM; Li, Chen et al., Nature 2015) in which 145 neurons were simultaneously imaged. To uncover the population's dynamics, we used Latent Factor Analysis via Dynamical Systems (LFADS; Pandarinath et al., Nature Methods 2018), a deep learning approach that uses artificial recurrent neural networks to uncover nonlinear dynamics from high-dimensional data in an unsupervised manner. We divided the imaged plane into two sections and used LFADS to infer single-trial latent dynamics from one half (76 neurons). The single-trial activity of the 69 held-out neurons - half the field of view - could be reconstructed from the inferred dynamics with high fidelity. In these reconstructions it was generally apparent whether the trial involved a left vs. right lick, even though this information was never provided to LFADS. These results demonstrate that single-trial dynamics can be captured in calcium imaging of mouse motor cortex during behavior, and that high-resolution temporal sampling of each neuron is not necessary in order to precisely capture their activity. These results lay the groundwork for sampling massive numbers of neurons without sacrificing temporal resolution, and pave the way for trial-by-trial understanding of motor activity in a system where cell types and layers can be readily identified.

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Poster

707. Data Analysis: Neuronal Networks

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Program #/Poster #: 707.23/DD57

Topic: I.07. Data Analysis and Statistics

Title: Null-space based sampling of brain networks

Authors: *A. NANDA, M. RUBINOV;
Vanderbilt Univ., Nashville, TN

Abstract: Much of network neuroscience is devoted to applying graph theory methods to analyze structural and functional neuroimaging datasets. Statistically principled modeling of these datasets represents a cornerstone of this field. Such modeling consists of two main steps: 1) the specification of constraints based on existing neuroscientific knowledge and obtained from empirical data, and 2) the sampling of networks that satisfy these empirical constraints.
The sampling of networks with arbitrary constraints is, in general, an NP-hard problem that has no known polynomial-time solution. Current network-science approaches to such sampling fall into two general types: 1) The so-called grand-canonical methods, which include analytic approaches based on maximum-likelihood maximization. These methods are fast but can sample networks in a way which only satisfies the imposed constraints in the ensemble average and which do not satisfy nonlinear constraints (such as correlations between timeseries). 2) The so-called microcanonical methods, which include numerical randomization approaches based on simulated annealing. These methods sample individual networks with exactly satisfied linear and nonlinear constraints, but are often slow.
There thus exists the need for a fast method that can sample networks exactly with linear and nonlinear constraints. Here we describe a "null-space" based sampling method that satisfies these criteria. This method consists of two steps. In the first step, we represent empirical constraints as an underdetermined set of equations with the weights of the network as variables. In the second step, we use the null-space of the coefficient matrix to sample networks accurately and with orders of magnitude faster than simulated annealing. We apply this method to study constraints associated with dynamic functional connectivity, as measured with resting-state functional MRI. We sample time-series with constrained correlations between brain regions and module averaged time-series and the global signal, and compare module partitions of the time-varying connectivity of the sampled and empirical data. Our results show that differences in node-to-module correlations capture substantially, but not completely, properties of time-varying connectivity. The speed and accuracy of our method allows it to be applied to a wide range of datasets, to answer a range of network neuroscientific questions. The combined strengths of this method fill a gap in the current repertoire of techniques for statistical modeling of neuroscience networks and timeseries.

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Poster

707. Data Analysis: Neuronal Networks

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Topic: I.07. Data Analysis and Statistics

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Title: Deep learning convolutional networks for segmenting vasculature in multiphoton microscopy images

Authors: *C. T. POON[1], P. TEIKARI[2], K. HYNYNEN[3];
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Abstract: Background: Despite advances in deep learning networks for segmentation of 3D medical images, networks for vasculature segmentation in basic science images, particularly volumetric multiphoton microscopy image stacks, remain sparse. Current standards for segmenting vasculature in multiphoton microscopy images require semi-automated 3D vasculature reconstruction, followed by manual annotation of vasculature types. Reproducible vasculature segmentation methods would facilitate easier, faster, and more subjective quantitative analyses of image stacks. We are particularly interested in vasculature segmentation to better understand focused ultrasound and microbubble (FUS+MB) treatments to increase the permeability of the blood-brain barrier. The change in barrier permeability poses a challenge in vasculature segmentation, as the fluorescent dye used to label vasculature leaks into the extravascular space during treatment. We demonstrate the use of our network to predict the type and characteristics of blood vessels that are more sensitive to FUS+MB treatments.
Rationale: To develop a deep convolutional network for volumetric vasculature segmentation in multiphoton microscopy images. We hope that our network will be easily used by others in the multiphoton microscopy field to analyze their datasets.
Methods: All multiphoton image stacks were taken using a FV1000MPE multiphoton laser scanning microscope (Olympus Corp., Japan) with an InSight DS tunable laser (Spectra-Physics, USA), and 25x water-immersion objective lens (XLPLN25XWMP2, NA 1.05, Olympus Corp., Japan). Brain and tumor vasculature were visualized by intravenous injection of Texas Red (70 kDa) or fluorescein (70 kDa) dextran. Our deep learning network consisted of 2D and 3D convolutional filters, derived from the ZNN framework designed by Lee *et al.* for electron microscopy image segmentation (arXiv:1508.04843).
Results: Using the Average Hausdorff Distance (AVD) as a performance metric, we find that VD2D3D ("Very Deep 2D-3D") provides a reasonable segmentation of volumetric multiphoton image stacks of vasculature.
Conclusion: We demonstrate the development of a deep convolutional network based on convolutional filters that yields reasonable segmentation of multiphoton fluorescence image stacks of brain and tumor vasculature that is less time-intensive and more objective than current semi-automatic gold standards.

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