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[Authors]. [Abstract Title]. Program No. XXX.XX. 2017 Neuroscience Meeting Planner. Washington, DC: Society for Neuroscience, 2017. Online.

Poster

197. Neuronal Differentiation Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 197.01/A1

Topic: A.01. Neurogenesis and Gliogenesis

Title: improving the reregenerative potential of olfactory ensheating cells by overexpressing prostacy synthetase and its application in spinal cord repair

Authors: *H. CHENG
Ctr. for Neural Regeneration, Dept. of Neurosurg., Neurolog. Inst., Taipei Veterans Gen. Hosp., Taipei, Taiwan

Abstract: Background: Olfactory ensheathing cells (OEC), specialized glia that ensheathe bundles of olfactory nerves, have been reported as a favorable substrate for axonal regeneration. Grafting OEC to injured spinal cord appears to facilitate axonal regeneration although the functional recovery is limited. In an attempt to improve the growth-promoting properties of OEC, we transduced prostacyclin synthase (PGIS) to OEC via adenoviral (Ad) gene transfer and examined the effect of OEC with enhanced prostacyclin synthesis in co-culture and *in vivo*. Prostacyclin is a vasodilator, platelet anti-aggregatory and cytoprotective agent. **Results:** Cultured OEC expressed high level of cyclooxygneases, but not PGIS. Infection of AdPGIS to OEC could selectively augument prostacyclin synthesis. When cocultured with either OEC or AdPGIS-OEC, neuronal cells were resistant to OGD-induced damage. The resulted OEC were further transplanted to the transected cavity of thoracic spinal cord injured (SCI) rats. By 6 weeks post-surgery, significant functional recovery in hind limbs occurred in OEC or AdPGIS-OEC transplanted SCI rats compared with nontreated SCI rats. At 10-12 weeks postgraft, AdPGIS-OEC transplanted SCI rats showed significantly better motor restoration than OEC transplanted SCI rats. Futhermore, regenerating fiber tracts in the distal spinal cord stump were found in 40-60% of AdPGIS-OEC transplanted SCI rats. **Conclusions:** Enhanced synthesis of prostacyclin in grafted OEC improved fiber tract regeneration and functional restoration in spinal cord injured rats. These results suggest an important potential of prostacyclin in stimulating OEC therapeutic properties that are relevant for neural transplant therapies.

Disclosures: H. Cheng: None.

Poster

197. Neuronal Differentiation Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 197.02/A2

Topic: A.01. Neurogenesis and Gliogenesis

Support: Grant-in-Aid for Scientific Research (C) 15K09317

Title: The potential role of G-protein-coupled receptor 3 in the formation of neuronal polarity in rat hippocampal neurons

Authors: *S. TANAKA, N. SHIMADA, T. MIYAGI, I. HIDE, T. SHIRAFUJI, N. SAKAI
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Abstract: During the course of neuronal development, an immature neuron forms an axon and a dendrite, and neuronal polarity is subsequently established. PI3 kinase- and PKA-dependent pathways have been suggested to be involved in the formation of neuronal polarity; however, intrinsic factors that modulate the activity of these kinases have not been fully elucidated. On the other hand, G-protein-coupled receptor 3 (GPR3) is a member of the class A rhodopsin-type GPCR family and is highly expressed in various neurons. A unique feature of GPR3 is its ability to constitutively activate Gαs protein without the addition of ligands, which results in the elevation of the basal level of intracellular cAMP. Recently, we clarified that the subcellular dynamics of GPR3 are associated with local activation of PKA in cerebellar granular neurons. In the present study, we determined the possible involvement of GPR3 in the formation of neuronal polarity in rat hippocampal neurons. When endogenous expression of GPR3 was suppressed by siRNA, the number of neurons with Tau-1-positive neurites significantly decreased 48-60 h after siRNA transfection. Conversely, upregulated expression of GPR3 resulted in accelerated formation of Tau-1-positive neurites 24-36 h after transfection. Furthermore, GPR3-mediated acceleration of axon formation was significantly reduced by the PI3-kinase inhibitor LY294002 (10 μM), whereas it was not significantly affected by the PKA inhibitor KT5720 (2 μM). Finally, we asked if the expression of GPR3 affected the de-phosphorylation of CRMP2, which is downstream in the PI3-kinase signaling pathway. When endogenous expression of GPR3 was suppressed by siRNA, the number of neurons with pCRMP2-negative neurites significantly decreased 60 h after GPR3 siRNA transfection. These results suggested that intrinsic expression of GPR3 plays a role in the formation of neuronal polarity via the PI3 kinase-dependent signaling pathway in rat hippocampal neurons.

Disclosures: S. Tanaka: None. **N. Shimada:** None. **T. Miyagi:** None. **I. Hide:** None. **T. Shirafuji:** None. **N. Sakai:** None.

Poster

197. Neuronal Differentiation Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 197.03/A3

Topic: A.01. Neurogenesis and Gliogenesis

Support: NSF Grant 1257895

Title: Differential response of xenopus homeologs following notch signaling perturbation

Authors: *M. POWNALL[1], R. CUTLER[1], C. GOLINO[1], A. HALLERAN[3], M. MCDONOUGH[4], S. PAUDEL[2], M. S. SAHA[1]
[1]Biol., [2]Applied Sci., Col. of William and Mary, Williamsburg, VA; [3]Caltech, Pasadena, CA; [4]Univ. of Cincinnati Med. Col., Cincinnati, OH

Abstract: The evolutionarily ancient and highly conserved Notch signaling pathway mediates binary cell fate decisions between stem cell maintenance and differentiation during neural development. We have investigated how *Xenopus laevis* embryos respond over time to initial up-regulation and down-regulation of the Notch signaling pathway. These experimental embryos demonstrate initial perturbations to neural development, followed by compensation, as shown by in situ hybridization to visualize spatial gene expression of various neural marker genes. Additionally, we have taken a global transcriptomic approach to further analyze the previously observed perturbation and compensation. RNA-seq analysis shows that differential gene expression between perturbed and unperturbed embryos is initially high, but declines over time as embryos recover. We have found that homeologs present in the pseudotetraploid *X. laevis* genome show biased expression in vehicle-injected control embryos. Further, our data show that certain homeologous genes respond differentially to Notch signaling perturbation. In some instances, the endogenous bias between Long (L) and Short (S) homeologs is modified. However, in other cases, the perturbation brings about differential expression between homeologs where no endogenous bias is seen in the absence of perturbation. This suggests that polyploidy may be involved in the compensatory abilities we have observed in *X. laevis*.
Funding: NSF Grant 1257895 to MSS

Disclosures: M. Pownall: None. **R. Cutler:** None. **C. Golino:** None. **A. Halleran:** None. **M. McDonough:** None. **S. Paudel:** None. **M.S. Saha:** None.

Poster

197. Neuronal Differentiation Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 197.04/A4

Topic: A.01. Neurogenesis and Gliogenesis

Title: Characteristics of neuronal differentiated cells derived from human dental pulp stem cells (hDPSCs)

Authors: *Y. ARIMURA[1], T. KIKUCHI[1], R. YAMANAKA[1], Y. SHINDO[1], K. HOTTA[1], M. MOCHIZUKI[2], T. NAKAHARA[2], K. OKA[1]
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Abstract: The animal brain consists of many types of cells including neurons and astrocytes. The number of astrocytes increases with the evolution in the brain more than that of neurons (Nedergaard et al., 2003). Astrocytes have a large surface area and occupy the large volume in the brain (Defelipe et al., 2002),and they are not only supporting neurons but also involved in development and control of the brain function. Astrocytes receive neurotransmitters from neighboring neurons, and they cause calcium mobilization in astrocytes (Clarke et al., 2013). Furthermore, astrocytes regulate neuronal activity by releasing modulators to the surroundings synaptic cleft (Bazargani et al., 2006). Although the crosstalk between neurons and astrocytes is important, it is difficult for investigating it by using human neurons and astrocytes. In this study, we investigate the feasibility for using the neurons and astrocytes deriving from human dental pulp stem cells (hDPSCs) by using the several fluorescent imaging techniques.
We obtained hDPSCs from the cell bank of The Nippon Dental University School of Life Dentistry. In the specific neurogenic culture condition, hDPSCs differentiated into neuron-like cells. We introduced fluo-4 (calcium ion indicator) to these cells at 0, 4, 7days after differentiation, and observed calcium mobilization before and after the application of several chemicals (glutamate, ATP, and high-KCl). We observed 4 types of hDPSC-derived neuron-like cells characterized by calcium responses: induction of calcium transient after glutamate application, calcium transient after ATP application, calcium transient after high-KCl application, and sustaining calcium increase after high-KCl application. After calcium imaging experiment, we identified the cell types (neurons or astrocytes) by immunostaining using the antibodies against glial fiber acidic protein (GFAP) as glial maker and βIII-tubulin as neuron marker, and characterized each cells with specific 4 types of calcium responses. The cells with calcium mobilization by the application of ATP showed intense immune reactivity of GFAP compared with that of βIII-tubulin.

Disclosures: **Y. Arimura:** None. **T. Kikuchi:** None. **R. Yamanaka:** None. **Y. Shindo:** None. **K. Hotta:** None. **M. Mochizuki:** None. **T. Nakahara:** None. **K. Oka:** None.

Poster

197. Neuronal Differentiation Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 197.05/A5

Topic: A.01. Neurogenesis and Gliogenesis

Support: Fondecyt grant 1140477

PIA-Conicyt ECM-12 CMA BIO BIO

Title: Comparative analysis of vitamin C and vitamin A in stimulating neurite growth in neural progenitors

Authors: *F. ESPINOZA ROMERO[1], R. MAGDALENA[1], K. A. SALAZAR[2], F. A. MARTINEZ ACUÑA[3], F. J. NUALART[4]
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Abstract: Vitamin A (retinoic acid, RA) and vitamin C (ascorbic acid, AA) are involved in the differentiation of neuronal precursors. However, no study has compared the effects of RA and AA on neurite induction, or analyzed whether these vitamins impact SVCT2 and GLUT1, which are transporters of vitamin C. The aim of this work is to compare the effects of RA and AA in neural differentiation as well as subcellular localization and expression of vitamin C transporters. Neural stem cell (NSC) neurospheres derived from rat embryos (E17) were treated with RA (10μM) or AA (100μM) for 12, 24, 48, or 72 h. The effect of both molecules on cellular-induced differentiation was observed by immunocytochemistry for ßIII-tubulin using a spectral confocal laser and SIM-superresolution microscopy. Additionally, the subcellular localization and expression of SVCT2 and GLUT1 were studied by qRT-PCR and Western blot analyses.
AA and RA induced the growth of ßIII-tubulin-positive processes in neurospheres maintained *in vitro*. AA was significantly more efficient in inducing the growth of neurite processes, with a higher density at 48 h. After 48 h, AA induced an important reduction in neurite process volume; however, RA maintained neuronal differentiation. RA preferably altered the subcellular localization of SVCT2; AA altered the expression of both vitamin C transporters.
Although both AA and RA stimulated neurosphere differentiation, AA was more efficient in inducing the growth of cellular processes during the first 48 h. Longer treatment with AA reduced the neuronal processes without affecting cell viability. These results suggest that during

NSC neuronal differentiation, a fine regulation of vitamin C uptake is necessary for maintaining neurite morphology.

Disclosures: F. Espinoza Romero: None. **R. Magdalena:** None. **K.A. Salazar:** None. **F.A. Martinez Acuña:** None. **F.J. Nualart:** None.

Poster

197. Neuronal Differentiation Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 197.06/A6

Topic: A.01. Neurogenesis and Gliogenesis

Support: Zvi and Ofra Meitar Family Fund

Title: The first neurons of the human cephalic ectoderm

Authors: *I. BYSTRON
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Abstract: Accumulated evidence indicates that developing human brain has a number of anatomical, cellular and molecular features that are underdeveloped or absent in non-primate species. We report here previously unknown early neuronal populations seen outside the brain which has not been described in any other mammalian species.
We used a battery of neuronal and proliferative markers to reveal the phenotypic characteristics and migratory potential of the earliest neurons of the human brain and neurogenic placodes. Embryos from Carnegie stages (CS) 10-18 (29-43 days post-conception) were obtained according to national guidelines in Russia and from the Human Developmental Biology Resource UK. We developed a new approach to reconstruct cells in sections of the human brain, cephalic ectoderm and retina by rapid, high-resolution volume rendering of multichannel 3D confocal data sets from a Zeiss LSM 710 confocal microscope.
The preplacodal cephalic epithelium is continuous with the prosencephalic neuroepithelium prior to the fusion of the anterior neuropore. By CS12, the major divisions of the brain and the neurogenic placodes are already detectable on the basis of morphological features. We found bipolar TU-20-positive neurons scattering through the several regions of the early cephalic ectoderm and adjacent mesenchyma. Some of them migrate into periocular mesenchyme and extend non-axonal processes through the prospective pigment epithelium into the neural retina at CS13-14. Others invade the diencephalon and the presumptive cortical wall perhaps providing additional signalling information to the local stem cell niche. We applied a battery of molecular markers to reveal that these cells do not belong to the diverse neural crest population delaminating from the neural tube, and to the pioneer neurons migrating from neurogenic placodes.

The human cephalic epithelium contains hitherto unrecognized niches generating very early migratory neurons. The genetic and molecular mechanisms that underlie the relationship between migratory ectodermal neurons and complex stem cell niches of human diencephalon, retina and cortex remain to be elucidated.

Disclosures: I. Bystron: None.

Poster

197. Neuronal Differentiation Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 197.07/A7

Topic: A.01. Neurogenesis and Gliogenesis

Support: National Cancer Institute award P30CA047904

NURSA Data Resource Project from U24 grant DK097748

NIH grant HD087288

ACS grant RSG-09-054-0 1-GMC

Harold and Leila Y. Mathers Charitable Foundation Award

University of Pittsburgh Physician Scientist Training Program

Title: Interactions between endocannabinoid and glucocorticoid signaling pathways in mouse neural stem/progenitor cells

Authors: *A. L. FRANKS[1], G. A. MCCARTHY[2], R. A. CARSON[3], L. WANG[4], A. P. MONAGHAN[5], D. B. DEFRANCO[4]
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Abstract: Premature delivery occurs in nearly 12% of pregnancies and is a significant cause of morbidity and mortality for infants. Although administration of synthetic glucocorticoids (sGC) in the setting of imminent preterm delivery has led to decreased rates of common complications of prematurity (e.g. neonatal respiratory distress syndrome, necrotizing enterocolitis, intraventricular hemorrhage), longitudinal studies have associated this treatment with neurodevelopmental consequences. This effect is of particular concern in the setting of other *in utero* co-exposures with compounds that may also affect long-term outcomes of brain development and behavior, including one drug for which rates of use during pregnancy are currently rising: marijuana. Phytocannabinoids in marijuana exert effects through the

endocannabinoid (EC) signaling system, which regulates neurotransmitter release in adult brain, affects axonal growth of newborn neurons, and alters proliferation of neural stem cells. At a systems level, endocannabinoids influence organismal responses to stress that are mediated by the hypothalamic-pituitary-adrenal-axis and endogenous GC hormones. Minimal information is available, however, evaluating concurrent effects of cannabinoids and sGC in the developing brain, particularly during a potentially vulnerable period of brain development when premature infants would be exposed to antenatal sGCs. To evaluate the relationship between sGC and EC signaling, we utilized primary embryonic mouse neural stem/progenitor cell (NSPC) cultures. NSPCs were exposed to sGC either with or without EC agonists and antagonists, and select mRNA and protein expression was measured using qRT-PCR and Western blots, respectively, and cellular differentiation was assessed using immunohistochemistry. We found that enzymes involved in synthesizing and degrading EC are upregulated at the mRNA level by sGCs. Overall expression of cannabinoid receptors does not change with sGC exposure, nor does expression of glucocorticoid receptor change with cannabinoid agonism or antagonism. Furthermore, preliminary data suggest that NSPC cellular fate is uniquely altered by exposure to sGC or EC agonists/antagonists or combinations thereof. These results suggest that sGC may affect signaling mediated by the cannabinoid receptor via altered metabolism or ECs, and that the GC and EC signaling systems may interact to uniquely modulate NSPC differentiation. These findings could have implications on neurodevelopmental outcomes for infants co-exposed to these compounds *in utero*.

Disclosures: A.L. Franks: None. **G.A. McCarthy:** None. **R.A. Carson:** None. **L. Wang:** None. **A.P. Monaghan:** None. **D.B. DeFranco:** None.

Poster

197. Neuronal Differentiation Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 197.08/A8

Topic: A.01. Neurogenesis and Gliogenesis

Support: NRF Grant 2016R1A6A3A11936076

Title: Histone deacetylase ihibitor enhances neurogenic differentiation through Wnt/MAPK signaling pathway in human mesenchymal stem cells

Authors: *S. JANG[1,2], H.-S. JEONG[1,2], J.-S. PARK[1,2], S.-H. PARK[1,2]
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Abstract: Histone deacetylase (HDAC) inhibitor has potential effects on cell homeostasis, cell cycle progression, and terminal differentiation. However, the roles and mechanisms of HDAC

inhibitors on neurogenic differentiation with a Wnt signaling pathway have not yet been completely elucidated in stem cells. We hypothesized that the HDAC inhibitors regulate downstream Wnt signaling and control stem cell maintenance and neurogenic differentiation. We examined the effect and mechanism of HDAC inhibitors, such as MS-275, sodium butyrate (NaB), trichostatin A (TSA), or valproic acid (VPA), on neurogenic differentiation of human mesenchymal stem cells (hMSCs) using RT-PCR, western blot, and immunocytochemistry. Following neurogenic induction with supplementary factors, hMSCs were differentiated into neuronal cells *in vitro*. The increase in the number of neurites and neural lineage specific markers was notable when MS-275, NaB, TSA, or VPA incorporated in the medium. The expression of neurofilament-L (NFL) and neurofilament-M (NFM) were highly increased in HDACi treatment compared control medium by RT-PCR. The microtubule-associated protein 2 (MAP2) level was increased after MS-275 or VPA treatment. The expression of Wnt1, Wnt2, and LRP5/6, which are canonical Wnt and Wnt ligands, in hMSCs treated with VPA was significantly greater compared to that of control medium. However, the expression of Wnt5 and Fzd4 were increased with MS-275, NaB or TSA in the medium. There were no changes in the expression of b-catenin and GSK-3b. Interestingly, Wnt3 expression was highly increased in MSCs with VPA and Wnt5a was expressed with MS-275, NaB, or TSA treatment by real time RT-PCR. Wnt5a level was upregulated after neurogenic induction with MS-275, NaB, or TSA treatment by western blot assay. Furthermore, we found that the JNK expression was increased after NaB or TSA treatment, whereas ERK level was decreased. Treatment of MS-275 and VPA upregulated GSK-3b and b-catenin. In conclusion, these findings indicated that HDACi could induce neurogenic differentiation of MSCs by activating canonical Wnt or non-canonical Wnt signaling pathway.

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

Poster

197. Neuronal Differentiation Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 197.09/A9

Topic: A.01. Neurogenesis and Gliogenesis

Support: Progetti Ateneo Sapienza 2014

Progetti Ateneo Sapienza 2015

Progetti Ateneo Sapienza 2016

Title: Exosome-induced differentiation of neural stem progenitor cells

Authors: *G. POIANA[1], E. STRONATI[1], R. CONTI[1], Z. BOUSSADIA[2], M. SARGIACOMO[2], E. CACCI[1], S. BIAGIONI[1]
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Abstract: Cell-cell communication is a crucial event during neural development and differentiation. Extracellular membrane vesicles, including exosomes, have been recently discovered to play an important role in these events. Exosomes originate from multivescicular bodies, which may fuse with the plasma membrane and release exosomes in the extracellular space. Exosomes may contain proteins and nucleic acids and can either reach the blood flow and be transported all over the organism, or can fuse with the plasma membrane of other cells and release their content into the target cell. They have been demonstrated to exhert an influence on a large number of biological functions and to be implicated in the progression of several pathologies. They may also play an important role during tissue development, and we have been specifically interested to investigate their role in neural differentiation.
Neural stem progenitor cells (NSPCs), obtained from E13,5 embyos, can be maintained in culture under proliferating conditions (i.e. in the presence of bFGF and EGF). Upon treatments with growth factors they may differentiate towards neuronal or glial phenotypes, or both.
In this work we were interested in determining whether NSPCs can produce and secrete exosomes and if exosome content may exhert a developmental effect on proliferating and differentiated cells.
The capability of these cells to produce and release exosomes was assessed by analyzing the presence of specific markers, such as CD63 and TSG101. Our results indicate that cultured NSPCs produce and secrete exosomes both under proliferating conditions as well as when they are cultured in differentiation medium (e.g. upon removal of EGF). Treatment of proliferating NSPCs with exosomes derived from differentiated cells triggers cell differentiation, as demonstrated by glial and neuronal marker expression; the expression of these markers is also enhanced when exosomes are added to differentiated NSPCs cultures. We also show that the effects of exosome treatment are dose dependent.
Characterization of protein and nucleic acid content of NSPCs exosomes is currently under way.

Disclosures: **G. Poiana:** None. **E. Stronati:** None. **R. Conti:** None. **Z. Boussadia:** None. **M. Sargiacomo:** None. **E. Cacci:** None. **S. Biagioni:** None.

Poster

197. Neuronal Differentiation Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 197.10/A10

Topic: A.01. Neurogenesis and Gliogenesis

Support: Stanley center

Title: Design and validation of an *In vivo* functional screen for key regulators of neocortical development

Authors: *A. S. SHETTY[1,2], F. SCHMIDT[3], F. ZHANG[4], R. J. PLATT[3], P. ARLOTTA[1,2]
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Abstract: Classical reverse genetic studies in mice have historically required long timescales, and the number of candidate genes that can be screened by such analysis is not easily scalable. Through advances in next-generation sequencing combined with methods for characterization of purified neuronal subtypes, we now have a much better understanding of the genes that define the transcriptional profile of different projection neuron subtypes. The next big question is which of these few 1000 genes are the key regulators of fate specification, survival, maintenance and function of a projection neuron subtype. Using (CRISPR)/Cas9 technology, a powerful and invaluable method of genetic manipulation, we have set up a platform for screening key regulators of neocortical development in mouse embryos. By delivering a pooled single-guide RNA library to the embryonic mouse brain we show that we can assay on the order of hundreds of candidate genes per experiment *in vivo*, and that differential effect can be detected within a few days of construct delivery, allowing rapid turnaround. This method offers promise for high throughput *in vivo* screening of candidate developmental regulators.

Disclosures: A.S. Shetty: None. **F. Schmidt:** None. **F. Zhang:** None. **R.J. Platt:** None. **P. Arlotta:** None.

Poster

197. Neuronal Differentiation Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 197.11/B1

Topic: A.01. Neurogenesis and Gliogenesis

Support: NICHD-R00HD058044

Title: Epigenetic regulation controls Fgf8 expression in the olfactory placode during gonadotropin-releasing hormone neuron emergence

Authors: *M. L. LINSCOTT, ***M. L. LINSCOTT**, W. C. CHUNG
Biol. Sci., Kent State Univ., Kent, OH

Abstract: The co-existence of histone modifications on chromatin architecture are key developmental regulatory components, which maintain genes in an active or inactive state. Two modifications, H3K27me3 (a repressive histone) and H3K4me3 (an activating histone), form bivalent domains that regulate the chromatin compaction status of genes, and are thought to respond to developmental cues. However, very little is known about how bivalent domains function to regulate gene expression. Here, we present evidence that fibroblast growth factor 8 (FGF8), a critical developmental regulatory gene, is significantly impacted by dynamic histone modifications. To this end, we used the mouse olfactory placode (OP) as a model of bivalent gene regulation in the context of FGF8-induced GnRH neuron fate-specification, a critical process that controls the hypothalamus-pituitary-gonadal axis, and therefore reproductive success. Currently, we are studying whether differential histone modifications at the *Fgf8* locus are under the control of epigenetic mechanisms. Indeed, at embryonic day (E) 9.5, *Fgf8* harbors both H3K4me3 and H3K27me3, while at E13.5 only H3K27me3 is present, indicating a possible role for *Fgf8*-dependent histone modifications in specifying GnRH cell fate. Furthermore, *Fgf8* in the E9.5 OP is enriched with 5hmC at selective CpG islands, which decreases with age. Concomitantly, robust increases in all three known Ten-eleven Translocation enzymes (*Tet*), and *Dnmt3a*, an enzyme responsible for *de novo* DNA methylation are also upregulated in the OP with age. Further studies will analyze how histone modifications and other transcription factors interact to coordinate histone modifications on the *Fgf8* gene.

Disclosures: M.L. Linscott: None. **W.C. Chung:** None.

Poster

197. Neuronal Differentiation Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 197.12/B2

Topic: A.01. Neurogenesis and Gliogenesis

Title: Inducing neurite outgrowth using a neuroblastoma cell culture model

Authors: *M. MURZELLO, E. CASEY, D. COOK-SNYDER
Carthage Col., Kenosha, WI

Abstract: Stroke is the fifth leading cause of death in America. When an ischemic stroke occurs, astrocytes become reactive and form a glial scar surrounding the area of dead neurons. The glial scar hinders the injury from spreading, but also prevents healthy neurons from repairing the dead tissue by inhibiting neurite regeneration. The focus of the research was to further understand neurite outgrowth using a neuroblastoma cell culture model. To induce differentiation, N2a neuroblastoma cells were either exposed to different concentrations of retinoic acid added at various time points in the cell's life cycle, serum starvation, or a combination of both. The retinoic acid was added over a period of two days. Both fetal bovine serum and calf serum were

tested. The results suggest that serum starvation and the addition of retinoic acid increases neurite length and outgrowth. Specifically, serum starved N2a cells in fetal bovine serum exposed to high concentrations of retinoic acid at plating showed the highest percentage of differentiated cells. Confocal microscopy will be used to examine the N2a neuroblastoma cells exposed to the various conditions. The conditions found to best differentiate N2a cells can aid future research in developing treatments in which the brain will repair connections lost through neurite regeneration. The long term goal of the project is to improve patient recovery after stroke by improving neurite outgrowth.

Disclosures: M. Murzello: None. **E. Casey:** None. **D. Cook-Snyder:** None.

Poster

197. Neuronal Differentiation Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 197.13/B3

Topic: A.01. Neurogenesis and Gliogenesis

Title: Regulation of Traf2 and Nck interacting kinase (TNIK) alternative splicing in human tissues and during neuronal differentiation

Authors: V. GUMINA[1,2], C. COLOMBRITA[1], P. BOSSOLASCO[1], A. MARASCHI[1], F. SASSONE[1], E. BURATTI[3], V. SILANI[1,4], *A. RATTI[1,4]
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Abstract: Traf2 and NcK interacting Kinase (TNIK) is a Ser/Thr kinase described as a genetic risk factor for psychiatric disorders. Highly expressed in the brain, it performs an important role in synapse formation, neurogenesis and cytoskeleton dynamics. Eight different splicing isoforms, resulting from combination of three alternative exons (ex15, 17, 22), are described for *TNIK*. All findings about TNIK protein are referred to the longest isoform, while the biological roles of the other isoforms are very poorly investigated. We have recently demonstrated that TDP-43, a RNA-binding protein (RBP) associated to neurodegenerative diseases amyotrophic lateral sclerosis (ALS) and frontotemporal lobar dementia (FTLD), promotes the skipping of TNIK exon 15 (87 bp), which encodes an in-frame 29 aminoacidic sequence in the intermediate region of the protein. As *TNIK* alternative exon 15 shows a strong conservation along phylogenesis and its biological function is not clear yet, we further characterized its alternative splicing in human tissues and in different *in vitro* neuronal differentiation models, including iPSC-derived neurons. We found that *TNIKex15* mRNA isoforms were prevalent in brain, spinal cord and skeletal muscle and less expressed in lung, kidney and testis. When we induced neuronal differentiation

in vitro by treating human neuroblastoma SK-N-BE cells with retinoic acid or by differentiating neurons from human iPSCs, a significant increase of TNIKex15 isoforms was observed both at transcript and protein level. Immunofluorescence analysis showed a prevalent perinuclear distribution of TNIKex15 protein in neuron-differentiated cells. TDP-43 protein levels remained unchanged during *in vitro* neuronal differentiation, suggesting the potential involvement of other splicing factors in regulation of *TNIK* exon 15 alternative splicing. We focused on NOVA1, a RBP with a specific splicing activity in neurons, and we observed an increase of *TNIKex15* mRNA isoforms upon NOVA1 over-expression. In a minigene splicing assay, NOVA1 completely abolished TDP-43 exon skipping activity on *TNIK* exon 15 although UV-CLIP assay excluded a direct binding of NOVA1 on exon 15 flanking introns, suggesting an indirect effect. Our data show that alternative splicing of *TNIK* gene is differently regulated in human tissues and during neuronal development, suggesting a specific role of TNIKex15 isoforms in human brain and during differentiation. As the TNIKex15 protein isoforms show a specific sub-cellular localization, their biological function needs to be further characterized also in relationship to psychiatric disorders.

Disclosures: **V. Gumina:** None. **C. Colombrita:** None. **P. Bossolasco:** None. **A. Maraschi:** None. **F. Sassone:** None. **E. Buratti:** None. **V. Silani:** None. **A. Ratti:** None.

Poster

197. Neuronal Differentiation Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 197.14/B4

Topic: A.01. Neurogenesis and Gliogenesis

Title: Expression of glycoprotein non-metastatic melanoma B in the prenatal rat brain

Authors: *S. YOKOYAMA, H. ZHU
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Abstract: The glycoprotein non-metastatic melanoma B (Gpnmb) is a type-I transmembrane protein that is produced by various types of normal cells including melanocytes, osteoclasts, osteoblasts, and dendritic cells in peripheral blood, as well as by various carcinoma cells. An increasing number of studies have described that Gpnmb is abundantly expressed in invasive glioblastomas, suggesting its involvement in tumor progression and metastasis. We previously reported that Gpnmb is produced by macrophages and microglia in the normal central nervous system of postnatal and adult rats (Huang, J.-J. *et al.*, Brain and Behavior 2, 85-96, 2012; Yokoyama, S. Soc. Neurosci. Abstr., 674.14, 2016). To further examine whether Gpnmb was expressed in the embryonic rat brain, we performed immunohistochemical analysis. Frozen coronal sections were prepared from normal rat brain at embryonal days (E) 13 and 16, and were processed for both immunoperoxidase and immunofluorescent staining. At E13, Gpnmb-

immunoreactive (IR) cells was detected in the ventricular wall surrounding neocortex neuroepithelium adjacent to the lamina terminalis. Weak Gpnmb-IR was observed in the ventricular wall close to the pineal gland, but not in pituitary gland and velum medullare. At E16, regional difference in Gpnmb-IR was prominent. Gpnmb-IR was predominantly distributed in the choroid plexus of the lateral ventricle, with only weak IR being detected in the ganglionic eminence. In the hippocampal formation, Gpnmb-IR was seen in the dentate gyrus, primary dentate neuroepithelium, and fimbrial glioepithelium. The Gpnmb-IR was also found in the ependymal cells of the pineal recess of the third ventricle. These results suggest that Gpnmb plays multiple roles in the development of prenatal rat brain. In double immunofluorescent staining of the choroid plexus and ventricular zone, Gpnmb-IR cells were frequently positive for Sox2, a marker for neural stem/ progenitor cells. These data suggest that Gpnmb plays important role in neuronal differentiation during early brain development.

Disclosures: S. Yokoyama: None. **H. Zhu:** None.

Poster

197. Neuronal Differentiation Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 197.15/B5

Topic: A.01. Neurogenesis and Gliogenesis

Support: ICMR- BMS/FW/CMB/2014-23710/oct-2014/14/DL/GOVT

Institutional Research Grant

Title: Stereological estimation of NeuN and GFAP labeled cells in the developing human cochlear nucleus

Authors: *S. SAINI[1], C. KAUR[1], T. G. JACOB[1], A. THAKAR[2], K. K. ROY[3], T. ROY[4]
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Abstract: Cochlear nucleus (CN) is a major relay center in the auditory pathway.Though extensive data is available regarding development of the animal CN, developmental and maturational studies in the human CN are still lacking. The present study reports the distribution and expression pattern of Neuron-specific nuclear protein (NeuN) that is a marker of both mature as well as progenitor neuronal cellsand Glial Fibrillary Acidic Protein (GFAP) during the developing human CN.Seven fetal brains (18-28 weeks of gestation) were collected after obtaining clearance from the Institutional Ethics Committee at All India Institute of Medical Sciences, New Delhi. The brainstem were dissected and fixed in 4% buffered paraformaldehyde (0.1M phosphate buffer, pH 7.4), cryopreserved in 30% sucrose and sectioned on a

cryomicrotome to obtain 40 µm thick serial sections and every 5th section were immunostained with NeuN (ab177487, 1:500) and GFAP (ab10062, 1;1000) using standard protocol. The total number of neurons and astrocytes were estimated by using the Optical Fractionator probe on StereoInvestigator software (Microbrightfield Inc. VT, US). NeuN staining was observed in nuclei, perikarya and in some neuronal processes. The estimated total number of neurons immunostained by NeuN were 30,694; 31,823; 37,546; 44,345; 74,054, and 81,228 in 18, 20, 22, 23, 25, 27 and 28 weeks respectively. The count by GFAP immunostaining were 32,049; 31,872; 34,049; 39,049; 39,889; 67,114 and 94,614 in the same ages, respectively. Thus, total cell counts increase with increasing gestational ages and neurogenesis precedes gliogenesis in the human CN.

Disclosures: S. Saini: None. **C. Kaur:** None. **T.G. Jacob:** None. **A. Thakar:** None. **K.K. Roy:** None. **T. Roy:** None.

Poster

197. Neuronal Differentiation Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 197.16/B6

Topic: A.01. Neurogenesis and Gliogenesis

Support: Fidia Farmaceutici grant n° 22789

Title: Liposomes treatment antagonized dendritic spine loss and reduction of neurogenesis in hippocampus of chronically stressed rats

Authors: *M. C. MOSTALLINO[1], F. BIGGIO[2], L. BOI[3], V. LOCCI[2], G. TOFFANO[4], G. BIGGIO[5,1]
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Abstract: Phosphatidylserine is a naturally occuring phospholipid wich is found in the cell membranes of a wide variety of organism from bacteria to man. The presence of phosphatidylserine in the neuronal membranes is not limited to a static structural function but it also important to the regulation of many metabolic processes, indicating that this phospholiopid may play a role in regulating crucial cerebral functions such as neuronal excitability, message tranduction, neurotransmitter activity and neuronal plasticity.
Given that treatment with phospholipids improves brain neuron activity while pathological processes and/or natural aging reduce the renewal of the phospholipids membrane component, we used phospholipids liposomes, containing phosphotidilserine and phosphatidilcoline to prevent or ameliorate the negative effects of stress in neruronal plasticity. Neurogenesis and

dendritic spine density were evaluated in stressed rats treated with liposomes. Liposomes were intraperitoneally administred (once of day) for 4 week in rats exposed to chronic unpredictable stress for 5 weeks. As expected the neureogenesis and dendritic spine density were decreased in rats exposed to chronic stress. On the contrary, liposomes treatment abolished the reduction of nerurogenesis and dendritic spine density elicited by chronic stress. Moreover, treatment with liposomes increased the density of dendritic spine in control not stressed rats. These results demonstrate that liposomes treatment has great efficacy in antagonizing the neurochemical and molecular consequences elicited by chronic exposure to stress in the brain. The mechanisms underlying the beneficial effects of liposomes might be mediated through actions exerted by phospholipids on neuronal membranes, neurotransmitters and/or interaction with trophic factors (NGF, BDNF). These mechanisms in turn might increase the efficacy of such treatment in people with impairment of cognitive function.

Disclosures: M.C. Mostallino: None. **F. Biggio:** None. **L. Boi:** None. **V. Locci:** None. **G. Toffano:** None. **G. Biggio:** None.

Poster

197. Neuronal Differentiation Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 197.17/B7

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grans EY024376

NIH Grant EY011930

NIH Grant EY013811

NIH Grant EY022228

Title: Essential roles for mitochondria biogenesis regulator Nrf1 in retina development and homeostasis

Authors: *T. KIYAMA[1], C.-K. CHEN[2], S. W. WANG[3], P. PAN[1], S. TAKADA[4], W. KLEIN[3], C.-A. MAO[1]
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Abstract: Mitochondria biogenesis is fundamental for energy metabolism. Dysregulation of mitochondrial biogenesis has been implicated in the pathologies of a number of neurodegenerative diseases. To better understand the function of mitochondria biogenesis in

neuronal development, we investigated the *in vivo* role that nuclear respiratory factor 1 (Nrf1) has in the mouse retina. Nrf1 encodes an evolutionarily conserved transcription activator that regulates a large number of nuclear genes required for mitochondrial biogenesis and respiratory function. Nrf1 is highly expressed in retinal progenitor cells (RPCs), photoreceptors (PRs), and ganglion cells (RGCs). We generated an $Nrf1^{flox}$ mouse line and conditionally deleted Nrf1 in RPCs with Six3-Cre, and in rod PRs with rhodopsin-iCre. An $Nrf1^{LacZ}$ knock-in mouse line was made to monitor the spatiotemporal expression of Nrf1. In RPC-Nrf1 KO retinas, proliferation of RPCs was reduced. Newly differentiated RGCs failed to migrate and eventually died. The mutant RGCs were defected in extending axons on coated petri dish. Using RNA-seq analysis, we uncovered 1085 genes whose expression was affected in RPC-Nrf1 KO retinas. Transcriptome analysis revealed that genes involved in neuronal projection were severely down-regulated in the absence of Nrf1, and the expression of 31 genes involved in various mitochondria functions were altered in RPC-Nrf1 KO retina. In Rod- Nrf1 KO retinas, severe rod degeneration was observed beginning at 6 weeks, followed by complete PR degeneration by 3 months. In Nrf1 KO PRs, the number of mitochondria increased, however the location and morphology of mitochondria were abnormal compared to control retinas. Consistent with these phenotypes, the Nrf1 KO PRs displayed impaired mitochondrial activity, and the dark-adapted ERG a-wave for rod-Nrf1 KO mice declined over time and completely diminished in 3 months. Furthermore, we examined Nrf1 expression in an optic nerve crush model for glaucoma and light-induced PR degeneration model. In both models, Nrf1 is downregulated prior to the onset of RGC and PR degeneration. Together, these results demonstrate the crucial role of Nrf1-mediated mitochondria biogenesis in retina development and homeostasis.

Disclosures: **T. Kiyama:** None. **C. Chen:** None. **S.W. Wang:** None. **P. Pan:** None. **S. Takada:** None. **W. Klein:** None. **C. Mao:** None.

Poster

197. Neuronal Differentiation Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 197.18/B8

Topic: A.01. Neurogenesis and Gliogenesis

Support: Medical Research Council, UK

Title: Mitotic cerebellar granule cell precursors can extend neurites, undergo migration and retract their processes prior to each cell division and their differentiation depends on the levels of NeuroD1 expression

Authors: *M. HANZEL[1], M. E. HATTEN[1], R. J. WINGATE[2]
[1]Developmental Neurobio., Rockefeller Univ., New York, NY; [2]King's Col. London, London, United Kingdom

Abstract: Cerebellar granule cell precursors (GCPs) are born at the rhombic lip and migrate dorsally across the cerebellar anlagen to form a secondary germinative epithelium, the external germinal layer (EGL). Here, the precursors undergo a period of transit amplification during which they proliferate extensively to produce the most numerous neuronal cell type in the brain. The morphological sequence of events that characterizes the differentiation of GCPs in the EGL is well established. However, no research has correlated GCP morphologies with their differentiation status *in vivo*. Here, we examine the morphological features and transitions of GCPs in the cerebellum. We label a subset of GCPs with a stable genomic expression of green fluorescent transgene and follow their development within the EGL in static images and using time-lapse imaging in chicken and mouse. Using immunohistochemistry, we observe cellular morphologies of proliferating and differentiating GCPs to better understand their differentiation dynamics. Results show that mitotic activities of GCPs are more complex and dynamic than currently appreciated. While most GCPs divide in the outer and middle EGL, some are capable of division in the inner EGL. Some GCPs remain mitotically active during tangential migration and retract their processes prior to each cell division. The mitotically active precursors can also express differentiation markers such as TAG1, Tuj1 and NeuroD1. Therefore, we explore the expression of NeuroD1 on a cellular level in GCPs using its conserved non-coding element and conclude that the levels of NeuroD1 expression can differ between neighboring GCPs. Additionally, we explore the function of NeuroD1 in cerebellar development by overexpressing the protein at the chicken rhombic lip at different developmental stages. Results suggest that misexpression of NeuroD1 promotes context-dependent differentiation and can alter cellular behavior. When misexpressed in GCPs, NeuroD1 leads to premature differentiation, defects in migration and reduced cerebellar size and foliation. Overall, the results provide the first characterization of individual morphologies of mitotically active cerebellar GCPs *in vivo* and explore in detail the expression and role of the differentiation factor NeuroD1 on the development of rhombic lip derivatives.

Disclosures: **M. Hanzel:** None. **M.E. Hatten:** None. **R.J. Wingate:** None.

Poster

197. Neuronal Differentiation Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 197.19/B9

Topic: A.01. Neurogenesis and Gliogenesis

Title: Erythropoietin overexpression in murine central nervous system accelerates postnatal GABAergic development

Authors: *K. KHALID[1], J.-M. FRITSCHY[2], E. SCHNEIDER GASSER[1]
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Abstract: Erythropoietin (Epo), a hypoxia-inducible hormone, is highly expressed in the neural tube during embryonic development, maintaining a low expression in the brain after birth. Epo's classical function in hypoxic conditions is haematopoietic, acting on proliferation and differentiation of erythroid precursor cells (EPCs). Our previous work has demonstrated that Epo overexpression (Tg21 mouse model) can accelerate postnatal brain maturation, by acting on proliferation and early differentiation of neural precursor cells (NPCs). Here, we determined whether the postnatal maturation of the GABAergic system is affected by Epo in the Tg21 mice. Immunohistochemical expression of four major hippocampal interneurons: two calcium-binding interneurons, Parvalbumin (PV) and Calbindin (CB), and two neuropeptide-expressing interneurons, Neuropeptide Y (NPY) and Somatostatin (SOM), was evaluated across postnatal ages (P3-P21) and adulthood (P60). Additionally, inhibitory postsynaptic potentials (IPSCs) in principal CA1 cells were evaluated. Overall, Epo overexpression led to an increase in the number of PV interneurons in CA3, CB interneurons in CA1 and NPY interneurons in hilus of the hippocampus at P14, with no changes observed in SOM interneurons. Our results indicate that Epo acts on the GABAergic system, accelerating the postnatal peak of expression of PV, CB and NPY from the second and third postnatal week to P14. Whether this phenomenon of accelerated interneuron maturation in a model of Epo overexpression persists under hypoxic injury conditions and is neuroprotective, remains to be investigated.

Disclosures: K. Khalid: None. **J. Fritschy:** None. **E. Schneider Gasser:** None.

Poster

197. Neuronal Differentiation Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 197.20/B10

Topic: A.01. Neurogenesis and Gliogenesis

Support: NSF Grant 1257895

NIH Grant 1R15HD077624-01

Title: An analysis of the downstream effects of ttyh perturbation

Authors: *C. RATNAYAKE
Biol., Col. of William and Mary, Williamsburg, VA

Abstract: The Notch signaling pathway, a highly conserved cell signaling system present in all metazoans, affects cell-cell communication, genetic regulation and cell differentiation during

embryonic and adult life. Notch perturbation in Xenopus laevis embryos shows severe defects at early stages of development (neural tube stages). However, as development progresses there is a compensatory response in which embryos show increasingly normal phenotypes. In an effort to discover the genes responsible for this compensatory response, we performed both microarray and RNA-Seq analysis comparing embryos with the Notch signaling pathway over-expressed and control embryos. One major gene family that was differentially expressed in response to the mis-regulation that may play an integral role in this compensatory mechanism was the tweety gene family. The tweety (ttyh) genes encode large chloride channels and are implicated in a variety of cellular processes from cell division to tumorigenesis. Here, we address the effects of ttyh1 perturbation on neural development, morphology, and function. Capped ttyh1 mRNA was unilaterally microinjected at the two cell state of Xenopus laevis. The injected embryos were tracked through development and assayed for growth, mortality, and downstream genetic expression. We found that ttyh overexpressed embryos exhibited delayed growth compared to GFP injected. Further, the injected embryos had severe morphological and developmental defects, exhibiting deformed blastopores and aberrant gastrulation. In situ hybridization revealed differential expression of downstream marker gene neural beta tubulin. This suggests that the ttyh plays an important role in the commitment of a cell to a differentiated neural state. Our work shows that the ttyh gene family plays an integral role in neural development, influencing both gastrulation and neural fate determination.

Disclosures: C. Ratnayake: None.

Poster

197. Neuronal Differentiation Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 197.21/B11

Topic: A.01. Neurogenesis and Gliogenesis

Support: JSPS 17H05775

JSPS 17K07102

The Cell Science Research Foundation

Mochida Memorial Foundation for Medical and Pharmaceutical Research

Takeda Science Foundation

Brain Science Foundation

Title: Assembly of inhibitory circuitry by FoxG1, a gene associated with autism spectrum disorders

Authors: *G. MIYOSHI[1], Y. UETA[1], H. OSAKI[1], M. TANAKA[1], C. HANASHIMA[2], G. FISHELL[3], M. MIYATA[1]
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Abstract: The mammalian cerebral cortex is composed of a sophisticated neuronal network that processes higher order information such as perception, consciousness and memory. Thus, mutations in genes involved in the specification and migration of neurons as well as the formation of the correct synapses within the six-layered neocortex often lead to neurological diseases. Recent discoveries of both gain- and loss-of-function mutations in the transcription factor FoxG1 in patients with autism spectrum disorders strongly suggest that proper FoxG1 gene dosage is essential for mental health. By taking advantage of mouse genetic strategies, we have recently revealed that FoxG1 expression levels change dramatically during the course of embryonic brain development in a manner that is tightly correlated with the differentiation and maturation stage of neurons. We have uncovered that these dynamic changes in FoxG1 expression are critical in the determination of the laminar identity of pyramidal neurons. Here, we demonstrate that FoxG1 is required at distinct developmental stages of specification, migration and maturation of GABAergic interneurons that play key inhibitory roles in the neocortical circuit. These findings provide clarity as to the dose-dependent requirement for FoxG1 and why even relatively minor changes in its expression during development result in severe neurological impairment.

Disclosures: G. Miyoshi: None. **Y. Ueta:** None. **H. Osaki:** None. **M. Tanaka:** None. **C. Hanashima:** None. **G. Fishell:** None. **M. Miyata:** None.

Poster

198. Axon: Adhesion and Cytoskeleton

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 198.01/B12

Topic: A.05. Axon and Dendrite Development

Support: NHMRC Grant APP1068317

Title: Remodelling of the endoplasmic reticulum into growth cone filopodia is mediated by STIM1

Authors: *M. P. PAVEZ[1], R. GASPERINI[2], L. C. FOA[2]
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Abstract: The spatial and temporal regulation of calcium signalling at the neuronal growth cone is essential for axon guidance and motility. Growth cone filopodia are the “first responders”

during axon guidance. Filopodia transduce guidance cues through receptor-mediated calcium transients however, the mechanisms that regulate and sustain spatiotemporal calcium signals at filopodia and precisely how these signals are instructional for growth cone motility are unknown. As a principal store of intracellular calcium, the endoplasmic reticulum (ER) would be predicted to have a vital role in growth cone calcium regulation, although ER function at growth cone filopodia is largely unexplored. Recently, synaptic calcium release by ER has been shown to be crucial for vesicle function in a mechanism that is regulated by stromal interacting molecule (STIM1). In growth cones, STIM1 expression is necessary for attractive turning towards the calcium-dependent attractant BDNF, where STIM1 functions to sustain calcium by refilling depleted ER stores through store-operated calcium entry (SOCE). STIM1 also regulates motility towards the calcium-independent cue Sema-3a, suggesting that STIM1 functions through multiple pathways. Here we demonstrate that filopodial ER, STIM1 and microtubules function cooperatively to regulate growth cone steering. STIM1 interacts with the microtubule cytoskeleton through direct binding to the plus-end-binding protein, EB1/3, and this interaction is required for the remodelling of ER to peripheral areas of steering growth cones. Filopodial protrusion and stabilisation by microtubules is a well-known correlate of directed growth cone motility, but how microtubules are recruited to facilitate SOCE at filopodia has not been determined. Here we report that microtubule-ER remodelling in sensory neuron filopodia is dependent on STIM1 expression. Our data indicate that STIM1 is necessary for microtubule polymerization and plus-end tip complex recruitment to the motile side of turning growth cones. Additionally, using an ER-targeted low affinity calcium indicator we demonstrate that ER-calcium dynamics and spatiotemporal localization of ER are perturbed in growth cones with reduced STIM1 expression. Together, these data demonstrate that in response to guidance cues, STIM1 provides a direct link between ER-derived calcium signals and cytoskeletal organisation. Our data support a mechanism whereby ER remodelling, particularly in filopodia, sustains crucial spatiotemporal regulation of calcium which is instructive for pathfinding axons during wiring of developing neural circuitry.

Disclosures: **M.P. Pavez:** None. **R. Gasperini:** None. **L.C. Foa:** None.

Poster

198. Axon: Adhesion and Cytoskeleton

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 198.02/B13

Topic: A.05. Axon and Dendrite Development

Support: GRF 15326416

PolyU internal funding 1-YW0Q,

PolyU internal funding 1-ZVGK

Title: Study Piezo1 localization and transportation dynamics by light-sheet microscopy

Authors: *F. CAO[1], R. ZHANG[2], Z. QIU[1], L. SUN[1]
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Abstract: The mechanosensitive ion channel piezo1 that acts as sensors of physical forces like shear stress, osmatic pressure in mammalian cells, is essential for various physiological processes such as touch, hearing and sensing blood flow. Its proper function is critical for regulating vessel formation during development, directing axon growth, red blood cell volume and cell fate etc. Recent studies showed that the subcellular localization is a key determinant of piezo1 function and its subcellular localization and dynamics can be altered by external stimulus. However, little is known about the mechanisms of piezo1 responding to external stimulus, regarding the localization and dynamics. In this present study, we utilized a multi-colour light-sheet microscopy to multiplex and visualize the previously characterized piezo1-GFP fusion protein and the cellular compartments such as cell membrane, cytoskeleton, Golgi or ER. The GFP fused Piezo1 was expressed on HEK 293T cells. After 24 hours, its expression and transportation of piezo1 from its origin to the membrane as well as the movement on the membrane were visualized longitudinally. The Piezo1 localization and transportation dynamics in HEK 293T cell with different cell density were quantified. Yoda1 which is a piezo1 specific agonist was utilized as a reference stimuli. Real-time and long-term effects of crowding and stretching on the piezo1 localization and dynamics in HEK 293T cells were visualized and characterized by light-sheet microscopy. The results show that the localization and dynamics of piezo1 in single cells can be visualized with unparalleled high spatiotemporal resolution. The cell density have a significant influence on the localization of piezo1. The Yoda1 drive piezo1 moving outward to the membrane. In the mean time, the actin shrinks and deformed. The piezo1 localization and transportation dynamics is significant different in crowding and stretching cells. Compared with other imaging techniques, light-sheet microscope provide confocal like spatial resolution with unexceed time resolution and low photo-toxicity, capable for investigating the mechanisms of the regulation of piezo1 to the external stimulus. The effects of external stimulus on the localization and dynamics of piezo1 in different cells and the detailed mechanisms will be investigated.

Disclosures: **F. Cao:** None. **R. Zhang:** None. **Z. Qiu:** None. **L. Sun:** None.

Poster

198. Axon: Adhesion and Cytoskeleton

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 198.03/B14

Topic: A.05. Axon and Dendrite Development

Title: Unexpected consequences of xyloside treatment on neuronal cytoskeleton assembly and function

Authors: *C. MENCIO[1], S. M. TILVE[2], C. AGBAEGBU[2], H. KATAGIRI[2], H. M. GELLER[3]
[1]NHLBI, Natl. Inst. of Hlth., Bethesda, MD; [2]Developmental Neurobio., NHLBI, Bethesda, MD; [3]Office of Educ., Natl. Heart, Lung, and Blood Institute, NIH, Bethesda, MD

Abstract: Proteoglycans (PGs) are important to a variety of neurological functions. From neural development to memory to regeneration and disease, both heparan sulfate (HS) and chondroitin sulfate proteoglycans (CSPGs) play both promoting and inhibitory roles. Xylosides are small molecules consisting of an aglycone attached to a xylose residue which serve as a competitor for glycosaminoglycan (GAG) chain biosynthetic machinery. Used in research since the 1970s, treatment with these molecules leads to the inhibition of endogenous PGs and the production of primed GAGs, or GAG chains built on the xyloside and as such lack a core protein. Primed GAGs are pushed out of the cell and can be found in the extracellular space. Much of the previous research has focused on high concentration treatment (≥ 1mM) by xyloside. We have found that low concentration (≤ 1μM) xyloside (LCX) treatment caused unexpected changes in cell behavior and morphology. LCX-treated neuronal cells demonstrate enlarged growth cones with microtubule looping that were absent in cells that were exposed to both vehicle and 1mM xyloside treatment. Neuronal cell bodies also exhibit significantly increased lamellipodia area and show altered f-actin in these enlarged structures. Analysis of other cytoskeletal elements such as neurofilament and TAU show changes in expression and phosphorylation state in LCX-treated primary neuronal cultures. Additionally, disruptions in cellular trafficking have been observed. *In vitro* visualization of lysosomes shows a lack of perinuclear localization in LCX-treated neurons as compared to vehicle treated neurons. Trafficking deficiencies may also explain increased CSPGs in cell lysate as changes in cytoskeleton may result in a disruption of vesicle transport within the cell and subsequent trafficking of proteins. This research serves as a first step to fully explore the potential of low concentration xyloside treatment as a research tool and better understand the role of proteoglycans in neural development and function.

Disclosures: C. Mencio: None. **S.M. Tilve:** None. **C. Agbaegbu:** None. **H. Katagiri:** None. **H.M. Geller:** None.

Poster

198. Axon: Adhesion and Cytoskeleton

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 198.04/B15

Topic: A.05. Axon and Dendrite Development

Support: Japan MEXT KAKENHI Grant #15K06769

Title: Coordinated membrane retrieval with actin bundling in the growth cone revealed by superresolution microscopy

Authors: *M. NOZUMI, M. IGARASHI
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Abstract: The growth cone is a motile structure in the axonal tip, and is essential for neural wiring, synapse formation, and axonal regeneration. During axon growth, both continuous reorganization of actin cytoskeleton and the membrane retrieval are observed in leading edge of the growth cone. Two different endocytic pathways, the clathrin-dependent/-independent endocytosis, have been reported as that they induces the membrane retrieval in the growth cone. Both those endocytosis and actin reorganization are thought to be essential to the precise navigation of an axon, however, the relationships between them are not clearly understood. To observe their coordinatory movements, we analyzed the dynamics of two endocytic components; 1) clathrin, 2) a BAR domain protein endophilin A3 (Endo3); and 3) F-actin in the growth cone, in a neuroblastoma NG108-15 cells, using a superresolution microscopy 3D-SIM, and total internal reflection fluorescence microscopy (TIRFM). Whereas clathrin was mainly accumulated in the basal membrane at the central domain, Endo3 appeared in the dorsal surface at the leading edge. The accumulation of Endo3 coincided with the F-actin bundling. When actin polymerization was inhibited by cytochalasin B or CK-666, Endo3 markedly reduced. RNAi against fascin, a cross-linker protein of F-actin, also reduced the numbers of Endo3 localized at the leading edge. GFP-synaptophysin (Syp) arose near the root portions of filopodium, a microspikes containing F-actin bundles, and most of them were moving with the actin retrograde flow. The retrogradely moving Syp puncta were colocalized with Endo3 and dynamin 1 (Dnm1), at the leading edge, but not with clathrin. The formation of Syp-positive vesicles was affected by RNAi against Endo3 and dominant-negative Dnm1 but not by a clathrin inhibitor, Pitstop2. Interestingly, in the primary cultured neurons, Endo3 knockdown inhibited axonal growth, and reduced the growth cone size. These results suggest that there is a novel mechanism of membrane retrieval in the leading edge of a growth cone, namely, the Syp-positive vesicle production by Endo3-, Dnm1-dependent and clathrin-independent endocytosis occurred at the apical membrane there, coinciding with actin bundling, and that these vesicles are moving along the actin retrograde flow.

Disclosures: **M. Nozumi:** None. **M. Igarashi:** None.

Poster

198. Axon: Adhesion and Cytoskeleton

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 198.05/B16

Topic: A.05. Axon and Dendrite Development

Support: NIH Grant R15NS098389

Title: RACK1 regulates point contact dynamics and local translation at point contacts

Authors: *L. J. KERSHNER[1], K. WELSHHANS[2]
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Abstract: In the developing nervous system, select mRNAs are transported to and locally translated within growth cones. Formation of appropriate connectivity in the developing nervous system depends on local translation within axonal growth cones, but the molecular mechanisms underlying this process are not well understood. We have previously shown that local translation of β-actin mRNA within growth cones is necessary for appropriate axon guidance and is dependent on receptor for activated C kinase 1 (RACK1), a multi-functional ribosomal scaffolding protein that can interact with several signaling molecules concurrently. In response to stimulation with brain-derived neurotrophic factor (BDNF), phosphorylation of RACK1 facilitates the local translation of β-actin mRNA. Additionally, we have shown that RACK1 is required for the formation of point contacts, which are growth cone adhesion sites that link the extracellular matrix to the cytoskeleton and regulate growth cone motility. In line with this, RACK1 is also required for axon outgrowth and growth cone spreading. Thus, RACK1 is vital for functional aspects of neuronal development. We recently found that RACK1 is localized to point contacts, which suggests that local translation may be regulated at these adhesion sites that are important for axonal pathfinding. Here we investigate whether local translation occurs at point contacts and examine the role of RACK1 in the regulation of point contact dynamics. First, we examined the location of components of the local translation complex relative to point contacts under both basal and growth factor stimulated conditions in cortical neurons of E17 mice. Indeed, both β-actin mRNA and RACK1 colocalize with point contacts, and this increases following BDNF stimulation, suggesting that local translation is regulated at point contacts. RACK1 is required for the BDNF-induced increase of β-actin mRNA at point contacts. Live cell experiments using total internal reflection fluorescence (TIRF) microscopy reveal a role for RACK1 in the regulation of point contact dynamics. Furthermore, fluorescent translation reporters demonstrate the role of point contacts in the local translation of β-actin mRNA. Taken together, these data suggest that point contacts are a targeted site of local translation within growth cones, and that RACK1 is critical to the formation of point contacts, the local translation process, and appropriate neural development. These data provide further insight into how and where local translation is regulated within growth cones, and thereby leads to appropriate connectivity formation in the developing nervous system.

Disclosures: L.J. Kershner: None. **K. Welshhans:** None.

Poster

198. Axon: Adhesion and Cytoskeleton

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 198.06/B17

Topic: A.05. Axon and Dendrite Development

Title: Peculiar cell phenotypes caused by plasticity related gene 3/5 due to RhoA/Rac1 imbalance

Authors: *S. M. TILVE, C. MENCIO, N. GEORGE, C. AGBAEGBU, H. KATAGIRI, H. M. GELLER
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Abstract: PRG-3 is a six-transmembrane protein that belongs to a protein family called plasticity-related gene (PRG-1 to -5), which is a novel brain-specific subclass of the lipid phosphate phosphatase superfamily. PRG1/2 have prominent roles in synapse formation and axonal pathfinding. We found that PRG-3 overexpression in the mouse neuroblastoma cell line (N2A) results in two peculiar phenotypes - long elastic fibrous structures that are left as a trail resulting from breaking plasma membrane and excess filopodia formation. These changes are caused by cytoskeletal re-arrangement brought about by PRGs. The cytoskeleton is governed by activation of molecular switches which are members of the Rho-GTPase protein family. We hypothesized that the PRG effect on cytoskeleton was due to a shift in the activity balance of RhoA/Rac1 GTPases, increasing Rho A and decreasing Rac1 levels. Focal adhesions (FA) grip the substrate for lamellipodium to protrude forward during motility. Their turnover is highly dependent on Rho activation. Overexpression of PRG3/5 decreased turnover of paxillin (FA protein) as observed by TIRF microscopy. To study substrate attachment further, we used Interference Reflection Microscopy and saw an increased attachment with PRG 3/5. PRG3/5 cells had reduced actin turnover and slower migrating speed. The PRG-induced phenotype of long fibres and filopodia was abolished by introducing active Rac1 and dominant negative RhoA. In summary, our data indicate that PRG3/5 decreases active Rac1 levels that lead to breaking of Rac1-dependent lamellipodia causing elastic trailing fibres. An increase in Rho A levels lead to stronger focal adhesions and increased formin generated filopodia.

Disclosures: S.M. Tilve: None. **C. Mencio:** None. **N. George:** None. **C. Agbaegbu:** None. **H. Katagiri:** None. **H.M. Geller:** None.

Poster

198. Axon: Adhesion and Cytoskeleton

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 198.07/B18

Topic: A.05. Axon and Dendrite Development

Support: NIH R01 NS038526

NIH P30 NS045758

Title: A dynamic cycle of severing and annealing of regulates neurofilament polymer transport

Authors: *A. UCHIDA[1], A. BROWN[2]
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Abstract: Neurofilaments (NFs) are space-filling polymers that function to expand axon caliber, and thus increase axonal conduction velocity. In addition to this structural role, NFs are also cargoes of axonal transport that move bidirectionally along axons in intermittent bursts of rapid movement interrupted by prolonged pauses. We have discovered that NFs lengthen by joining end-to-end (annealing), and that they can also be shortened by a severing mechanism. To explore the significance of these novel phenomena, we developed a longterm multi-field tracking method that uses time-lapse fluorescence microscopy and a motorized stage to follow single GFP-tagged NFs along axons at high magnification across multiple fields of view. Short filaments (<10 μm long; average=4.6 μm, n=50) exhibited more frequent end-to-end annealing (1.24 annealing events/hour; 0.34 severing events/hour) whereas long filaments (>20 μm long; average=29.46 μm, n=51) exhibited more frequent severing (0.15 annealing events/hour; 1.52 severing events/hour). Filaments of all lengths were capable of rapid movement, but short filaments moved more persistently, pausing and reversing direction less often compared to long filaments. Since N-terminal phosphorylation can result in fragmentation of intermediate filaments, we investigated whether this could be a mechanism for NF severing. We focused on four sites (serines 2, 55, 57 and 66) in NF protein L (NFL) that have been reported to be phosphorylated in vivo. GFP-fusions of NFL in which all four serines were mutated to either alanine (S2,55,57,66A-NFL) or aspartate (S2,55,57,66D-NFL) both assembled into filaments, but filaments containing S2,55,57,66A-NFL were about 2.5-fold longer and moved about 2.5-fold less frequently than those containing S2,55,57,66D-NFL. In addition, filaments containing S2,55,57,66A-NFL severed less frequently than those containing S2,55,57,66D-NFL. We treated cultures with 8-bromo-cAMP and Okadaic acid to activate protein kinase A. because two of these phosphorylation sites are thought to be substrates for protein kinase A. NF length was reduced by >50%, and this effect was rescued partially by expressing S2,55,57,66A-NFL. These results suggest that there is a dynamic cycle of severing and annealing that regulates NF transport. Severing liberates short filaments that move more readily, whereas end-to-end

annealing of these short filaments sequesters them in the form of long polymers that move less readily. We propose that local destabilization of NFs by site-directed N-terminal phosphorylation of their constituent polypeptides may be a mechanism for intermediate filament severing.

Disclosures: A. Brown: None.

Poster

198. Axon: Adhesion and Cytoskeleton

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 198.08/B19

Topic: A.05. Axon and Dendrite Development

Support: NIH Grant 2T32GM008136-26

NIH grant R01NS081674

Title: Intermediate filament mediated phospho-regulation of doublecortin during neuronal development

Authors: *C. BOTT, C. YAP, B. WINCKLER
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Abstract: Intermediate filaments (IFs) are known to regulate both kinase and phosphatase activity in various developmental, physiological, and pathological contexts. IFs are known to locally scaffold and regulate kinase activity but little is known about the role of IF mediated kinase regulation in neuronal development. DCX is a neuronal microtubule (MT) associated protein important for neuronal migration and axon outgrowth, and mutations in the DCX gene lead to cortical malformations (lissencephaly) in humans. Phosphorylation of DCX negatively regulates DCX MT binding affinity, in turn-destabilizing MTs. Since localized regulation of MT stability facilitates growth cone guidance in response to extracellular cues, local regulation of DCX phosphorylation could be an important mechanism to regulate axon growth and guidance. DCX is phosphorylated downstream of multiple kinases, including cyclin dependent kinase 5 (CDK5). CDK5 is critical in early cortical development and is downstream of axon guidance cues.
We investigated the role of the IF protein nestin, which is a known regulator of CDK5, in regulating DCX phosphorylation during axonogenesis. Nestin co-expresses with DCX transiently in an early window in axonogenesis in culture and in the embryonic cortex. Nestin colocalizes with DCX in the most distal region of the axon proximal to the growth cone, and is absent from secondary neurites. A DCX and nestin complex can be detected by co-immunoprecipitation and proximity ligation assay in neurons. When expressed in 293T cells, nestin enhances phosphorylation of DCX by CDK5 and nestin enhances the association of DCX with CDK5 by

co-immunoprecipitation. These results suggest that nestin modulates DCX phosphorylation by CDK5 through scaffolding. In neurons, DCX is phosphorylated by CDK5 downstream of the repulsive cue semaphorin 3a, at site which is known to reduce DCX-MT binding and therefore decrease MT stability. Nestin expressing neurons are more responsive to semaphorin 3a (1nM 5minutes)- suggesting nestin enhancement of the CDK5 signaling pathway, leading to increased DCX phosphorylation, less DCX-MT binding, greater MT instability, and growth cone collapse. Nestin siRNA results in neurons that are insensitive to semaphorin3a, and have large MT filled growth cones. Finally, DCX null neurons, are more sensitive to semaphorin 3a, *but in a nestin independent manner*. These data suggests that nestin is a negative regulator of the MT stabilizer DCX, which may allow for cell intrinsic and temporal variation in response to guidance cues during cortical development. Future studies will directly asses the effects of nestin depletion on MT stability and polymerization.

Disclosures: C. Bott: None. **C. Yap:** None. **B. Winckler:** None.

Poster

198. Axon: Adhesion and Cytoskeleton

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 198.09/B20

Topic: A.05. Axon and Dendrite Development

Support: NIH NS43474

NMSS RG 4748-A-13

Title: Myosin II activity regulates the assembly and plasticity of the axon initial segment

Authors: *S. L. BERGER[1], A. LEO-MACIAS[1], S. YUEN[1], S. PFENNIG[1], Y. ZHANG[1], E. AGULLO-PASCUAL[1], M.-S. ZHU[2], E. ROTHENBERG[1], C. V. MELENDEZ-VASQUEZ[3], M. DELMAR[1], J. L. SALZER[1]
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Abstract: The axon initial segment (AIS) is the site of action potential generation and a locus of activity-dependent homeostatic plasticity. A multimeric complex of sodium channels, linked via a cytoskeletal scaffold of ankyrin G and beta IV spectrin to submembranous actin rings, underlies these functions. The mechanisms that specify the AIS complex to the proximal axon and underlie its plasticity are incompletely known. Here we show that phosphorylated myosin light chain (pMLC), an activator of contractile myosin II, is an early component of the assembling AIS. MLC phosphorylation and myosin II contractile activity are required for AIS assembly and regulate the distribution of AIS components along the axon. pMLC is rapidly and

substantially lost during depolarization, thereby destabilizing the actin cytoskeleton and providing a mechanism for activity-dependent remodeling of the AIS. Together, these results identify pMLC/myosin II as a common link between AIS assembly and activity-dependent plasticity.

Disclosures: **S.L. Berger:** None. **A. Leo-Macias:** None. **S. Yuen:** None. **S. Pfennig:** None. **Y. Zhang:** None. **E. Agullo-Pascual:** None. **M. Zhu:** None. **E. Rothenberg:** None. **C.V. Melendez-Vasquez:** None. **M. Delmar:** None. **J.L. Salzer:** None.

Poster

198. Axon: Adhesion and Cytoskeleton

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 198.10/B21

Topic: A.05. Axon and Dendrite Development

Support: NIH grant NS044916

NIH grant NS069688

Title: The roles of β1-spectrin and β4-spectrin in axons

Authors: *C.-H. LIU[1], S. STEVENS[1], M. STANKEWICH[2], P. MOHLER[3], M. RASBAND[1]
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Abstract: Highly-concentrated ion channels at axon initial segments (AIS) and Nodes of Ranvier are necessary to initiate and propagate action potentials in axons. The cytoskeletal protein β4-spectrin is a primary stabilizer of the voltage-gated sodium (Nav) channels found at nodes. Erythrocytic β1-spectrin can rescue this function after loss of β4-spectrin. However, whether β1-spectrin can rescue for AIS is unknown. Also, the possibility of a tertiary compensatory mechanism has not been tested. Furthermore, the function of β1-spectrin in the nervous system has not been studied. To investigate the roles of β1 and β4-spectrin at nodes and AIS, we generated conditional knock-out (cKO) mice. Mice lacking β1-spectrin in the central nervous system showed normal motor performance, whereas β4-spectrin cKO animals showed tremor and poor motor behavior throughout development. We found that cortical AIS integrity was not altered in β1-spectrin cKO mice. Unexpectedly, β1-spectrin only targeted to the cortical interneuron AIS of β4-spectrin cKO mice. In addition, loss of β1-spectrin retained Nav channel clustering at nodes, and loss of β4-spectrin also showed normal Nav channel clustering due to the compensatory effects from β1-spectrin. These results suggest that β4-spectrin is the primary spectrin that stabilizes AIS and nodes, while β1-spectrin performs secondary functions in a context-dependent manner.

Disclosures: **C. Liu:** None. **S. Stevens:** None. **M. Stankewich:** None. **P. Mohler:** None. **M. Rasband:** None.

Poster

198. Axon: Adhesion and Cytoskeleton

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 198.11/B22

Topic: A.05. Axon and Dendrite Development

Support: NRF-2013R1A1A2074251

NRF-2015M3C7A1030964

NRF-2012R1A4A1028200

Title: The novel NDEL1 phosphorylation mediated by TARA-GSK3β complex regulates neuronal development

Authors: Y. WOO[1], Y. KWAK[1], J.-H. HONG[1], S. KIM[1], D. MUN[1], M. NGUYEN[2], *S. PARK[1]
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Abstract: Nuclear distribution element-like 1 (NDEL1) plays pivotal roles in diverse biological processes and is implicated in the etiology of multiple neurodevelopmental disorders. Multiple independent phosphorylations of NDEL1 have been reported as the regulatory mechanism for its function. Recently, TRIO-associated repeat on actin (TARA), an actin-bundling protein, was proposed as a regulatory component of Ndel1 in the cell migration. Here, we discovered that TARA strongly induces multiple phosphorylations of NDEL1 at previously unidentified residues and we acquired evidence for the involvement of GSK3β in the regulation of TARA-mediated NDEL1 phosphorylation. Also we observed NDEL1-TARA complex significantly affected neuronal development process in a Ndel1 phosphorylation-dependent manner. Collectively, these findings uncover the novel molecular mechanism of NDEL1-TARA complex in the regulation of neuronal development.

Disclosures: **Y. Woo:** None. **Y. Kwak:** None. **J. Hong:** None. **S. Kim:** None. **D. Mun:** None. **M. Nguyen:** None. **S. Park:** None.

Poster

198. Axon: Adhesion and Cytoskeleton

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 198.12/B23

Topic: A.05. Axon and Dendrite Development

Support: NIMH/NIH R00

Title: The microtubule plus-end-tracking protein TACC3, is an important regulator of microtubule dynamics, axon outgrowth and guidance

Authors: *B. ERDOGAN[1], G. CAMMARATA[2], E. LEE[2], B. PRATT[2], L. A. LOWERY[2]
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Abstract: Precise neuronal connection requires proper axon guidance. Microtubules (MTs) of the growth cone are the driving force to navigate the growing ends of axons. Pioneering microtubules and their plus-end resident proteins, +TIPs, play integrative roles during this navigation. Recently, we introduced the protein TACC3 as a member of the +TIP family regulating microtubule dynamics in Xenopus laevis growth cones and showed manipulation of TACC3 levels affects axon outgrowth by regulating axon outgrowth velocity and the frequency of axon retraction. Here, we examine the impact of the highly conserved domains of TACC3 on MT dynamics regulation and axon outgrowth. We find that deletion of the TACC domain, the domain that ensures plus-end localization, significantly reduces both MT and axon growth length. Additionally, we show that over expressing TACC3 mitigates Nocodazole-induced reduction in MT dynamics parameters, such as MT growth speed, length and lifetime. While this mitigation could result from increased MT stability, immunocytochemical analysis of growth cones for stable (de-tyrosinated tubulin) and dynamic (tyrosinated tubulin) MTs demonstrates that neither TACC3 knockdown nor its overexpression have impact on the levels of dynamic versus stable MTs, suggesting TACC3 antagonizes Nocodazole-induced reduced MT dynamics by a different mechanism. We had previously shown that TACC3 co-localizes with its well-known partner XMAP215 at the extreme plus-ends of MTs in a co-dependent manner. Our epistasis analysis demonstrates that TACC3 and XMAP215 cooperate to promote axon outgrowth and rescue axon growth defects. Moreover, we demonstrate that manipulation of TACC3 levels interferes with the growth cone response to the axon guidance cue Slit2 ex vivo. We also show that ablation of TACC3 causes pathfinding defects in axons of developing spinal cord motor neurons and retinal ganglion cells in Xenopus laevis in vivo. Together, our results suggest that by regulating MT behavior, the +TIP TACC3 is involved in axon outgrowth and pathfinding decisions of neurons during embryonic development.

Disclosures: B. Erdogan: None. **G. Cammarata:** None. **E. Lee:** None. **B. Pratt:** None. **L.A. Lowery:** None.

Poster

198. Axon: Adhesion and Cytoskeleton

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 198.13/B24

Topic: A.05. Axon and Dendrite Development

Support: National Natural Science Foundation of China Grant 81601066

Natural Science Foundation of Guangdong Province (2016A030313096)

Title: The effect of CSPGs on neuronal cell adhesion, spreading and neurite growth in culture

Authors: *J. JIN[1], S. M. TILVE[3], L. SHI[1], Z. HUANG[1], L. ZHOU[1], H. M. GELLER[4], P. YU[2]
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Abstract: As one major component of extracellular matrix in the CNS, chondroitin sulfate proteoglycans (CSPGs) have long been known as axon growth inhibitors enriched in the glial scar that prevent axon regeneration after injury. Although many studies have shown that CSPGs inhibit neurite growth *in vitro* using different types of neurons, it is difficult to relate the concentrations used in culture to the situation in vivo after injury. It is also noteworthy that the CS glycosaminoglycan chains are highly negatively charged and would hence affect cell adhesion when used as a cell culture substrate. Here, using cerebellar granule neuron (CGN) and cortical neuron cultures, we evaluated the effects of different concentrations of both immobilized and soluble CSPGs on neuronal growth, including cell adhesion, spreading and neurite growth. When neurons were plated on PLL plus different concentrations (0, 1, 2, 4 μg/mL) of CSPGs coated substrates, indeed, we observed neurite length decrease while CSPGs concentration arises. Meanwhile, a decrease in cell density accompanied by an increase in cell aggregate formation was observed. Soluble CSPGs also showed an inhibition on neurite growth at 2 and 4 μg/mL concentrations and the number of neurite-bearing cells significantly reduced at 4 μg/mL CSPGs, but comparing to coated CSPGs, it required a higher concentration to induce cell aggregate formation. To further investigate the effect of CSPGs on neuron adhesion, we next looked at cell spreading shortly after plating. Neurons growing on PLL displayed a pancake shape at 30 min after plating by spreading out lamellipodia. However, the neurons on CSPGs remained as sphere shapes with restrained lamellipodia extension. The effect of CSPGs on neuron adhesion was further evidenced by interference reflection microscopy (IRM). We also noticed the growth cone size was significantly reduced in CSPGs group comparing to PLL group, attributing to the smaller lamellipodial size in the peripheral domain. This suggested that CSPGs inhibited growth cone spreading by limiting lamellipodia extension at the leading edge. Our results indicated that the inhibitory effect of CSPGs on neurite growth could result from

both a direct inhibition of CSPGs on neurite extension and a poor adhesion which hence affected neurite extension or stabilization.

Disclosures: J. Jin: None. **S.M. Tilve:** None. **L. Shi:** None. **Z. Huang:** None. **L. Zhou:** None. **H.M. Geller:** None. **P. Yu:** None.

Poster

198. Axon: Adhesion and Cytoskeleton

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 198.14/B25

Topic: A.05. Axon and Dendrite Development

Support: NIH Grant 5R01MH107305-03

Title: Defining links between an intellectual disability-associated RNA-binding protein and planar cell polarity in neurodevelopment

Authors: *E. B. CORGIAT, III[1], J. ROUNDS[1], R. BIENKOWSKI[1], D. YU[3], P. CHEN[1], A. CORBETT[2], K. MOBERG[1]
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Abstract: The human *ZC3H14* gene encodes a ubiquitously expressed zinc-finger polyadenosine RNA-binding protein. Mutations in *ZC3H14* that impair function of it encoded protein have been linked to an inherited form of non-syndromic intellectual disability (NS-ID). We developed a *Drosophila melanogaster* model of ZC3H14 NS-ID by deletion of *dNab2*, the fly ortholog of *ZC3H14*. These *dNab2*-deficient animals display defects in survival, locomotion, and memory which correlate at a cellular level with neurodevelopmental defects. Importantly, pan-neuronal expression of human ZC3H14 in *Drosophila* neurons can rescue the overt locomotor and survival phenotypes of *dNab2*-deficient flies, suggesting that dNab2 and ZC3H14 serve conserved roles in neurons. To probe this role, we used a dominant-modifier approach to identify alleles of genes that interact with *dNab2*. This approach has uncovered genetic interactions between *dNab2* and multiple components of the planar cell polarity (PCP) pathway, such as *Disheveled*, that can rescue dNab2-deficient neurodevelopmental defects. Here we show that dNab2 null flies and ZC3H14 knockout mice both show classic PCP defects in wing hair orientation and cochlea inner hair cell orientation, respectively. Furthermore, loss of function alleles of PCP components can rescue a portion of dNab2 null neuro-morphology defects observed in the mushroom bodies, twin neuropil structures analogous to the mammalian hippocampus. These data suggest that dNab2 may regulating mushroom body neurodevelopment through the PCP pathway. Importantly, dNab2 has previously been shown to translationally repress its targets, indicating that it regulate PCP this way. To begin to test this, we have taken a

global proteomic approach to characterize alterations to the translational profile resulting from dNab2 loss.

Disclosures: E.B. Corgiat: None. **J. Rounds:** None. **R. Bienkowski:** None. **D. Yu:** None. **P. Chen:** None. **A. Corbett:** None. **K. Moberg:** None.

Poster

198. Axon: Adhesion and Cytoskeleton

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 198.15/B26

Topic: A.05. Axon and Dendrite Development

Support: Scholarship

Title: Magnetic organization of neural networks via micropatterned substrates

Authors: *M. MARCUS[1,2], N. VARDI[3], I. LEVY[4], A. SHARONI[3], O. SHEFI[1]
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Abstract: Positioning neurons and guidance of nerve cell processes is important for interfacing the nervous system for neuro-electronic devices and for therapeutic applications. Guidance and positioning can be used to lure regenerating axons to form predesigned structures of neural networks and to pattern synaptic contacts. Many studies focus on achieving cell and axonal guidance by using a variety of chemical and physical modifications. A recent innovative and promising approach to achieve site specific targeting in vitro and in vivo is to form complexes of cells interacting with magnetic nanoparticles (MNPs). Due to their magnetic properties, MNPs experience force in inhomogeneous magnetic fields and hence can be manipulated through such fields. By incorporating MNPs within neuronal cells, cells can be guided and controlled by external magnetic field gradients. In the present study, we used such nano-complexes in order to locate cells at specific sites, promote neuronal growth and affect growth orientation. Neuronal cells were incubated with iron oxide nanoparticles and turned sensitive to magnetic stimulation with no cytotoxic effect. We setup several profiles of magnetic tips for cell positioning. Moreover, based on theoretically modeled magnetic fluxes, we designed and fabricated micro-patterned substrates consisting of arrays of magnetic pads and stripes that can be magnetized selectively. We investigated cell motility and network organization of MNPs-loaded cells on these substrates along their differentiation process. MNPs-loaded cells were plated atop the micro-patterned substrates and showed high affinity to the patterns, adhering and clustering at magnetic pad sites. The majority of cell somas were found on the magnetic stripes and neurites were seen to align according to stripes orientation. Molecular and morphological measurements are performed to evaluate viability and network formation. Our study presents an emerging

magneto-chemical method for the manipulation of neuronal migration and growth opening new directions in non-invasive neuronal repair.

Disclosures: **M. Marcus:** None. **N. Vardi:** None. **I. Levy:** None. **A. Sharoni:** None. **O. Shefi:** None.

Poster

199. Axon: Intrinsic Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 199.01/B27

Topic: A.05. Axon and Dendrite Development

Title: A modified western blot protocol for chondroitin sulfate-proteoglycan detection and its applications

Authors: *H. NAGASE[1], S. HIGASHI[1], Y. HIRATA[1], Y. KATAGIRI[2], H. M. GELLER[2]
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Abstract: Sulfated glycosaminoglycans (GAGs) such as chondroitin sulfate (CS) and heparin sulfate (HS) are expressed on proteoglycans at the cell surface and are secreted in the extracellular matrix. Proteoglycans are known to be involved in cell proliferation, axon extension, and regeneration. However, their roles in signal transduction and their ligand-receptor interactions remain unknown. CS-56 is a monoclonal antibody against CS-GAGs that has been widely used to detect chondroitin sulfate proteoglycans (CSPGs) in tissue staining. However, reproducible data from Western blot (WB) are rare, due to a lack of sensitivity and proper controls. The resulting gap between immunostaining and WB data is substantial. In many studies, CS-GAGs are identified by a different antibody, MAB2030, which binds to 4-sulfated unsaturated disaccharide neoepitope generated at the non-reducing end of CS-GAGs that have been pre-digested by the enzyme chondroitinase ABC (cABC). This study proposes a modified WB technique that enables reproducible detection of CSPGs using CS-56, which will enable analysis of sulfated GAGs and exploration of the relationship between sulfated GAGs and intracellular signaling pathways. Here, we verified CS specificity with both CS-56 and MAB2030 following cABC treatment in mouse brain tissue. We described the lack of evidence from the existing method by solid phase binding assays showing the emergence of the MAB2030 epitope and disappearance of the CS-56 epitope. We also examined the effect of sodium chlorate on levels of CS-GAGs in rat pheochromocytoma (PC12) cells using our modified WB protocol. Sodium chlorate is a metabolic inhibitor of CS and HS production, decreasing the availability of the sulfate donor 3’-phosphoadenosine 5’-phosphosulfate. As expected, SC decreased the intensity of CS-GAGs in WB in a concentration-dependent manner. Taken together, these data

demonstrate that our WB protocol reliably detects CSPGs and has broad potential for applications in studying the mechanisms of sulfated sugar chains.

Disclosures: H. Nagase: None. **S. Higashi:** None. **Y. Hirata:** None. **Y. Katagiri:** None. **H.M. Geller:** None.

Poster

199. Axon: Intrinsic Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 199.02/B28

Topic: A.05. Axon and Dendrite Development

Support: Strategic Research Foundation Grant-aided Project for Private Universities from Ministry of Education, Culture, Sport, Science, and Technology, Japan (MEXT), 2014-2018 (S1411003)

Title: Native dynamics of mitochondrial membrane potential and ATP levels in growing neurites visualized by simultaneous imaging

Authors: *R. SUZUKI[1], K. HOTTA[2], K. OKA[2]
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Abstract: Mitochondria are organelles that produce adenosine triphosphate (ATP), a major energy source for living body, and they are known to be enriched in regions that have a high-energy demand at both the organ and subcellular levels. This is especially true for neurons, because their highly polarized morphology which is indispensable for proper neuronal activities requires in-place and highly effective energy production *via* mitochondria. In fact, many neurodegenerative diseases, where a loss of neuronal function and morphology are observed, accompany mitochondrial dysfunctions. Additionally, in some neuronal injury model, unimpaired mitochondria are shown to be crucial for neuronal energy recovery and neuronal survive.
In most cases, however, mitochondrial activity is estimated through measurements of mitochondrial inner-membrane potential (MIP), and little is known about native mitochondrial ATP dynamics. This study conducted simultaneous imaging of MIP and mitochondrial ATP levels in neurons to unveil the correlation between them, and to explore how mitochondrial activity relates to cellular phenomenon.
Under physiological conditions, MIP and mitochondrial ATP levels had a positive correlation on average. However, not only positive correlations but also negative or no correlation were observed tentatively, and a correlation pattern shown by one mitochondria frequently undergo changing with time.
MIP decreased during mitochondrial fission and increased during fusion. Additionally,

mitochondrial ATP levels increased after fusion. Furthermore, anterogradely transported mitochondria had high ATP levels, while retrogradely transported mitochondria had lower MIPs. Mitochondria localized more densely in growth cones (GCs) than in neuronal processes; gross mitochondrial ATP levels were therefore higher in GCs. Additionally, gross ATP levels correlated with neurite elongation. However, while averaged MIP was high in GCs, there was no correlation between MIP and elongation.
These results indicate that MIP and mitochondrial ATP levels have complicated and time-dependent correlations under physiological conditions, and that as for neurite elongations, mitochondrial ATP levels, but not MIP, is an essential factor.

Disclosures: R. Suzuki: None. **K. Hotta:** None. **K. Oka:** None.

Poster

199. Axon: Intrinsic Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 199.03/B29

Topic: A.05. Axon and Dendrite Development

Support: DOD W81XVVH-12-1-0051

Title: Axon tortuosity during new axon growth in the nigro-striatal projection in the adult mouse brain

Authors: S. PADMANABHAN[1], A. P. TAGLIAFERRO[2], T. OO[2], T. KAREVA[2], N. KHOLODILOV[2], *R. E. BURKE[2]
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Abstract: A prevailing concept in neuroscience has been that the adult central nervous system is incapable of an axonal regenerative response. Recent evidence, however, suggests that reactivation of intrinsic cell signaling pathways that mediate axon growth during development may restore this ability. One such pathway is Akt/mammalian target of rapamycin (mTOR) signaling. We have previously shown that AAV-mediated transduction of dopamine (DA) neurons in the substantia nigra (SN) with constitutively active forms of either Akt (myristoylated-Akt) or human Rheb (hRheb (S16H)), an upstream activator of mTOR, induces long-range axon re-growth that reaches striatal target and partially restores behavior function in adult mice after retrograde axon degeneration due to the neurotoxin 6-OHDA (Kim et al., 2011). Many of these axons demonstrate a highly tortuous appearance that is not normally observed among adult DA axons. Such morphology suggests that new axon growth has occurred (Steward et al, 2003). Very little is known about the cell biology of tortuosity, or how new axons eliminate tortuous axon segments. We have developed morphologic criteria to identify and quantify

tortuous axon segments in order to perform a time course analysis of their appearance and to initiate studies of their neurobiology. Adult mice received an intranigral injection with AAV2/1-cAPP-TagRFP-T to pre-label the DA neurons and their axons. Three weeks later, mice received an intrastriatal injection of 6-OHDA to induce retrograde axonal degeneration and, three weeks after lesion, when the process of degeneration is complete, AAV2/1-Rheb(S16H) was injected into the SN. The number of tortuous axons was determined at 0, 3, 7, 10 and 14 days after AAV2/1-Rheb(S16H) delivery. Tortuous axons were observed at low levels at Time = 0, increased to a maximum by day 3 and then decreased back to baseline by day 14. Interestingly, although axonal spheroids have generally been observed in degenerating axons, they were identified in these growing axons in tortuous segments. Macroautophagy has been associated with axon and terminal remodeling or breakdown in a number of contexts. We therefore sought to identify autophagic vacuoles (AVs) in tortuous segments by injecting AAV2/1-GFP-LC3 with AAV2/1-cAPP-TagRFP-T. We observed GFP-LC3-positive puncta in tortuous profiles, both in axons and spheroids. The functional significance of these findings will require further investigation. We conclude that tortuosity is a prominent feature of new axon growth in the adult brain and that understanding the mechanisms of its appearance and elimination will enhance our ability to devise effective restorative therapies.

Disclosures: S. Padmanabhan: None. **A.P. Tagliaferro:** None. **T. Oo:** None. **T. Kareva:** None. **N. Kholodilov:** None. **R.E. Burke:** None.

Poster

199. Axon: Intrinsic Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 199.04/B30

Topic: A.05. Axon and Dendrite Development

Support: Grants-in-Aid for Scientific Research, Japan

Title: The role of Plexin-A1 receptor in the guidance of cingulate pioneering axons during the corpus callosum development

Authors: *K. YUKAWA, M. M. HOSSAIN, M.-S. J. LABONI, M. E. R. BHUIYAN, I. TAKAHASHI, T. NEGISHI
Meijo Univ., Nagoya, Japan

Abstract: The corpus callosum (CC) is the large bundle of axons that mainly link similar regions of the left and right cerebral hemisphere. Both semaphorins and the receptors critically contribute to the CC development. Sema3A in the class 3 semaphorins and the receptor, Plexin-A1 are crucially implicated in callosal axon fasciculation. Neuropilin 1 (Npn1), a high affinity receptor for class 3 semaphorins localized on the cingulate pioneers exhibits a crucial role in the midline

crossing of the pioneer axons through the interactions with semaphorins including Sema3C. However, it remains unsolved if the plexin family of receptors are actually involved in the axonal extension of cingulate pioneering neurons during the early phase of CC development. To get a clue as to the contribution of Plexin-A1 in the axon guidance of pioneering neurons, our study examined the extension pattern of pioneer axons in both wild-type (WT) and Plexin-A1-deficient mice under the BALB/c genetic background. To initially know the expression pattern of semaphorins and the receptors in the CC development, immunohistochemistry was performed to examine the localization of Npn1 in the pioneer axons and Sema3C in the guidepost on the CC midline. The analysis confirmed the localization of Npn1 positive pioneer axons and the expression of Sema3C in the calretinin-positive cells on the midline of the embryonic day 15.5 (E15.5) brain. To next examine the extension pattern of the pioneer axons, immunohistochemistry of Npn1 was performed on both WT and Plexin-A1-deficient embryonic mice brains. The incidence in which Npn1 positive pioneer axons crossed the midline was significantly lower in E17.5 Plexin-A1-deficient brain as compared with E17.5 WT. Thus, Plexin-A1-deficient pioneer axons may be hard to respond to the chemoattractive guidance molecule such as Sema3C and may exhibit the delay of midline crossing. To trace the pioneer axonal pathway in more detailed manner, we are currently analyzing the projection pattern of pioneer axons by microinjecting diI into E17.5 mouse cingulate cortex.

Disclosures: K. Yukawa: None. **M.M. Hossain:** None. **M.J. Laboni:** None. **M.E.R. Bhuiyan:** None. **I. Takahashi:** None. **T. Negishi:** None.

Poster

199. Axon: Intrinsic Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 199.05/B31

Topic: A.05. Axon and Dendrite Development

Support: NIH R56NS050414

NIH RO1NS098780

CureSMA Foundation (BEA1617)

Title: The function of survival of motor neuron protein and RNA binding proteins complexes during vertebrate motoneuron development and disease

Authors: *L. HAO[1], ***L. HAO**[1], J. TALBOT[2], P. GANGRAS[3], D. PHAN[1], M. AN[1], G. SINGH[3], M. WOLMAN[4], C. BEATTIE[1]
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Abstract: The motoneuron disease Spinal Muscular Atrophy (SMA) is caused by low levels of the ubiquitously expressed Survival of Motor Neuron (SMN) protein and leads to paralysis and early death of infant/children. The SMN protein is involved in facilitating protein:RNA complexes and has a well-characterized role in snRNP assembly and splicing. However, it is also present in axons and binds neuronal RNA binding proteins (RBPs) indicating additional functions. We hypothesize that SMN:RBP and their cargo RNAs are critical for normal motoneuron development. There is debate in the field whether motoneurons develop normally or if they only exhibit defects after reaching their target muscle. We have shown in zebrafish genetic models that *smn* mutants reach their target muscle, but have motor axon outgrowth defects with fewer motor axon filopodia, axonal branches, dendrites and neuromuscular synapses supporting a developmental defect. Using in vivo motoneuron specific immunoprecipitations, we showed that SMN interacts with the neuronal RBP, HuD, during motoneuron development whereas SMN with a patient mutation does not interact with HuD. Importantly, SMN and HuD do not interact after motoneuron development is complete suggesting a need for this complex during motoneuron development. We generated a zebrafish *HuD* mutant and found that they had motoneuron defects very similar to *smn* mutants with fewer motoneuronal dendrites and axonal arbors. To determine whether these defects affected motor function, we examined spontaneous motor behavior in both *smn* and *HuD* mutants. Using high-speed video analysis, we found that both mutants exhibited significant defects in initiating both swims and turns. Interestingly, we had shown that HuD levels were decreased in *smn* mutants. Thus, we asked whether expressing HuD in *smn* deficient motoneurons could rescue the defects caused by low levels of SMN. Indeed, we found that genetically driving HuD expression in *smn* mutant motoneurons rescued both the motoneuron developmental defects and motor function. These data indicate that SMN and HuD are critical for motoneuron development. We are currently analyzing the RNAs associated with this complex and are using mass spectrometry to identify other SMN:RBP complexes that may function during motoneuron development. These identified RBPs and RNAs will lend insight into the function of SMN:RBP complexes in motoneuron development and in motoneuron defects present in SMA.

Disclosures: L. Hao: None. **J. Talbot:** None. **P. Gangras:** None. **D. Phan:** None. **M. An:** None. **G. Singh:** None. **M. Wolman:** None. **C. Beattie:** None.

Poster

199. Axon: Intrinsic Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 199.06/B32

Topic: A.05. Axon and Dendrite Development

Support: Australian Postgraduate Award

Title: Sensitivity and robustness of nerve growth factor signaling

Authors: *B. A. BICKNELL[1], P. DAYAN[2], G. J. GOODHILL[1]
[1]Queensland Brain Inst. & Sch. of Mathematics and Physics, The Univ. of Queensland, St Lucia, Australia; [2]Gatsby Computat. Neurosci. Unit, Univ. Col. London, London, United Kingdom

Abstract: Building the brain during development requires the orderly wiring of billions of cells. An important mechanism that mediates this is the regulation of neurite growth, guidance and survival by secreted neurotrophic factors. A canonical example is the finely tuned developmental control of sensory and sympathetic neurons by nerve growth factor (NGF). Although well studied, critical biophysical details of the effects of NGF remain elusive, and a systems-level understanding of growth and survival signaling is lacking. It is difficult for developing cells to sense and respond robustly to limiting concentrations of NGF, as unavoidable biological noise corrupts all aspects of signal transduction. Here, we show how a balance of positive and negative feedback within aggregrates of cells can explain the remarkable chemosensory sensitivity observed in vitro. We performed a detailed analysis of the experimental data of ref. [1], which characterizes the neurite growth of ~3000 rat dorsal root ganglia explants in very shallow NGF gradients. This led to a model of NGF signaling and neurite growth in which a general feedback rule yields ultrasensitive sensing via receptor trafficking, while also conferring robustness to multiple sources of noise. We suggest that paracrine signaling within the aggregate accounts for the often observed, though currently unexplained, inhibition of growth by high NGF concentrations. The model gives a unified and quantitative account of experimentally observed behavior, and yields testable predictions with implications for understanding brain development and repair after injury.
[1] Mortimer, D. et al (2009). A Bayesian model predicts the response of axons to molecular gradients. Proc. Natl. Acad. Sci. U.S.A, 106(25), 10296-10301.

Disclosures: **B.A. Bicknell:** None. **P. Dayan:** None. **G.J. Goodhill:** None.

Poster

199. Axon: Intrinsic Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 199.07/B33

Topic: A.05. Axon and Dendrite Development

Title: Beta-catenin cooperates with Cannabinoid Receptor CB1R to regulate optic axon pathfinding and growth cone protrusions in the optic tract

Authors: *T. M. ELUL, S. WEDEE, K. FARLEY, M. BURK
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Abstract: The retino-tectal projection of lower vertebrates is an experimentally amenable model neuronal circuit for studying mechanisms of axon pathfinding *in situ*. To establish the retino-tectal projection, optic axons must extend through the optic tract to their target - the optic tectum. Here, we studied how β-catenin coordinates with the main cannabinoid receptor to regulate optic axon pathfinding and growth cone protrusions in the optic tract of whole brains taken from *Xenopus* tadpoles. We expressed a mutant of β-catenin that contains the α-catenin but lacks the Cadherin binding site (β-catNTERM) in, and applied the CB1R inhibitor AM251 to, optic axons in the optic tract of intact brains. Expression of both β-catNTERM and AM251 increased dispersion of optic axons in the dorsal optic tract. However, only application of AM251 caused optic axons to turn and miss their target. In addition, optic axons that expressed β-catNTERM formed growth cones that lacked filopodial protrusions, whereas growth cones of optic axons that were exposed to AM251 had increased numbers of filopodial protrusions. These data suggest that β-catenin and CB1R coordinately sculpt optic axonal projections and growth cone filopodial protrusions *in situ.*

Disclosures: **T.M. Elul:** None. **S. Wedee:** None. **K. Farley:** None. **M. Burk:** None.

Poster

199. Axon: Intrinsic Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 199.08/B34

Topic: A.05. Axon and Dendrite Development

Support: UQ postdoctoral fellowship

NHMRC project grant 1107986

Title: Axon growth regulation by a bistable molecular switch

Authors: *P. PADMANABHAN[1], G. J. GOODHILL[1,2]
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Abstract: For the brain to function properly, its neurons must make the right connections during neural development. A key aspect of this process is the tight regulation of axon growth as axons navigate towards their targets. Here, we used mathematical modelling to show that the molecular interaction network involved in axon growth exhibits bistability, with one stable steady state representing a growth state and the other a paused state. Due to stochastic effects, even in an unchanging external environment, axons in the model reversibly switch between the growth and paused states. Environmental signals bias the basin of attraction of the steady states in the model, and, thereby, regulate axon growth rate by altering the switching rates. These results suggest that

axon guidance may be controlled not just by cell-extrinsic factors such as molecular gradients, but also by cell-intrinsic growth regulatory mechanisms.

Disclosures: P. Padmanabhan: None. **G.J. Goodhill:** None.

Poster

199. Axon: Intrinsic Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 199.09/B35

Topic: A.05. Axon and Dendrite Development

Support: JSPS KAKENHI 17J02057

Title: Molecular mechanisms underlying the regulation of R-Ras activation and R-Ras-mediated axon branching formation in primary cultured cortical neurons

Authors: *K. UMEDA, H. KATOH, M. NEGISHI
Kyoto Univ., Kyoto City, Japan

Abstract: Neurons are highly polarized cells with a single axon and multiple dendrites. The appropriate development and regulation of neuronal morphology are crucial to establish a correct neuronal network and exhibit the higher function of central nervous system. Axonal morphological changes, including outgrowth, guidance and branching, are strictly controlled by extrinsic factors and intrinsic signals. We have been identified R-Ras, a Ras-family small GTPases, as one of the essential players for the regulation of axonal morphology. A member of Ras-family small GTPases serves as molecular switch between GDP-bound inactive state and GTP-bound active state. Activation of them requires GDP-GTP exchange catalyzed reaction by guanine nucleotide exchange factors (GEFs) and only activated form is capable of binding to its downstream effectors. Activated R-Ras reorganizes actin filament and microtubules through sending signals to its many downstream effectors resulting in the regulation of axonal morphology. However, little is known about the upstream regulators for R-Ras activation in neurons. Therefore, the goal of our current study is to investigate the upstream regulatory mechanisms for R-Ras activation and R-Ras-mediated axonal morphological control. Here, we report that brain-derived neurotrophic factor (BDNF) has positive effect on the activation of R-Ras and axonal branching formation in primary cultured cortical neurons. In addition, we observed that BDNF treatment dramatically increased the phosphorylation level of Ras-GRF1, a member of GEFs for R-Ras. We also checked the involvement of Ras-GRF1 in BDNF- and R-Ras-mediated axonal branching formation. These results suggest that BDNF is one of the critical extrinsic factors for R-Ras activation and Ras-GRF1 is intrinsic key mediator for R-Ras activation from extracellular BDNF signaling.

Disclosures: **K. Umeda:** None. **H. Katoh:** None. **M. Negishi:** None.

Poster

199. Axon: Intrinsic Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 199.10/B36

Topic: A.05. Axon and Dendrite Development

Support: NIH Grants R00AA01838705

NIH Grants R01AA025215

NIH Grants UL1TR000075

NIH Grants 1U54HD090257-01

The Avery Translational Research Career Development Program Award

The Kavli Institute for Neuroscience at Yale

The Scott-Gentle Foundation

Title: Developmental refinement of axonal projections of the corpus callosum is mediated by the signaling receptor plexin-A4

Authors: *A. I. SON[1], F. SUTO[2], X. FU[3], Y. M. MOROZOV[6], S. ISHII[4], P. RAKIC[7], P. R. LEVITT[8], J. S. LIU[5], K. HASHIMOTO-TORII[5], M. TORII[4]
[1]Ctr. for Neurosci. Res., Children's Natl. Hlth. Syst., Washington, DC; [2]Natl. Inst. of Neuroscience, NCNP, Tokyo, Japan; [3]Neurosci., [4]Ctr. for Neurosci. Res., [5]Children's Natl. Med. Ctr., Washington, DC; [6]Dept Neurobiol, Yale Univ. Sch. Med., New Haven, CT; [7]Yale Univ. Sch. Med, Dept of Neurosci., New Haven, CT; [8]Children's Hosp. Los Angeles, Los Angeles, CA

Abstract: The controlled elimination of initially-overproduced axonal projections during the maturation of the corpus callosum is an important developmental process that has been observed in multiple mammalian species. However, the molecular mechanisms regulating this process remain unknown. In our analysis of the developing mouse corpus callosum proteome via SILAM mass spectrometry, we identified a class of proteins that show a distinct transient increase in expression during the first two postnatal weeks. Cross-referencing of these identified proteins with autism spectrum disorder (ASD)-susceptible genes identified Plexin-A4 as a candidate of strong interest. Analysis of neonatal *plexin-A4-/-* mice showed grossly normal corpus callosum formation; however, these mice experience severe corpus callosum hypoplasia within the first two weeks of development. *In vivo* gene manipulation of callosal projection neurons via *in utero* electroporation indicated that Plexin-A4 promotes the preservation of callosal axons during this

specific period of corpus callosum refinement. Using molecular markers commonly for axon degeneration and pharmacological analysis, we also found this preservation includes inhibition of Caspase-mediated tubulin cleavage in callosal axons. Together, these data demonstrate a critical and novel function of Plexin-A4 in regulating axon preservation in corpus callosum refinement.

Disclosures: A.I. Son: None. **F. Suto:** None. **X. Fu:** None. **Y.M. Morozov:** None. **S. Ishii:** None. **P. Rakic:** None. **P.R. Levitt:** None. **J.S. Liu:** None. **K. Hashimoto-Torii:** None. **M. Torii:** None.

Poster

199. Axon: Intrinsic Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 199.11/B37

Topic: A.05. Axon and Dendrite Development

Title: Protein targeting of L1CAM mutants in cultured neurons

Authors: G. M. RAIMONDI, E. MURPHY, C. LEW, S. K. PIGNATELLI, D. R. CANNATA, *M. I. JAREB
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Abstract: The correct targeting of proteins to axons and dendrites of neurons is essential for the proper development of the nervous system. L1CAM is an axonally-targeted protein responsible for multiple aspects of neuronal development. L1CAM mutations are known to result in a developmental syndrome characterized by cognitive and motor disabilities. We investigated the cellular distribution of known L1CAM mutant proteins, P941L and D544N, in cultured embryonic chick forebrain neurons to test the hypothesis that aberrant protein targeting of these mutants plays a role in the developmental abnormalities associated with the syndrome. Preliminary data suggests that the P941L L1CAM mutant is targeted normally to the axon suggesting that downstream signaling events are abnormal. In contrast, the D544N L1CAM mutant does not appear to reach the cell surface of the neuron.

Disclosures: G.M. Raimondi: None. **E. Murphy:** None. **C. Lew:** None. **S.K. Pignatelli:** None. **D.R. Cannata:** None. **M.I. Jareb:** None.

Poster

199. Axon: Intrinsic Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 199.12/B38

Topic: A.05. Axon and Dendrite Development

Title: Structure-function relationship of the multifunctional axon guidance receptor Robo3

Authors: *Z. DELOUGHERY, N. ACHARYA, A. JAWORSKI
Mol. Pharmacol. and Physiol., Brown Univ., Providence, RI

Abstract: Developing axons are guided to their targets by attractive and repulsive molecular cues, sensed by receptors on the axonal growth cone. Axons can respond to multiple cues simultaneously, integrating many sources of guidance information for a unified response. Growth cones are also able to filter information from guidance molecules, allowing them to differentially respond to cues at discrete time-points. The mechanisms of guidance cue integration and filtering are poorly understood. Commissural neurons project axons across the floor plate at the spinal cord ventral midline. Commissural axons grow towards the midline in response to the growth-promoting and attractive cue Netrin-1, which is produced by radial glia and floor plate cells and signals through the receptor DCC. At the same time, the repulsive cue Nell2 helps guide these axons to the midline by preventing them from entering the ventral horn. After midline crossing, floor plate-derived repellants of the Slit family signal through the receptors Robo1 and Robo2 to expel commissural axons from the midline, but Slit repulsion is suppressed before crossing. The receptor Robo3, which directly binds NELL2 but neither Netrin-1 nor Slits, plays a central role in guiding precrossing commissural axons, as it inhibits Slit repulsion, potentiates Netrin-1 attraction, and mediates Nell2 repulsion. Thus, Robo3 integrates the Netrin-1 and Nell2 signals and filters out Slit signaling. It remains unclear how Robo3 is able to execute its three functions simultaneously. Here, we study molecular mechanisms of Robo3 signaling. First, we investigated the extracellular interaction between Robo3 and Nell2. Through domain mapping studies, we identified the FNIII domains in Robo3 and EGF domains in NELL2 that mediate ligand-receptor binding. To elucidate intracellular mechanisms of Robo3 signaling, we established an *in vitro* system for Robo3 structure-function studies; we use Dunn chambers to examine turning of commissural axons in response to gradients of Netrin-1, Slits, or Nell2, and we test Robo3 constructs lacking defined structural motifs for their ability to restore individual Robo3 functions. We used this rescue platform to parse out specific domains of Robo3 that contribute to each of its diverse functions. These studies provide deep mechanistic insights into the integration and filtering of axon guidance information provided by different cues and serve as a starting point to elucidate signaling pathways that mediate growth cone turning in response to multiple cues.

Disclosures: **Z. Deloughery:** None. **N. Acharya:** None. **A. Jaworski:** None.

Poster

199. Axon: Intrinsic Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 199.13/B39

Topic: A.05. Axon and Dendrite Development

Support: the China Postdoctoral Science Foundation 2013M530282

UESTC Central University Basic Research Fund ZYGX2016J178

Title: Role of FOR20/FOPNL in neuronal development

Authors: *Y. ZHOU[1,2], P. YAN[2], T. ZHOU[2]
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Abstract: FOR20(FGFR1 oncogene partner-related protein of 20kb, Fgfrlop N-terminal in mouse) is a highly conserved centrosomal protein, which is involved in cell cycle regulation and ciliogenesis in human cell. In cultured rat hippocampal neurons, we found that FOR20/FOPNL expresses in cell body (including nucleus), axon and dendrites, colocalizing with acetyl-tubulin and MAP2. After knockig down FOR20 in hippocampal neurons, we found that both neurites outgrowth and axonal transport were inhibited, which suggests that FOPNL is crucial for neuronal development. The current research provides the cellular basis of understanding physiological roles of FOPNL in vivo and suggests a potential target for the diagnosis and treatment of neurodevelopmental disorders.

Disclosures: **Y. Zhou:** None. **P. Yan:** None. **T. Zhou:** None.

Poster

199. Axon: Intrinsic Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 199.14/B40

Topic: A.05. Axon and Dendrite Development

Support: BID PICT 1646 FONCyT

Secretaria de Ciencia y Técnica

Ministerio de Ciencia y Tecnología, Argentina

Title: The role of exocyst complex in the insertion of new membrane at the growth cone at inicial stages of axon formation

Authors: *J. BUSTOS[1], S. QUIROGA[2]
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Abstract: The initial signals and pathways that determine neuron polarity are largely unknown, placing the mechanisms underlying the axon formation as the scope of our investigation. Two interconnected process are essential for axon formation: Axonal specification and rapid plasma membrane outgrowth. The exocytic pathways that function to translocate membrane structural elements to the plasmalemma, occurs by regulated non secretory exocytosis. It has been shown in hippocampal neurons that the axolemmal expansion occurs by the insertion of plasmmalemal precursor vesicles (PPVs) at the growth cone, a process regulated by the neurotrophic factor Insulin like growth factor type 1 (IGF1). Also the assembly of the machinery related to the fusion process is highly regulated trough several steps, including the exocyst complex and SNARE proteins. Expression silencing of three proteins involved in the SNARE family (VAMP4, Syntaxin6 and SNAP23) repressed axonal outgrowth and the establishment of neuronal polarity, by inhibiting IGF-1 receptor exocytotic polarized insertion, necessary for neuronal polarization. The exocyst complex is an octameric well conserved complex and a important candidate for the regulation of PPV fusion into the plasmmalea. Its biochemical composition is still unknown in neurons. We have previously reported that IGF-1 activates the GTP-binding protein TC10, which triggers translocation to the plasma membrane of the exocyst component exo70 at the distal axon and growth cone and this can trigger exocyst complex assembly. Our results show that several proteins of the exocyst complex are present at hippocampal cultures in vitro in early stages of development and present at growth cone. Moreover, Sec3, one of the conserved protein components in exocyst complex, seem to have an important role as a membrane marker of vesicle fusion at hippocampal neurons at the growth cone. The implication of silencing Sec3 and some of the excoyst complex proteins in two polarity models such as hippocampal cultures in vitro and in utero electroporation of cortical neurons are currently our main research study.

Disclosures: J. Bustos: None. **S. Quiroga:** None.

Poster

199. Axon: Intrinsic Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 199.15/B41

Topic: A.05. Axon and Dendrite Development

Support: NIH Grant P20-GM103464

NIH Grant R21-NS085691

Institutional Development Award P30-GM114736 and P20-GM103446

ACCEL CTR Grant U54 GM104941

Title: Axonal localization of precursor microRNA-433 is directed by sequence- and structure-specific cis-elements

Authors: *M. PHAY[1,2], S. YOO[2,1]
[1]Biol. Sci., Univ. of Delaware, Newark, DE; [2]Nemours Biomed. Res., Wilmington, DE

Abstract: Localized mRNAs in axons have been shown to play important roles in axon growth, injury responses, and regeneration through local protein synthesis. Over the past decade, miRNA-mediated regulation of gene expression has been gaining functional importance in neurons. Our recent data suggest that specific miRNAs are highly enriched in axons to regulate axon extension and growth cone steering. Although the role of miRNA-mediated regulation of intra-axonal protein synthesis is beginning to emerge, molecular mechanisms underlying the localization of specific miRNAs into distal axons remain unknown. We previously showed that selective precursor miRNAs (pre-miRNAs) are localized into axons of sensory neurons and that the levels of these pre-miRNAs were altered in response to injury. Furthermore, we showed that miRNA biogenesis machinery such as *Dicer* and *KH-type splicing regulatory protein* is present in axons. Collectively, these evidences led us to hypothesize that pre-miRNAs contain *cis*-acting element(s) that direct their transport into distal axons. Using mRNA reporter constructs in combination with fluorescence *in situ* hybridization, fluorescence recovery after photobleaching, and RT-qPCR, we showed that the reporter mRNA containing complete sequences of the axonally localizing pre-miR-433 can drive axonal transport of the reporter mRNA. In contrast, the reporter mRNA containing complete sequences of cell body restricted pre-miR-138-1 remained in the cell body. To map axon localization *cis*-acting element(s) within pre-miR-433, we generated chimeric pre-miRNAs containing a combination pre-miR-433 and pre-miR-138-1 sequences and assessed whether these chimeric precursors can drive the localization of the reporter mRNA into distal axons. The results indicated that the *cis*-acting elements for axonal localization of pre-miR-433 are sequence and structure specific.

Disclosures: **M. Phay:** None. **S. Yoo:** None.

Poster

199. Axon: Intrinsic Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 199.16/B42

Topic: A.05. Axon and Dendrite Development

Title: Adaptor protein 2 (AP-2) complex is essential for functional axogenesis in hippocampal neurons

Authors: *J. KYUNG[1], I. CHO[2], T. A. RYAN[3], S. KIM[4]
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Abstract: The complexity and diversity of a neural network requires regulated elongation and branching of axons, as well as the formation of synapses between neurons. In the present study we explore the role of AP-2, a key endocytic adaptor protein complex, in the development of rat hippocampal neurons. We found that the loss of AP-2 during the early stage of development resulted in impaired axon extension and failed maturation of the axon initial segment (AIS). Normally the AIS performs two tasks in concert, stabilizing neural polarity and generating action potentials. In AP-2 silenced axons polarity is established, however there is a failure to establish action potential firing. Consequently, this impairs activity-driven Ca2+ influx and exocytosis at nerve terminals. In contrast, removal of AP-2 from older neurons does not impair axonal growth or signaling and synaptic function. Our data reveal that AP-2 has important roles in functional axogenesis by proper extension of axon as well as the formation of AIS during the early step of neurodevelopment

Disclosures: J. Kyung: None. **I. Cho:** None. **T.A. Ryan:** None. **S. Kim:** None.

Poster

199. Axon: Intrinsic Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 199.17/B43

Topic: A.05. Axon and Dendrite Development

Support: NIH Grant 4T32GM007367

NIH Grant R01NS081333

Title: Decreased axonal caspase-9 activity in dorsal root ganglion neurons dysregulates mitochondrial dynamics and causes axon degradation *In vitro*

Authors: *J. A. BELARDE[1], J. C. MARTINEZ[1], M. QIU[2], M. RAMACHANDRAN[2], U. HENGST[3], C. M. TROY[3]
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Abstract: The caspase family of cell death proteases is known to play an important role in various forms of programmed cell death. However, several studies have suggested additional non-death functions for these proteases given their detected presence and activation in healthy, functioning cells. For example, caspase-9 is essential in carrying out the routine apoptotic cell death of excess neurons during development, but remains present in mature neurons after completion of this process, hinting at the possibility of such non- apoptotic roles. Most research into these roles has focused on either the degradation or regeneration of neurites, but almost no attention has been paid to a potential function in neurite maintenance. Specifically, given that caspase-9 can be detected in stable axons, a highly specialized and tightly regulated cellular compartment, it is reasonable to ask if the protease is required in any way to support that stability. To explore this question, we employ a microfluidic model of neuronal culturing, using a chamber that capitalizes on the unique qualities of fluid dynamics on a microscale (channels ~3μm thick) to establish isolated compartments that allow for localized treatment of axons without affecting the cell body. After culturing embryonic dorsal root ganglion (DRG) neurons in these chambers and allowing them to grow for three days to establish stable axonal processes, we show presence of active caspase-9 in the axons that is not accompanied by cell death or degradation of the processes. Furthermore, we show that by decreasing activity of caspase-9 in the axons using a novel, highly specific caspase-9 inhibitor developed by our lab, we see extensive degradation of processes in the axonal compartment without an associated effect on the cell body compartment. Taken together these results suggest a functional role for caspase-9 activity in maintaining the health and stability of DRG axons, and ongoing work is exploring the mechanism behind this role. One possibility emerging from this work involves mitochondrial fusion and fission dynamics. These homeostatic processes are vital to ensuring functional mitochondria in axons and thus maintaining axonal viability. Our early data suggests a dysregulation of this balance when we reduce capase-9 activity in the axons, and we are currently exploring potential candidate proteins that mediate this suspected effect.

Disclosures: **J.A. Belarde:** None. **J.C. Martinez:** None. **M. Qiu:** None. **M. Ramachandran:** None. **U. Hengst:** None. **C.M. Troy:** None.

Poster

199. Axon: Intrinsic Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 199.18/B44

Topic: A.05. Axon and Dendrite Development

Support: NIH Grant U01-NS094340

NSF Grant DGE-1321851

Title: A novel self-contained three-dimensional platform to model intra-axonal contractile forces and tension-mediated elongation in post-synaptic axonal tracts

Authors: *W. J. GORDIAN VELEZ[1,2,3], D. O. ADEWOLE[1,2,3], L. A. STRUZYNA[1,2,3], E. R. CULLEN[3], J. C. O'DONNELL[2,3], D. K. CULLEN[2,3]
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Abstract: The ability of axons to internally produce mechanical forces and respond to externally generated forces is crucial for nervous system development, maintenance, and plasticity. Indeed, axonal retraction is essential for developmental pruning, while “stretch-growth” occurs as post-synaptic axons are elongated in response to tension as an organism grows. Such axonal mechanobiological phenomena have typically been modeled *in vitro*, but these systems are often limited by a failure to emulate important anatomical and three-dimensional features of native tissue. We have pioneered the development of micro-tissue engineered neural networks (micro-TENNs) comprised of discrete neuronal populations at either end of hydrogel micro-columns spanned by long-projecting axonal tracts. Micro-TENNs recapitulate the general gray matter – white matter architecture of the brain, and thus may serve as physiologically-relevant investigational platforms with controllable cell phenotype(s), architecture, physical/mechanical properties, and biochemical signaling. In this study, we utilized micro-TENNs to model contractile forces generated by integrated, post-synaptic axonal tracts within 3-10 millimeter-long engineered micro-columns (outer and inner diameter: 345 and 180 microns) with an extracellular matrix lumen. Phenotype-specific primary rat neurons (e.g., cerebral cortical, spinal motor, or dorsal root ganglia) were dissociated and re-aggregated into spheres. An alpha (large) aggregate was seeded into one end while a beta (smaller) aggregate was plated at the other end. Over several days *in vitro*, traditional growth-cone mediated axonal outgrowth resulted in the formation of integrated axonal tracts between the aggregates. This was followed by axonal tract contraction and the beta aggregate being pulled inwards at rates on the order of 0.5-0.8 mm/day. In turn, these internal forces from the retracting axons caused ancillary axons projecting outward from the beta aggregate to be mechanically “stretch-grown”. Contraction ended with the fusion

of both aggregates and their axonal tracts. We have observed retraction of integrated axonal tracts in all neuronal subtypes evaluated to date, implicating fundamental mechanobiological mechanisms yet to be described. This is the first demonstration of an *in vitro* test bed capable of modeling contractile and tensile forces in integrated axonal tracts absent the application of external forces. As such, ongoing efforts include employing this platform to elucidate mechanisms of intra-axonal force generation important for proper nervous system development and implicated in neurodegenerative disorders.

Disclosures: W.J. Gordian Velez: None. **D.O. Adewole:** None. **L.A. Struzyna:** None. **E.R. Cullen:** None. **J.C. O'Donnell:** None. **D.K. Cullen:** None.

Poster

199. Axon: Intrinsic Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 199.19/B45

Topic: A.05. Axon and Dendrite Development

Support: National Research Foundation of Korea (NRF) Grant 2015R1C1A1A02036674

Title: Axonal mRNA dynamics in live hippocampal neurons

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Abstract: Local protein synthesis has a critical role in axonal guidance and regeneration. Yet it is not clearly understood how abundantly mRNA molecules are present in axons and how the mRNA localization is regulated in axons. To address these questions, we investigated mRNA motion in live axons using a transgenic mouse that expresses fluorescently labeled endogenous β-actin mRNA. By culturing hippocampal neurons in a microfluidic device that allows separation of axons from dendrites, we performed single particle tracking of β-actin mRNA selectively in axons. We found that β-actin mRNAs frequently localize at the neck of filopodia which can grow as an axon collateral branches and at varicosities where synapses typically occur. Since both filopodia and varicosities are known as actin-rich areas, we investigated the dynamics of actin filaments and β-actin mRNAs simultaneously by using high-speed dual-color imaging. We found that axonal mRNAs colocalize with actin filaments and show sub-diffusive motion within the actin-rich regions. Although axonal mRNAs need to travel a long distance, we observed that most of axonal mRNAs show much less directed motion than dendritic mRNAs.

The novel findings on the dynamics of β-actin mRNA will shed important light on the biophysical mechanisms of mRNA transport and localization in axons.

Disclosures: B. Lee: None. **S. Bang:** None. **S. Lee:** None. **N. Jeon:** None. **H. Park:** None.

Poster

199. Axon: Intrinsic Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 199.20/B46

Topic: A.05. Axon and Dendrite Development

Title: mTOR upregulation in Neuro2a cells alters spontaneous intracellular calcium signaling

Authors: *C. L. KUBERA, J. HIMMELREICH, K. FITTIPALDI, H. COUGHLIN, R. BASTIAN
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Abstract: The mechanistic target of rapamycin (mTOR) is an atypical serine/threonine protein kinase involved in a wide variety of cellular pathways contributing to normal cell growth and development. During brain development, dysregulation of mTOR activity has been implicated in disorders including autism, epilepsy, and tuberous sclerosis. In particular, hyperactive mTOR activity can lead to aberrant axon growth and targeting, indicating an important role in cell process extension. Cytosolic calcium elevation within the cell is also important for neurite outgrowth and steering, though a connection between mTOR activity and calcium signaling is not well established. In this study, we hypothesized that increasing mTOR activity would elevate calcium signaling levels important for neurite extension and outgrowth. *Mus musculus* Neuro2a neuroblastoma cells were transfected with constitutively active Rheb plasmid (pCAG-CA-Rheb) to drive continuous mTOR activity, and a genetically encoded calcium sensor (pCAG-GCaMP3) to detect oscillations in cytosolic calcium. Live calcium imaging was performed to assess the duration, frequency, and location of calcium elevations. Preliminary results indicate that CA-Rheb treatment increases both duration and frequency of spontaneous calcium signals. However, increased mTOR activity does not influence calcium levels differently according to location; calcium activity increases similarly in both cell bodies and in cell processes. These results suggest calcium signaling may be generally increased as a function of mTOR activity, indicating a potential relationship between mTOR and calcium signaling in regulating cellular processes such as neurite extension. As such, these findings contribute to the understanding of important aspects of intracellular signaling related to nerve cell development.

Disclosures: C.L. Kubera: None. **J. Himmelreich:** None. **K. Fittipaldi:** None. **H. Coughlin:** None. **R. Bastian:** None.

Poster

199. Axon: Intrinsic Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 199.21/B47

Topic: A.05. Axon and Dendrite Development

Title: Regulation of DISC1 by FBXL14 during neurodevelopment

Authors: *P.-H. HUANG[1], H.-J. CHENG[2]
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Abstract: Schizophrenia, characterized by disorders of thought and cognitive function, accounts for the top ten leading causes of disability. Although etiologically heterogeneous in nature, multiple lines of study support the idea that schizophrenia is a neurodevelopmental disorder that leads to aberrant neuronal connectivity. Many susceptibility risk factors for schizophrenia have been identified, among which DISC1 (for Disrupted-in-Schizophrenia-1) is recognized as the leading risk factor. DISC1 functions by interacting with various molecules in different subcellular compartments to regulate multiple signaling pathways during neurodevelopment. Here, we report that the level of DISC1 protein is controlled by SCF^{FBXL14} via the ubiquitin/proteasome degradation pathway. FBXL14 (F-box and leucine-rich repeat 14) forms protein complex with DISC1 through direct binding with DISC1's N-terminal domain, which has been shown to be required for GSK3β interaction. Using *in utero* electroporation (IUEP), we found that either knock-down or overexpression of *mFbxl14* causes mouse embryonic cortical neuron migration defect, which phenocopies those caused by knock-down of *mDisc1*. Using the mDISC1-transgenic worm model we have established previously, we demonstrate that the worm *C. elegans* FBXL gene *C02F5.7b* suppresses transgenic *disc1's* effects on axon guidance in the Rac-independent pathway. In addition, overexpression of *C02F5.7b* in *C. elegans* VCCMNs causes axon guidance defect. Our data suggest that DISC1 protein level is critically regulated by FBXL during neurodevelopmental processes.

Disclosures: P. Huang: None. **H. Cheng:** None.

Poster

199. Axon: Intrinsic Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 199.22/B48

Topic: A.05. Axon and Dendrite Development

Support: T32 GM007226-40

Title: Growth cone subcellular RNA-proteome mapping in subtype-specific cortical circuit development

Authors: *J. HATCH[1], A. POULOPOULOS[3], J. D. MACKLIS[2]
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Abstract: During development, growth cones (GCs) of diverse cortical or other projection neuron (PN) subtypes navigate complex extracellular environments to reach distant, subtype-specific targets. These axon-terminal structures must respond to substrate-bound and diffusible signals in a subtype- and stage/context-specific fashion to construct specific functional circuitry. Recent studies strongly indicate that subcellular localization of specific molecular machinery to GCs might underlie the precise behaviors of these structures during circuit "wiring." While great progress has been made toward identifying diffusible and substrate-bound signals that guide axon growth, it is becoming increasingly clear that intracellular local growth cone biology underlies the distinct responses of specific neuronal subtypes at specific stages in specific contexts. Molecular determinants of these critical processes remain largely unstudied with respect to distinct neuronal subtypes under physiological conditions. Because most current knowledge of growth cone biology was identified *in vitro,* often with heterogeneous populations, access to subtype-specific growth cones in their native environment during normal development will substantially elucidate molecular bases of cortical and other neural circuit formation.
Our laboratory has recently developed an innovative approach that enables high-throughput proteomic and transcriptomic investigation of GCs from fluorescently labeled subtype-specific cortical projection neurons. This approach has already revealed unanticipated depth of GC molecular machinery, subtype-specificity, and GC enrichment of hundreds of transcripts and proteins. Building on this foundational work, GCs have been isolated from closely-related PN subtypes with distinct axonal trajectories at critical developmental stages to investigate whether and how subtype-specific GC molecular machinery might functionally enable specific subtypes to build and maintain specific circuitry. In particular, we compare GCs from corticothalamic PN that implement a corticofugal trajectory and from callosal PN during development of interhemispheric corticocortical projections. These data inform planned functional experiments to investigate whether and how subtype-specific GC-localized transcripts regulate the formation of precise and intricate functional circuitry in the CNS.

Disclosures: J. Hatch: None. **A. Poulopoulos:** None. **J.D. Macklis:** None.

Poster

199. Axon: Intrinsic Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 199.23/DP01/B49 (Dynamic Poster)

Topic: A.05. Axon and Dendrite Development

Support: NIH-NICHD grant P01 HD083157

Title: On the right track: Building the circuit for feeding and swallowing

Authors: *Z. MOTAHARI[1,2], A. S. POPRATILOFF[1,2,3], S. A. MOODY[1,2], A. S. LAMANTIA[2,4]
[1]Anat. and Regenerative Biol., [2]Inst. for Neurosci., [3]Nanofabrication and Imaging Ctr., [4]Pharmacol. and Physiol., George Washington Univ., Washington, DC

Abstract: Pediatric dysphagia, feeding and swallowing difficulty, is a serious complication that can be recognized in 35% to 80% of children with neurodevelopmental disorders. The consequences of pediatric dysphagia include malnutrition, acute choking, and food aspirations leading to nasal, middle ear, and lung infections. Although the causes are unknown, studies in *LgDel* mouse model of dysphagia suggest the aberrant development of several cranial nerves. Particularly affected is the trigeminal nerve (CNV), which provides sensory innervation to the face and oral cavity as well as motor innervation to the muscles of mastication. Furthermore, in *LgDel* animals the retinoic acid-mediated anterior-posterior patterning of the hindbrain is disrupted. Since CNV sensory as well as motor/inter neurons arise form distinct rhombomeric locations in the hindbrain, the altered hindbrain patterning suggests that the neural circuits for feeding and swallowing is disrupted. We retrogradely labeled trigeminal sensory and motor axons in living E11.5 embryos using Alexa Fluor® 594 biocytin injected into pharyngeal arch 1B. Embryos were incubated at 37° in cell culture medium for one hour, fixed, cleared and prepared as a whole mount for confocal 3D imaging. In wild type animals, both sensory and motor CNV axons project directly toward the correct target, pharyngeal arch 1B. Their pathway is direct, with no indications of wandering or branching. *LgDel* CNV axons also project to the correct target, However, they branch, misroute, or loop. Our preliminary results suggest that CNV phenotype in *LgDel* can be rescued by diminishing retinoic acid signaling genetically. Thus 3D imaging in whole E11.5 embryos can resolved compromised axon pathfinding in *LgDel* animals that might otherwise have been missed using conventional techniques. Thus abnormal individual axon trajectories are at least partially responsible for disrupted construction of a key component of the sensory and motor circuitry that may underlie feeding and swallowing difficulties that accompany 22q11 gene deletion.

Disclosures: Z. Motahari: None. **A.S. Popratiloff:** None. **S.A. Moody:** None. **A.S. LaMantia:** None.

Poster

199. Axon: Intrinsic Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 199.24/B50

Topic: A.05. Axon and Dendrite Development

Title: Mechanisms of Robo1/2-mediated motor neuron cell body and axon positioning in the spinal cord

Authors: *K. NICKERSON[1], Y. ZHOU[1], A. JAWORSKI[2]
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Abstract: Neurons are wired up during development through the action of attractive and repulsive molecular cues that guide migrating neuronal cell bodies and axons to their destinations by activating receptors on the leading process of the neuron, the growth cone. Growth cones are frequently exposed to both attractive and repulsive cues at the same time, and axonal responses to these signals are dictated by one of two main modes of cue integration: parallel or hierarchical signaling. In parallel signaling, there are few interactions between signaling pathways, and growth cone behavior is dictated by a sum of total attractive and repulsive signals from different directions. Hierarchical cross-talk, however, relies heavily on the intersection of signaling cascades, and the response to select cues can dominate growth cone behavior by silencing signaling from other cues.
The receptors Robo1 and Robo2 mediate repulsion from secreted guidance cues of the Slit family, and DCC is a receptor for the attractive ligand Netrin-1. Previous research on the guidance of spinal commissural axons supports the idea that Slit-Robo1/2 signaling can silence DCC-mediated attraction to Netrin-1. Thus, Robo signaling might dominate over DCC signaling in commissural neurons, but whether this hierarchy of the Robo and DCC pathways is at work in other cell types has remained elusive.
Recent studies have identified several defects in spinal motor neuron migration and motor axon guidance of *Robo1/2* double mutant mice. In mice lacking Robo1 and Robo2, motor neuron cell bodies aberrantly migrate from the ventral horn into the commissure, and motor axons cross the spinal cord midline. The floor plate at the ventral midline expresses both Netrin-1 and Slits, and it has remained unclear whether motor neuron invasion of the midline in *Robo1/2* mutant mice is caused by a loss of Slit repulsion or a gain of Netrin-1 attraction due to absence of Robo1/2-mediated DCC silencing. Here, we address this question by combining mouse genetics, *in vivo* phenotype analysis, and *in vitro* motor neuron migration and axon guidance assays. Our results demonstrate that at least some of the *Robo1/2* mutant motor neuron phenotypes are caused by a loss of Slit-mediated midline repulsion, not a gain of Netrin-1 attraction. Hence, Slit-Robo1/2 and Netrin-1-DCC can signal in parallel in motor neurons.

Disclosures: **K. Nickerson:** None. **Y. Zhou:** None. **A. Jaworski:** None.

Poster

199. Axon: Intrinsic Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 199.25/B51

Topic: A.05. Axon and Dendrite Development

Title: Role of EphB1 in axon guidance and context fear memory

Authors: A. ASSALI[1], B. ZIRLIN[1], G. CHENAUX[2], M. ROBICHAUX[3], M. HENKEMEYER[4], *C. W. COWAN[1]
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Abstract: The EphB receptor tyrosine kinases and their Ephrin family ligands are transmembrane proteins critical in the developing brain for axon growth cone guidance, axonal pruning and synaptogenesis. In the mature brain, they are enriched at mature synapses and reported to regulate synapse plasticity. Analysis of EphB1 expression patterns reveals a strong enrichment of EphB1 in the developing and mature cortex, CA3 hippocampal region, striatum and habenula, but no detectable expression in the basolateral amygdala and thalamus. We showed previously that EphB1 controls proper navigation of a subset of thalamocortical and corticothalamic projections through the ventral telencephalon (Robichaux et al., 2014) and EphB1 is involved in formation of the corpus callosum (Robichaux et al, 2015). We report here that EphB1 global knockout mice show a significant deficit in contextual, but not cued, freezing behavior in the fear/threat conditioning paradigm. To address whether EphB1 influences fear memories through a role in brain development vs. adult plasticity, we generated floxed EphB1 mutant mice that allow for cre-dependent spatial, temporal and cell type-specific EphB1 gene deletion (conditional knockouts). Interestingly, embryonic deletion of EphB1 in most forebrain excitatory neurons (Emx1-lineage) did not produce cortical axon guidance deficits, suggesting that EphB1 is not functioning in the developing cortical projection neurons to mediate proper subcortical axon navigation. Moreover, the EphB1 conditional knockout mice have normal contextual fear conditioning phenotypes, suggesting that EphB1 is not acting in excitatory neurons of the cortex or hippocampus to mediate contextual fear learning and memory.

Disclosures: **A. Assali:** None. **B. Zirlin:** None. **G. Chenaux:** None. **M. Robichaux:** None. **M. Henkemeyer:** None. **C.W. Cowan:** None.

Poster

199. Axon: Intrinsic Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 199.26/B52

Topic: A.05. Axon and Dendrite Development

Title: Transcriptional signatures of inspiratory and expiratory motor neuron development

Authors: *S. KIM[1,2], A. H. YOON[1,2], K. KAM[1,3], S. SWARTWOOD[1], D. L. ROUSSO[1,2], D. MEIJER[4], M. LEID[5], J. L. FELDMAN[1], B. G. NOVITCH[1,2]
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Abstract: Respiration is an essential motor behavior, required from birth to death in all terrestrial species. At the core of this vital function are respiratory motor neurons (MNs) in the spinal cord that innervate distinct muscle targets such as the diaphragm, intercostals, and abdominals to produce alternating inspiratory and expiratory movements. The mechanisms accounting for the diversity of respiratory MN subtypes remain unclear. Here, we identify two transcription factors, Pou3f1 and Bcl11b as characteristic signatures of inspiratory and expiratory MNs, respectively. We further show that Pou3f1 function is required for multiple aspects of inspiratory MN and motor circuit development. In the absence of Pou3f1, phrenic and a subset of intercostal MN numbers are reduced. Moreover, distal innervation of the diaphragm is reduced, and rhythmic inspiratory motor activities disrupted. Bcl11b loss on the other hand leads to aberrant expression of Pou3f1 and disruptions in respiratory motor axon projections. Together, these data identify new functional regulators of respiratory motor neuron identity, and provide evidence for the deployment of distinct transcriptional programs for inspiratory and expiratory motor functions.

Disclosures: S. Kim: None. **A.H. Yoon:** None. **K. Kam:** None. **S. Swartwood:** None. **D.L. Rousso:** None. **D. Meijer:** None. **M. Leid:** None. **J.L. Feldman:** None. **B.G. Novitch:** None.

Poster

199. Axon: Intrinsic Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 199.27/B53

Topic: A.05. Axon and Dendrite Development

Support: Stowers Institute for Medical Research

NIH Grant 008003

Title: Pilot neurons regulate early postnatal axon projections in the olfactory system

Authors: *Y. WU[1], L. MA[1], H. SCHEERER[1], W. XU[1], R. YU[1,2]
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Abstract: In the murine olfactory system, the olfactory sensory neurons expressing the same olfactory receptor converge into stereotypic glomeruli, forming a topographic map. Despite continuous neurogenesis, we found that there is a critical period in the formation of the olfactory map during early postnatal development, when OSNs can correct mistargeting and re-organize the map. In this study, we genetically labeled the neurons generated at different development time and traced the dynamic changes in axon projection patterns. We found neurons born around birth are capable of exuberant axon growth and project through multiple glomeruli before terminating in a specific target. These neurons have short lifespan and are eliminated soon after the closure of the critical period. Premature elimination of these cells with genetic manipulations leads to mistargeted OSN axons, suggesting that they are required for map formation. Extending the lifespan of this population leads to excessive exuberant axons beyond the critical period. For their specific role in establishing the olfactory map, we define the perinatally generated OSNs as the pilot neurons. The pilot neurons are capable of forming the map de novo, whereas the late-generated populations rely on the existing projection pattern of established by the pilot neurons to maintain the map.

Disclosures: Y. Wu: None. **L. Ma:** None. **H. Scheerer:** None. **W. Xu:** None. **R. Yu:** None.

Poster

200. GABAA and Other Ligand-Gated Ion Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 200.01/B54

Topic: B.02. Ligand-Gated Ion Channels

Support: NIAAA INIA U01-020935

North Carolina A&T State University Division of Research and Economic Development

R25 GM076162

Title: Pregnenolone administration increases brain 3α,5α-THP levels in male C57BL/6J mice

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Abstract: Neuroactive steroids are endogenous neuromodulators synthesized in the brain that impact neuronal activity and influence emotional behavior. They have anticonvulsant and anti-inflammatory properties and have been shown to have therapeutic efficacy in several neuropsychiatric and neurodegenerative disorders. Neuroactive steroids help regulate brain homeostasis and are potent positive allosteric neuromodulators to $GABA_A$ receptors, where they can potentiate brain inhibition. Pregnenolone is derived from cholesterol in the brain and serves as the endogenous precursor for neuroactive steroid synthesis. Currently pregnenolone is used in human clinical trials, however, it is not clear if it is producing its effects by increasing brain neuroactive steroid levels. Therefore, the present work determined if exogenous pregnenolone administration would increase local brain levels of the most potent GABAergic neuroactive steroid, (3α,5α)-3-hydroxy-pregnan-20-one (3α,5α-THP). Pregnenolone (50 mg/kg, i.p.) or vehicle was administered to C57BL/6J male mice. After 45 minutes, the mice were euthanized, perfused, and brains were collected for immunohistochemical analysis. Exogenous pregnenolone administration increased 3α,5α-THP levels in the amygdala, hippocampus, and nucleus accumbens. Pregnenolone administration increased 3α,5α-THP levels by 42.9±16.2% in the lateral amygdala and by 68.1±24.7% in the basolateral amygdala compared to vehicle-administered mice. There was a 34.2±14.4% increase in 3α,5α-THP levels in the polymorph cell layer of the dentate gyrus of the hippocampus and a 41.8±19.6% increase in 3α,5α-THP levels in nucleus accumbens core. These results show that exogenous pregnenolone administration increases local brain 3α,5α-THP levels in all limbic brain regions examined. This work is important given that pregnenolone administration could be used as a potential therapeutic strategy to ameliorate or reverse deficits in neuroactive steroid levels induced by neuropsychiatric disease.

Disclosures: K.J. Davidson: None. **T. Little:** None. **A. Morrow:** None. **A.M. Maldonado-Devincci:** None.

Poster

200. GABAA and Other Ligand-Gated Ion Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 200.02/B55

Topic: B.02. Ligand-Gated Ion Channels

Support: Wellcome Trust Grant

Title: Neurosteroid regulation of excitability and tonic inhibition at GABA-α4 receptors

Authors: *M. MINERE[1], T. G. SMART[2]
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Abstract: Type A γ-aminobutyric acid receptors ($GABA_A$Rs) are crucial for controlling excitability in the central nervous system by mediating phasic (synaptic) and tonic (extrasynaptic) inhibition. Typically, phasic and tonic inhibition are mediated by $GABA_A$Rs with different subunit composition with synaptic receptors comprising α1-3βγ whereas extrasynaptic receptors also include α4-6βδ isoforms. Dysfunctional inhibition causing disruption to the excitation-inhibition balance has been implicated in many psychological disorders such as anxiety and sleep, and circadian rhythm disturbance (Yizhar et al. 2011).
An important innate modulator class of GABA inhibition are the neurosteroids, allopregnanolone and allotetrahydrodeoxycorticosterone (THDOC). These endogenous modulators act at $GABA_A$Rs, with some preference for δ-containing $GABA_A$Rs and thus are highly effective in modulating tonic inhibition. Neurosteroid production increases in response to stress (Möhler 2012), providing a rapid homeostatic regulatory mechanism. In addition, catamenial epilepsy also occurs as a result of hormonal fluctuations, which in turn affect neurosteroid production (Maguire et al. 2005).
Following the discovery of the neurosteroid binding site on $GABA_A$Rs (Hosie et al. 2007), we have created a new mouse line containing a knock-in mutation of a conserved glutamine to methionine in the α4 subunit. This substitution should prevent neurosteroid binding and modulation of α4 subunit-containing $GABA_A$Rs, and thus allow the role of neurosteroid modulation at receptors containing α4 subunits to be investigated.
Quantitative Western blots for receptor subunit expression in various brain regions revealed no significant differences between wild-type and homozygote knock-ins. The incorporation of the mutation in recombinant and neuronal α4 subunit receptors were characterised. The mutation selectively disrupts neurosteroid modulation without altering any other properties of the receptors. Using acute slices, the consequences of the binding site mutation and lack of neurosteroid modulation revealed a significant effect on GABA tonic currents and a smaller effect α4 receptor mediated inhibitory synaptic currents. Finally, current clamp experiments show that the knock-in mutation significantly reduced THDOC modulation of cell excitability.

These findings will be used to understand the physiological importance of neurosteroid modulation at α4 receptors.

Disclosures: **M. Minere:** None. **T.G. Smart:** None.

Poster

200. GABAA and Other Ligand-Gated Ion Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 200.03/B56

Topic: B.02. Ligand-Gated Ion Channels

Support: Whitehall Foundation

NINDS T32 NS086749

Pharmacology and Chemical Biology Department Startup Funds

Title: Rapid agonist induced GABAergic synaptic and functional plasticity

Authors: ***T. C. JACOB**, M. L. BRADY, J. PILLI, J. M. LORENZ-GUERTIN, S. DAS, C. E. MOON, N. GRAFF
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Abstract: γ-aminobutyric acid (GABA) begins as the key excitatory neurotransmitter in newly forming circuits, with chloride efflux from $GABA_A$ receptors ($GABA_ARs$) producing membrane depolarization, which promotes calcium entry, dendritic outgrowth and synaptogenesis. As development proceeds, GABAergic signaling switches to inhibitory hyperpolarizing neurotransmission. Despite the evidence of impaired GABAergic neurotransmission in neurodevelopment disorders, little is understood on how agonist dependent $GABA_AR$ activation controls the formation and plasticity of GABAergic synapses. We have identified a weakly depolarizing and inhibitory $GABA_AR$ response in cortical neurons with well-established GABAergic synapses that occurs during the transition period from $GABA_AR$ depolarizing excitation to hyperpolarizing inhibitory activity. We show here that $GABA_AR$ agonist treatment at this stage mediates structural changes that diminish GABAergic synapse strength through postsynaptic and presynaptic plasticity via intracellular Ca2+ stores, ERK and BDNF/TrkB signaling. We show that $GABA_AR$ stimulation results in delayed activation of the ERK pathway, a cellular response distinct from early excitatory depolarizing $GABA_AR$ activity. Application of the $GABA_AR$ agonist muscimol decreases synaptic localization of surface γ2 $GABA_ARs$ and gephyrin postsynaptic scaffold while β2/3 non-γ2 $GABA_ARs$ accumulate in the synapse. Concurrent with this structural plasticity, muscimol treatment decreases synaptic currents while enhancing γ2 containing $GABA_AR$ tonic currents in an ERK dependent manner. We further demonstrate that $GABA_AR$ activation leads to a decrease in presynaptic GAD-65 levels via

BDNF/TrkB signaling. Together these data reveal a novel mechanism for agonist induced GABAergic synapse plasticity that can occur on the timescale of minutes, contributing to rapid modification of synaptic and circuit function.

Disclosures: **T.C. Jacob:** None. **M.L. Brady:** None. **J. Pilli:** None. **J.M. Lorenz-Guertin:** None. **S. Das:** None. **C.E. Moon:** None. **N. Graff:** None.

Poster

200. GABAA and Other Ligand-Gated Ion Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 200.04/B57

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH Training Grant T32GM008424

The Whitehall Foundation

William C. deGroat Neuropharmacology Departmental Fellowship

Pharmacology & Chemical Biology Startup Funds

Title: Diazepam induces bidirectional modulation of the GABA type A receptor

Authors: *J. LORENZ-GUERTIN[1], S. DAS[1], J. PILLI[1], M. MACDONALD[2], T. JACOB[1]
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Abstract: Despite 50+ years of clinical use as anxiolytics, anti-convulsants, and sedative/hypnotic agents, the mechanisms underlying benzodiazepine (BZD) tolerance are poorly understood. BZDs potentiate the actions of gamma-aminobutyric acid (GABA), the primary inhibitory neurotransmitter in the adult brain, through positive allosteric modulation of γ2 subunit containing GABA type A receptors ($GABA_AR$). Our work uses the classical BZD, diazepam (DZP), for in-vitro and in-vivo experiments combined with novel live imaging approaches, biochemical methods and mass spectrometry to identify BZD-induced changes in $GABA_AR$ signaling. Previous findings from our lab and others have implicated trafficking mechanisms in the loss of BZD potentiation associated with tolerance. To identify cellular mechanisms contributing to BZD insensitivity, we engineered a novel $GABA_AR$ γ2 subunit that is capable of tracking receptors through nearly all phases of trafficking. An N terminal fluorogen-activating peptide (FAP) was genetically inserted into a γ2 subunit tagged with pH-sensitive green fluorescent protein ($γ2^{pH}FAP$). The FAP selectively binds and activates malachite green dyes that are otherwise non-fluorescent in solution. Ongoing experiments are investigating DZP-induced modifications of receptor trafficking using this novel optical reporter. Complementary microscopy studies of endogenous $GABA_ARs$ in rat cortical neurons indicate

24h exposure of 1μM DZP causes a reduction in extrasynaptic γ2 levels and modification of the inhibitory synaptic scaffolding protein gephyrin. Immunoprecipitation experiments reveal enhanced ubiquitination of the γ2 subunit and reduced total levels in-vitro following DZP. Pilot biochemical studies of mice injected with 10mg/kg DZP vs vehicle also show a significant decrease in γ2 subunit cortical levels 12 hr post DZP injection. In contrast, mice with robust sedative tolerance following daily DZP treatment for 1 week have increased cortical $GABA_AR$ and excitatory *N*-methyl-D-aspartate receptor (NMDAR) subunit levels. Quantitative mass spectrometry experiments confirmed enhanced NMDAR expression, although no significant change in $GABA_AR$ levels was detected. Acute slices from 7 day DZP treated mice show loss of DZP potentiation of miniature inhibitory postsynaptic currents (mIPSCs), verifying DZP tolerance had occurred. Overall, our work suggests initial DZP exposure induces a decrease in γ2 $GABA_ARs$ and gephyrin scaffolding function, while compensatory mechanisms restore and potentially enhance overall $GABA_AR$ levels during functional and behavioral DZP tolerance.

Disclosures: J. Lorenz-Guertin: None. **S. Das:** None. **J. Pilli:** None. **M. MacDonald:** None. **T. Jacob:** None.

Poster

200. GABAA and Other Ligand-Gated Ion Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 200.05/B58

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH Grant GM58448

Title: Structural determinants for selective binding of drugs to intersubunit general anesthetic binding sites in the α1β3γ2 γ-aminobutyric acid type A receptor transmembrane domain

Authors: *S. S. JAYAKAR[1], X. ZHOU[3], P. Y. SAVECHENKOV[4], K. S. BRUZIK[4], K. W. MILLER[3,2], J. B. COHEN[1]
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Abstract: γ-aminobutyric acid type A receptors ($GABA_AR$) are targets for important classes of clinical agents (e.g. anxiolytics, anticonvulsants and general anesthetics). In αβγ $GABA_ARs$, the most abundant subtype in the central nervous system, subunits are ordered β^+-α^--β^+-α^--γ^+, counterclockwise, with the agonist and benzodiazepine binding sites located in the extracellular domain at β^+-α^- and α^+-γ^- subunit interfaces, respectively. Previously, using photoreactive analogs of general anesthetics, we identified two homologous but pharmacologically distinct classes of general anesthetic binding sites in the $GABA_AR$ transmembrane domain at β^+-α^-

(β^+sites) and α^+-β^-/γ^+-β^- (β^- sites) subunit interfaces (Chiara et al., J. Biol. Chem. 2013, 288:19343). In the presence of GABA, [^{3}H]azietomidate, a photoreactive etomidate analog, binds with 100-fold selectivity to β^+ sites (IC_{50} = 3 μM), and [^{3}H]*R*-*m*TFD-MPAB, a photoreactive mephobarbital analog, binds to β^- sites (IC_{50} = 1.3 μM) with 60-fold selectivity. Propofol, a widely used general anesthetic of simple chemical structure, binds to both classes of sites with similar affinity. Developing propofol analogs with greater structural complexity may increase selectivity for a class of interface sites within a $GABA_AR$ subtype, limiting undesirable interactions with off-targets. Here, we use [^{3}H]azietomidate and [^{3}H]*R*-*m*TFD-MPAB to identify para-substituted propofol analogs and other drugs that bind selectively to intersubunit anesthetic sites. Analogs with small electronegative substitutions (*p*-chloro-propofol, *p*-acetyl-propofol) bind with similar affinities to the β^+ and β^- sites. Analogs with bulkier lipophilic substitutions (*p*-(tert-butyl)-propofol; 4-(hydroxyl(phenyl)methyl)-propofol) bind with ~20-fold higher affinity to β^- than to β^+sites. Similar to *R*-*m*TFD-MPAB and propofol, these drugs bind in the presence of GABA with similar affinity to the α^+-β^- and γ^+-β^- sites. However, *p*-benzoyl-propofol binds with >100- fold higher affinity to the α^+-β^- site than to either the γ^+-β^- or the β^+-α^- sites. Drugs that act as sedatives and anticonvulsants can also bind non-equivalently to intersubunit anesthetic binding sites. Stiripentol binds with >10-fold selectivity to β^- sites (IC_{50} = 75 μM). Loreclezole binds with 100-fold higher affinity to β^+-α^- (IC_{50} = 4 μM) and α^+-β^- sites than to the γ^+-β^- site. Tracazolate binds with 15-fold higher affinity to β^+ (IC_{50} =2 μM) than to α^+-β^- . These studies show that it is possible to develop propofol derivatives and other drugs that bind selectively to specific subunit interface sites in heteromeric $GABA_ARs$.

Disclosures: S.S. Jayakar: None. **X. Zhou:** None. **P.Y. Savechenkov:** None. **K.S. Bruzik:** None. **K.W. Miller:** None. **J.B. Cohen:** None.

Poster

200. GABAA and Other Ligand-Gated Ion Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 200.06/B59

Topic: B.02. Ligand-Gated Ion Channels

Title: The effect of neonatal sevoflurane on adult $gaba_a$ receptor

Authors: *D. LIN[1], J. LIU[2], J. COTTRELL[2], I. KASS[1]
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Abstract: Introduction:
Sevoflurane (sevo) targets the $GABA_A$ receptor by enhancing inhibitory synaptic transmission in neurons. This is one of the main targets of sevo in the CNS to produce an anesthetic state. The early developing brain is especially vulnerable to insults from different anesthetics, including

sevo, which can result in long lasting behavioral changes. How is the $GABA_A$ receptor being modulated after exposure to sevo during the neonatal period? To address this question, we first investigated the changes in the electrophysiological properties of $GABA_A$ receptors in adults that had undergone P7 sevo treatment. We then examined the functional correlates of these changes by challenging the locomotion of mice with amphetamine, an inhibitory modulator of the $GABA_A$ receptor.

Methods:

Postnatal day 7 (P7) C57/BL6 male pups were exposed to 2-2.3% sevo in a 40% oxygen (O2) 60% nitrogen (N2) gas mixture for 2 hours. Pups were reared and weaned under standard condition. Electrophysiology and behavior experiments were conducted when the mice were adults (7-9 weeks old). Extracellular population spikes were recorded from the CA 1 region of hippocampus slices. Paired-pulse stimulation was carried out at 20ms intervals using stimulations that that evoked 50% of the maximum response. For the amphetamine challenge experiments, mice were given an I.P injection of 3mg/kg of amphetamine and their locomotion behavior was examined in an open field apparatus.

Results:

Paired-pulse stimulation in the CA1 region of the hippocampus showed that adult mice treated with sevo at P7 had significantly less inhibition/increased excitation compared to no sevo treated mice ($P<0.05$). This inhibition in the no sevo group started to gradually diminish when the interval between the paired-pulse was increased to 200ms. When given an amphetamine challenge as adults, P7 sevo treated mice showed significant less locomotion (total distance travelled) compared to no sevo treated mice ($P<0.05$).

Conclusions:

The $GABA_A$ receptor plays a putative role in P7 sevo treatment, resulting in decreased inhibitory transmission during adult. This possible role of $GABA_A$ receptor is further observed when the P7 treated adults showed a decreased response to amphetamine challenge. It is plausible that the $GABA_A$ receptor mediated excitation-inhibition imbalance is the underlying mechanism of P7 sevo exposure related behavioral changes.

Disclosures: D. Lin: None. **J. Liu:** None. **J. Cottrell:** None. **I. Kass:** None.

Poster

200. GABAA and Other Ligand-Gated Ion Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 200.07/B60

Topic: B.02. Ligand-Gated Ion Channels

Support: NHMRC Grant APP1081733

Title: The role of the extrasynaptic δ-containing $GABA_A$ receptors early in stroke

Authors: *L. Y. HARTIADI[1], P. S. VAN NIEUWENHUIJZEN[1], E. GOWING[2], L. BOOTHMAN-BURRELL[2], A. CLARKSON[2], M. CHEBIB[1]
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Abstract: Stroke is the leading cause of disabilty world wide. Stroke survivors suffer from muscle weakness, paralysis and impaired cognitive function. To date, tissue plasminogen activator (t-PA) is the only pharmacological agent approved for stroke and t-PA must be given in the first 4.5 hours after stroke onset to be effective. Because of the limited time window for administration, new pharmacological treatment is needed for stroke. There is little translation of treatment from animal models to the clinic because of significant side-effects, targeting specific $GABA_A$ receptors could provide stroke specific treatments without the side-effects. Decreasing tonic inhibition using the negative allosteric modulator of α5-containing receptors, L655,708, 3-days post-stroke resulted in motor recovery in a mouse model of phototrombotic ischaemia (Clarkson *et. al*., 2010). However, the application of L655,708 early after stroke resulted in a significant increase of infarct size, indicating that decreasing tonic inhibition too early exacerbates stroke. Overall, these results showed that timing of intervention plays a crucial role. To investigate the role of tonic inhibition early after stroke, THIP, an agonist that has preference for δ-containing receptors, was given 1 hour post-stroke in photothrombotic mouse model. Stroke outcomes were evaluated using sensorimotor function tests and infarct size measurement. Mice-treated THIP showed improvement compared to mice-treated vehicles. To establish whether the recovery-promoting effect is mediated via the δ-containing receptors, δ knock-out mice was used. The results of this study will unravel whether the extrasynaptic receptors, in particular the δ-containing receptors, could serve as a potential novel drug target for the treatment of stroke.
Reference
Clarkson AN, Huang BS, Macisaac SE, Mody I, Carmichael ST. Reducing excessive GABA-mediated tonic inhibition promotes functional recovery after stroke. Nature. 2010;468(7321):305-9.

Disclosures: L.Y. Hartiadi: None. **P.S. van Nieuwenhuijzen:** None. **E. Gowing:** None. **L. Boothman-Burrell:** None. **A. Clarkson:** None. **M. Chebib:** None.

Poster

200. GABAA and Other Ligand-Gated Ion Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 200.08/B61

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH Grant 1F31DA042564-01

Title: Electrostatic interactions of the $GABA_AR$ influence benzodiazepine action

Authors: *N. C. PFLANZ[1], A. W. DASZKOWSKI[2], S. J. MIHIC[2]
[1]Col. of Pharm., Univ. of Texas At Austin, Austin, TX; [2]Univ. of Texas at Austin, Austin, TX

Abstract: Benzodiazepines enhance α(1-3,5)βγ $GABA_A$ Receptor ($GABA_AR$) function by acting as positive allosteric modulators at the alpha-gamma subunit interface. However, the molecular process by which this enhancement occurs remains to be fully elucidated. Using molecular modelling of the $GABA_AR$, we identified electrostatic interactions between charged amino acids which were broken or formed at the alpha-gamma interface before and after benzodiazepine binding. Using two-electrode voltage clamp electrophysiology with *Xenopus laevis* oocytes, we probed these interactions by mutating one or both amino acids of each potential pair. Our data suggests that Lysine 104 and Aspartic Acid 75 form an electrostatic interaction after benzodiazepine binding, as cysteine linkage of these two residues reduces benzodiazepine effects and left-shifts the concentration-response curve. This cysteine linked receptor closely resembles a benzodiazepine-bound wildtype $GABA_AR$ receptor pharmacologically. Breaking this interaction results in increased benzodiazepine effects and a right-shifting of the concentration-response curve. Interestingly, this interaction does not seem to play a role in ethanol or neurosteroid modulation of the $GABA_AR$, suggesting that different modulators produce different conformational changes of the receptor. These findings may help explain the additive and/or synergistic effects of modulators of the $GABA_AR$.

Disclosures: N.C. Pflanz: None. **A.W. Daszkowski:** None. **S.J. Mihic:** None.

Poster

200. GABAA and Other Ligand-Gated Ion Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 200.09/B62

Topic: B.02. Ligand-Gated Ion Channels

Support: National Institute on Aging (R01AG047296) to RM

Louisiana Board of Regents RCS (LEQSF(2016-19)-RD-A-24) to RM

COBRE on Aging and Regenerative Medicine (5P20GM103629) to RM

The Oliver Fund Scholars Award of Tulane University to RM

Louisiana Board of Regents Graduate Research Fellowship LEQSF (2013-18)-GF-17 to RV

Title: Higher IPSC frequencies in non-adapting than in adapting layer 5 pyramidal neurons in the somatosensory cortex of mice

Authors: *I. R. POPESCU[1], K. LE[2], R. VOGLEWEDE[1,2], R. MOSTANY[1,2]
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Abstract: Synaptic input is shaped by intrinsic electrophysiological properties that vary amongst cortical pyramidal neurons. Thus, small amplitude slow afterhyperpolarization, large amplitude sag, and lack of spike frequency adaptation characterize pyramidal tract-type neurons. Conversely, large amplitude slow afterhyperpolarization, small amplitude sag, and pronounced adaptation characterize intratelencephalic neurons. Since intrinsic electrophysiological properties determine neurons' responses to synaptic input, these properties may be functionally matched to synaptic inputs. Here we determined that spike frequency adaptation and the frequency of inhibitory synaptic input co-vary. We found that the frequency of inhibitory postsynaptic currents was several fold higher in non-adapting neurons compared with adapting neurons in layer 5 pyramidal neurons of the mouse primary somatosensory cortex. This difference persisted during action potential blockade, suggesting this phenomenon was activity independent, likely caused by higher numbers of GABAergic synapses on non-adapting neurons. Additionally, thy1-expressing neurons, previously shown to project beyond the telencephalon, were confirmed to be non-adapting, and we found that they also had higher spontaneous inhibitory postsynaptic current frequencies than adapting neurons. The larger inhibitory drive to non-adapting neurons suggests that, in conditions diminishing or enhancing GABAergic function, the excitation/inhibition balance is more susceptible to perturbation in these neurons than in adapting pyramidal neurons.

Disclosures: I.R. Popescu: None. **K. Le:** None. **R. Voglewede:** None. **R. Mostany:** None.

Poster

200. GABAA and Other Ligand-Gated Ion Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 200.10/B63

Topic: B.02. Ligand-Gated Ion Channels

Title: The role of $GABA_A$ receptor β subunits in the regulation of GABAergic synaptic transmission in hippocampus

Authors: *J. DUAN
NINDS, Bethesda, MD

Abstract: In the brain, the majority of fast inhibitory synaptic transmission is mediated by GABA acting on $GABA_A$ receptors. $GABA_A$ receptors are pentameric assemblies of five

subunits that belong to different subfamilies, including six α, three β, three γ, one δ, one ε, one π, three ρ, and one θ subunits. Despite the extensive heterogeneity of the $GABA_A$ receptor subunits, most native $GABA_A$Rs expressed in the brain are composed of two α subunits, two β subunits and one γ subunit. Recent studies have shown that $GABA_A$ receptor β subunits play important roles in the regulation of $GABA_A$ receptor assembly, trafficking, channel biophysical properties and pharmacology. In mouse hippocampus, all three β subunits are expressed in principal neurons. However, the contribution of individual β subunits to GABAergic synaptic transmission remains largely unclear. Here we have characterized β subunit expression and distribution in hippocampal neurons, and found that β subunits have overlapping, but also differential, subcellular distributions. Furthermore, we have employed a single-cell CRISPR-based gene knockout technique to genetically delete β subunits, either alone or in combination, and have utilized cell biological and electrophysiological approaches to examine GABAergic synaptic transmission, $GABA_A$ receptor trafficking and inhibitory synapse development. We found that $GABA_A$ receptor β subunits play differential roles in the regulation of the strength and maturation of GABAergic synaptic transmission in hippocampal neurons. These data provide functional characterization of $GABA_A$ receptor β subunits in the regulation of inhibitory synaptic transmission in hippocampus and suggest novel roles of β subunits in synaptic targeting of $GABA_A$ receptors.
Key words: GABA, synapse, inhibition, patch-clamp

Disclosures: J. Duan: None.

Poster

200. GABAA and Other Ligand-Gated Ion Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 200.11/B64

Topic: B.02. Ligand-Gated Ion Channels

Title: Selective alteration of inhibition in D1 spiny projection neurons in the nucleus accumbens of MMP-1 overexpressing mice

Authors: *N. AL-MUHTASIB[1], K. CONANT[2], S. VICINI[3]
[1]Dept. of Pharm, [2]Neurosci., [3]Pharmacol. & Physiol., Georgetown Univ., Washington, DC

Abstract: Matrix metalloproteinases (MMPs), including MMP-1, have been studied in the context of their effect on neuronal excitation in the hippocampus and several other brain regions. Similarly, activation of protease activated receptor-1 (PAR-1), a known MMP-1 target, induced a change in both miniature and spontaneous inhibitory post synaptic currents (mIPSCs and sIPSCs) in a subset of hippocampal neurons. The effect of MMP-1 and PAR-1 signaling on neuronal inhibition has yet to be studied in the ventral striatum. Recent evidence has implicated the ventral striatum with the coordination of motor movement. The neuronal makeup of the

ventral striatum includes two subtypes of GABAergic spiny projection neurons (SPNs), cholinergic interneurons, and GABAergic interneurons. The SPNs consist of dopamine D1 receptor containing SPNs (D1 SPNs) part of the direct pathway and dopamine D2 receptor containing SPNs (D2 SPNs) part of the indirect pathway. We studied the role of MMP-1 in the ventral striatum using mice in which the D1 SPNs fluoresce red and the D2 SPNs fluoresce green, allowing for the differentiation between the two subsets of SPNs crossed with a transgenic mouse that overexpresses MMP-1. This breeding scheme has allowed us to study transgenic mice (Tg) and their wild-type littermate controls (WT). The Tg mice display improved rotarod performance and alterations in spontaneous and amphetamine induced locomotion. Using the whole-cell patch clamp method and a potassium chloride based internal solution, we recorded mIPSCs and sIPSCs in D1 and D2 SPNs in the MMP-1 Tg mice and their WT littermates. Our data revealed a selective increase in frequency in sIPSCs (WT-0.65 Hz, Tg-1.29 Hz, n=13 per group) and mIPSCs (WT-0.45 Hz, Tg- 0.94, n=12 per group) in the D1 SPNs of the MMP-1 Tg mice. More specifically, there was a selective increase in shorter inter-event intervals suggesting alterations in firing properties of D1 SPNs. This was accompanied with the emergence of smaller peak amplitude sIPSCs and mIPSCs in the MMP-1 Tg mice. In accordance with the this, we observed an increase in membrane capacitance of D1 SPNs of MMP-1 Tg mice (WT-34.28 pF, Tg-53.54 pF, n=18 cells per group). Average amplitude, decay time, and rise time were similar in both D1 SPNs and D2 SPNs of the MMP-1 Tg and WT mice. Western blot data revealed unaltered PAR-1 expression in the striatum of the MMP-1 Tg mice. These phenotypes were not observed in PAR-1 knockout mice that also overexpress MMP-1. Our data suggest that PAR-1 mediated MMP-1 actions lead to alterations in inhibition selectively in D1 SPNs that correlate with a distinct motor behavioral phenotype.

Disclosures: **N. Al-Muhtasib:** None. **K. Conant:** None. **S. Vicini:** None.

Poster

200. GABAA and Other Ligand-Gated Ion Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 200.12/B65

Topic: B.02. Ligand-Gated Ion Channels

Title: Optimizing methods for the functional screening at $GABA_A$ receptor subtypes

Authors: *F. KNOFLACH[1], M.-C. HERNANDEZ[1], S. BERTRAND[2], D. BERTRAND[2]
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Abstract: With 19 genes encoding for separate protein subunits and the capacity to form pentameric receptors by combining multiple subunit types, the $GABA_A$ receptors is one of the most versatile ligand gated ion channel expressed in the central nervous system. The rich repertoire of possibilities offered by the $GABA_A$ receptors is magnificently exploited in the

central nervous system with the fine tuning of synaptic receptors and the high sensitivity of the extrasynaptic receptors. The therapeutic potential of designing $GABA_A$ specific molecules is illustrated by the importance of benzodiazepines and other related molecules in neurological treatments, important novel targets were recently identified. Whereas exploration of large libraries of compounds ranging up to several hundred thousand is often conducted using binding or functional assays using optical signal detection, successive steps in drug development pathways requires a precise characterization of the physiological and pharmacological properties of the lead compounds that is often tested using electrophysiological means. Taking advantage of automated electrophysiological recordings of recombinant $GABA_A$ receptors expressed in *Xenopus* oocytes and expression into HEK293 cells, we have examined the contribution of the γ and δ subunits at α1, α4 and α5 containing receptors. As a first step, expression of heteromeric receptors comprising only α and β subunits was compared to results obtained with receptors comprising in addition γ1, γ2 or γ3 and versus receptors containing a δ subunit. Subsequently effects of prototypal allosteric modulators including diazepam and DS2 were tested at the different receptor combinations. Comparison of results obtained at receptors with different compositions offers additional possibilities to explore the role of the different subunit interfaces within a receptor complex on the overall physiological and pharmacological properties.
By expending our knowledge on the properties of a broader repertoire of $GABA_A$ receptors, these studies are further bridging the gap between our understanding of the contribution of specific receptors and certain brain functions and illustrate the importance of thorough functional characterization.

Disclosures: **F. Knoflach:** A. Employment/Salary (full or part-time):; F. Hoffmann-La Roche AG. **M. Hernandez:** A. Employment/Salary (full or part-time):; F. Hoffmann-La Roche Ltd. **S. Bertrand:** A. Employment/Salary (full or part-time):; Hiqscreen. **D. Bertrand:** A. Employment/Salary (full or part-time):; Hiqscreen.

Poster

200. GABAA and Other Ligand-Gated Ion Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 200.13/C1

Topic: B.02. Ligand-Gated Ion Channels

Support: DFG586

Title: Impact of myrtenol on $GABA_A$ receptor function

Authors: S. MILANOS[1], T. FRIMURER[2], *C. VILLMANN[1]
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Abstract: $GABA_A$ receptors enable fast inhibitory synaptic neurotransmission in the central nervous system. They belong to the superfamily of Cys-loop receptors due to a conserved cysteine bridge in the extracellular ligand-binding domain. $GABA_A$ receptors form pentameric arrangements of various subunit combinations. Many positive allosteric modulators of the $GABA_A$ receptor have been reported with some of them extracted from plants, while others are synthesized analogs of known $GABA_A$ receptor targeting drugs. The identification of potential modulators from natural sources such as plants leaves or tea extracts will help to understand their sedative physiological effects. Recently, we identified monoterpenes, e.g. linalool, myrtenol, and verbenol as positive allosteric modulators on alpha1beta2 $GABA_A$ receptors, which mediate sedation processes. Here, along with pharmacophore base virtual screening studies, we investigated the scaffold of the positive allosteric modulator myrtenol and tested structurally similar compounds on $GABA_A$ receptor expressing cell lines and primary neurons. Olfactory bulb neurons, expressing different $GABA_A$ receptor configurations, showed again an enhanced GABAergic response following myrtenol or verbenol application. Cells were always recorded in a whole cell configuration with an EC5-10 concentration of the agonist GABA and 300 µM of the appropriate compounds. For analysis in transfected HEK293 cells, we used the alpha2beta3gamma2 $GABA_A$ receptor configuration. None of the compounds was as potent as myrtenol on GABA-induced chloride currents. One ‘mytenol-like’ compound exhibited a negative potential of modulating GABAergic activity. This compound was further investigated at other $GABA_A$ receptor configurations and clearly demonstrated a significant inhibition at alpha1beta2gamma2 receptors but only reduced amplitudes on alpha4beta2delta receptors. Our combined approach of pharmacophore base virtual screening based on myrtenol and electrophysiological readouts identified a novel negative allosteric modulator of $GABA_A$ receptors.

Disclosures: S. Milanos: None. **T. Frimurer:** None. **C. Villmann:** None.

Poster

200. GABAA and Other Ligand-Gated Ion Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 200.14/C2

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH Grant U01 NS090527

Title: The alpha-subunit $GABA_A$ receptor connectom in cortical inhibitory microcircuit

Authors: *M.-C. TSAI, W.-C. LIN, R. H. KRAMER
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Abstract: Dozens of $GABA_A$ receptor isoforms that mediate synaptic inhibition in the brain differ in their kinetics and cellular expression, and are the primary targets of many pharmacology. While the connectivity of GABAergic interneuron microcircuit has been documented, there is no circuit level investigation for $GABA_A$ receptors composition at individual inhibitory synapses. Previously, we created an Optogenetic Pharmacology toolkit with knock-in mouse that allows us to interrogate $GABA_A$ receptor with isoform specificity (Lin, Tsai, et. al. 2015). Here we present the first functional survey of "receptor connectome" of α1-containing $GABA_A$ receptor (α1-$GABA_AR$) in cortical inhibitory microcircuit. While α1-$GABA_AR$ is the most abundant $GABA_AR$ in the brain, we observed a synapse-specific presence of α1-$GABA_A$Rs that depends on the presynaptic interneuron classes. For example, in layer 2/3 Pyramidal neurons (L2/3 PYNs), the inhibitory postsynaptic currents (IPSCs) mediated by α1-$GABA_AR$ are two fold larger from parvalbumin positive (PV^+) interneuron synapses than from somatostatin postive (SOM^+) interneuron synapses. Kinetically, IPSCs from PV^+ synapses are also 2 fold faster than those from SOM^+ synapses. Interestingly, α1-$GABA_AR$ mediated IPSCs from SOM^+ to PV^+ synapses are 3.5 fold larger than those from SOM^+ to L2/3 PYN synapses, suggesting a postsynaptic origin of the receptor connectome. Indeed, we found that PV^+ interneurons express more α1-$GABA_AR$ than L2/3 PYNs do. Furthermore, when populating more α1-$GABA_AR$ in L2/3 PYNs, we can increase its contribution to the IPSCs from SOM^+ synapses, further supporting the hypothesis. The receptor connectome implies that the cortical neural circuit dynamics might be constrained by the synaptic inhibition kinetics differences within cortical inhibitory microcircuit as a result of the differential expression of the α1-$GABA_A$ receptor.

Disclosures: **M. Tsai:** None. **W. Lin:** None. **R.H. Kramer:** None.

Poster

200. GABAA and Other Ligand-Gated Ion Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 200.15/C3

Topic: B.02. Ligand-Gated Ion Channels

Support: Stanford FIDL Research from Department- 1027995-191-EAFGT

The Stanford Innovations Program Grant is Stanford SIP Funds from OTL-1185084-100-DBIRD

NIH NIGMS R01GM095653

Title: A completely novel class of intravenous anesthetics without hemodynamic sequelae

Authors: *M. DAVIES[1,2], N. S. CAYLA[3], Y. LU[4], Y. WU[4], B. A. DAGNE[4], E. R. GROSS[4], B. MACIVER[4], E. J. BERTACCINI[5,6]
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Abstract: Background: Despite safe anesthesia for over 170 years, the molecular mechanism of anesthetic action remains unknown. Recently our lab has demonstrated a model of the heteropentameric $GABA_A$ receptor ($GABA_AR$) that not only contains an important anesthetic binding site but also one that has computationally validated binding for a series of propofol analogs. Our group has designed this *in silico* modeling to develop a new class of anesthetic compounds. These compounds are now shown here to be relatively devoid of hemodynamic effects and have a highly specific mechanism via the $GABA_AR$-slow channel. **Methods:** Our computational $GABA_AR$ model has been utilized for high-throughput *in silico* docking-based screening to predict the binding affinities of a compound database. After changing a nitrogen to a carbon to eliminate the possibility of adrenal suppression effects, 12 analog structures were computationally docked to our $GABA_AR$ binding site model utilizing the Flexible CDocking Algorithms from Discovery Studio. The results of their binding scores were graphically correlated with *in vitro* EC_{50} for $GABA_AR$ potentiation. Subsequent high scoring candidates were tested in tadpoles for loss of righting reflex (LORR). The most promising candidate was then tested for its electrophysiology responses in hippocampal brain slice preparations, as well as for LORR and hemodynamic effects in rats in comparison to propofol. **Results:** Initial *in silico* flexible docking calculations demonstrated a log-linear correlation between the CDocker Interaction Energy score and known EC_{50} for $GABA_AR$ potentiation across the compound set. The most potent and commercially available agent, compound B, showed an EC_{50} of about 500 nM. This compound demonstrated clear enhancement of $GABA_AR$-mediated paired-pulse inhibition in hippocampal brain slices with exclusive effects upon the second pulse alone. Compound B produced LORR in rats at 4mg/kg, far more potent than the typical 10mg/kg dose required for propofol. Furthermore, while propofol clearly caused gross decreases in blood pressure and heart rate, our compound B was devoid of such effects at doses up to 20mg/kg. **Conclusions:** Thanks to our *in silico* screening predictions of compounds which bind to our model of the $GABA_AR$, we have now identified a completely novel class of lead compounds. They demonstrate overt anesthetic activity in both tadpoles and rats, with a potency greater than propofol. These effects are mediated by specific $GABA_AR$-slow channels. Of even greater importance is the fact that our new class of compounds shows minimal to no suppression of blood pressure, in stark contrast to the deleterious hemodynamic effects of propofol.

Disclosures: M. Davies: None. **N.S. Cayla:** None. **Y. Lu:** None. **Y. Wu:** None. **B.A. Dagne:** None. **E.R. Gross:** None. **B. MacIver:** None. **E.J. Bertaccini:** None.

Poster

200. GABAA and Other Ligand-Gated Ion Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 200.16/C4

Topic: B.02. Ligand-Gated Ion Channels

Support: Max Planck Society

German Research Foundation CNMPB FZT103

German Research Foundation SFB1190/P10

European Commission Marie Curie IRG

Alexander von Humboldt Foundation

Brain and Behavior Research Foundation NARSAD YI Grant 22830

Title: Neuroligin 2 regulates anxiety behaviors through effects on amygdala inhibitory synapses

Authors: *D. KRUEGER, O. BABAEV, H. CRUCES-SOLIS, M. HAMMER, C. PILETTI CHATAIN, H. TASCHENBERGER, H. EHRENREICH, N. BROSE
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Abstract: Mutations in the Neuroligin family of synaptic adhesion molecules have been prominently associated with psychiatric and neurodevelopmental disorders, but the mechanisms by which these mutations affect the synapses and circuits underlying psychiatrically relevant behaviors are largely unknown. Here we report that Neuroligin 2, which has been previously linked to schizophrenia, autism and anxiety disorders, plays a central role at inhibitory synapses in the anxiety circuitry. Deletion of Neuroligin 2 in mice results in a prominent anxiety phenotype and alters the composition and function of inhibitory synapses in the basal amygdala, leading to an overactivation of amygdala projection neurons under anxiogenic conditions. Strikingly, both the anxiety phenotype and the overactivation of amygdala output neurons are normalized by deletion of an additional inhibitory synapse adhesion molecule, IgSF9b. Our results indicate that adhesion systems at inhibitory synapses are essential for the normal functioning of the anxiety circuitry and provide insights into the mechanisms by which these molecules may be linked to psychiatric disorders.

Disclosures: D. Krueger: None. **O. Babaev:** None. **H. Cruces-Solis:** None. **M. Hammer:** None. **C. Piletti Chatain:** None. **H. Taschenberger:** None. **H. Ehrenreich:** None. **N. Brose:** None.

Poster

200. GABAA and Other Ligand-Gated Ion Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 200.17/C5

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH Grant R01 DK107966

Title: Peripheral $GABA_B$ receptors regulate colonic afferent excitability

Authors: *J. E. LOEZA ALCOCER[1], M. S. GOLD[2]
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Abstract: While the presynaptic modulation of sensory input to the dorsal horn via ionotropic $GABA_A$ receptors has receive a considerable amount of attention, several lines of evidence suggest the activation of presynaptic $GABA_B$ receptors may also contribute to the antinociceptive effects of spinal GABA. $GABA_B$ receptors are present in a subpopulation of nociceptive afferents that have been shown mediate the inhibition of voltage-gated Ca^{2+} currents and transmitter release in the spinal cord dorsal horn. However, there is also evidence that these receptors are trafficked to peripheral terminals as well where at least in the presence of tissue injury they appear to be functional. And while immune cells may be a source of GABA responsible for the activation receptors in peripheral terminals in the presence of injury, there are several sources of GABA in the colon in the absence of tissue injury. As with other tissues, the nociceptive threshold of the colon is determined by the excitability of the afferents innervating this structure, and this excitability appears to be dynamically regulated. Thus, we hypothesized that $GABA_B$ receptors contribute to the regulation visceral nociception via an action on the peripheral terminals of colonic afferents. To test this hypothesis, we utilized an *in vitro* mouse colorectum-pelvic nerve preparation in which the excitability of functional identified colonic afferents was assessed before and after application of $GABA_B$ receptor agonists (baclofen) or antagonists (CGP-55845) were applied to the receptive field. Baclofen decreased colonic afferent excitability as manifest by an increase in the amount of colon stretch required to evoke an action potential and a decrease in the number of stretch-evoked action potentials. Baclofen also increased the electrical-threshold to evoke an action potential. Conversely, CGP-55845 decreased the stretch threshold and increased the number of stretch-evoked action potentials. CGP-55845 also decreased the threshold to evoke an action potential evoked by electrical stimulation. These results suggest that peripheral $GABA_B$ receptors are not only present and functional in the peripheral terminals of colonic afferents but that activation of these receptors via endogenous GABA contributes to the establishment of colonic afferent stimulus-response properties. These results raise the intriguing possibility that approaches to selectively increase

peripheral $GABA_B$ receptor signaling could be used to treat visceral pain in the absence of central nervous system side effects.

Disclosures: J.E. Loeza Alcocer: None. **M.S. Gold:** None.

Poster

200. GABAA and Other Ligand-Gated Ion Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 200.18/C6

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH R01GM108799,

NIH R21AI120490

Taylor Family Institute for Innovative Psychiatric Research

Title: Molecular mapping of neurosteroid binding sites in GLIC protein

Authors: *Z.-W. CHEN[1], W. W. CHENG[1], M. M. BUDELIER[1], D. F. COVEY[2], A. S. EVERS[1]
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Abstract: Neurosteroid analogues produce general anesthesia by binding to $GABA_A$ receptors and enhancing neuronal inhibition in the brain. The number of binding sites for neurosteroids on $GABA_A$ receptors and their molecular localization has been incompletely defined. The $GABA_A$ receptor is a member of the Cys-loop pentameric ligand-gated ion channel (pLGIC) superfamily, which includes nicotinic acetylcholine receptors, glycine receptors and $5\text{-}HT_3$ receptors. GLIC, a protein from the bacteria Gloeobacter, is a homolog to this Cys-loop superfamily and has been used to study the structure of pLGICs and the binding sites of anesthetics and other allosteric ligands. In this study, we used photolabeling coupled with mass spectrometry to identify two neurosteroid binding sites on GLIC. Purified GLIC was photolabeled with the neurosteroid analogue photolabeling reagent (3α5α)-3-hydroxy-6-azi-pregnane (5α-6-AziP). Top-down mass spectrometric analysis revealed that the 5α-6-AziP photolabels each GLIC monomer with a stoichiometry of two. Middle-down mass spectrometric analyses identified a peptide that was photolabeled with high efficiency on TM3 and two peptides labeled with low efficiency on TM1 and TM4. Based on the published crystal structures of GLIC, the residues labeled on TM1 and TM4 are in close proximity, suggesting that they represent the same binding site. The labeled peptides in the TM3 and TM1-TM4 sites were also photolabeled by other (3α,5α)-3-hydroxy-pregnane photolabeling analogues in which the photolabeling moiety (diazirine group) was moved to the 12-, 15- or 20-positions. The efficiency of photolabeling varied markedly with the location of the diazirine on the steroid backbone and between the two sites, providing evidence

about the preferred orientation of the neurosteroids in each binding site. Computation simulation analysis strongly supported the two neurosteroid photolabeling sites as preferred docking locations.

Disclosures: Z. Chen: None. **W.W. Cheng:** None. **M.M. Budelier:** None. **D.F. Covey:** None. **A.S. Evers:** None.

Poster

200. GABAA and Other Ligand-Gated Ion Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 200.19/C7

Topic: B.02. Ligand-Gated Ion Channels

Support: Human Frontiers Science Program P. Szyszka PI, BH Smith co-PI

National Science Foundation grant 1556337 to BH Smith

Title: Disruption of gabaa receptor RDL subunits by RNAI and its effects on odor discrimination in the honey bee apis mellifera

Authors: *I. SINAKEVITCH[1], *I. SINAKEVITCH[1], G. AGABITINI[1], S. KREISSL[2], P. SZYSZKA[2], C. G. GALIZIA[2], B. H. SMITH[1]
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Abstract: The aim of our study is to characterize expression of the honey bee ortholog receptor AmRDL (BEEBASE GB40975) in the brain and evaluate its role in olfactory behavior. First, we developed antibodies against the AmRDL receptor using the conjugated peptides in the N (extracellular) and C (intracellular) domains of the RDL subunit. Antibodies specifically recognized all isoforms of the RDL subunit. We then combined anti-amRDL immunostaining with neurobiotin injection into antennal lobe neurons and labelling with anti-allatostatin antibodies to identify cell processes that express the receptor and allatostatin. Anti-AmRDL labeled all glomeruli in the antennal lobe but not the aglomerular neuropil, suggesting that AmRDL plays an important role in each glomerulus. The anti-AmRDL was not in the pre-synaptic processes that labeled with anti-synapsin, but rather in post-synaptic processes that resembled processes of local interneurons immunoreactive to GABA and allatostatin. The widespread nature of anti-AmRDL staining in homogenous local interneurons suggests that RDL codes for a major component of GABAa receptor and plays a role in modulation of odor responses via inhibitory local interneurons. Finally, Dicer substrate interference (Dsi)RDL RNA was employed to disrupt translation of the RDL subunit in the GABAa receptor. We used a behavioral conditioning protocol that is easy to implement for measuring odor detection and discrimination - Proboscis Extension Reflex (PER) conditioning. Our results show that

disruption of the AmRDL gene could disrupt the specific recall of a learned odor 18 hours after injections. This new approach will help in disentangling the different roles of different GABA receptor types in neural processing in the honey bee brain. Because of the similarity of the AL to the mammalian Olfactory Bulb, this work broadly contributes to an understanding of how GABA processing works to manage neural networks in olfaction.

Disclosures: I. Sinakevitch: None. **G. Agabitini:** None. **S. Kreissl:** None. **P. Szyszka:** None. **C.G. Galizia:** None. **B.H. Smith:** None.

Poster

200. GABAA and Other Ligand-Gated Ion Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 200.20/C8

Topic: B.01. Neurotransmitters and Signaling Molecules

Support: NRF-2017R1A2B3011098

The Brain Korea 21+ Program

Title: Tonic and phasic inhibition in vb thalamus

Authors: *H. J. KWAK[1], W. KOH[2], K. SONG[1], G. HA[1], E. H. LEE[1], C. J. LEE[2], E. CHEONG[1]
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Abstract: Tonic inhibition mediated by extrasynaptic GABAA receptors tightly regulates the excitability of neurons. Thalamocotical (TC) neurons in the thalamus is known to display a large tonic inhibition as well as phasic inhibitory inputs from thalamic reticular nuclei (TRN). While it is assumed that non-synaptic tonic inhibition in TC neurons is mediated by spillover of GABA from TRN-TC synapses, the origin of tonic GABA has not been fully revealed yet. Studies have shown that GABA can be released by several mechanisms such as vesicular release, GAT reversal release, or channel mediated release. Here we report a novel non-neuronal source of tonic GABA in TC region and its underlying mechanisms.

Disclosures: H.J. Kwak: None. **W. Koh:** None. **K. Song:** None. **G. Ha:** None. **E.H. Lee:** None. **C.J. Lee:** None. **E. Cheong:** None.

Poster

200. GABAA and Other Ligand-Gated Ion Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 200.21/C9

Topic: B.02. Ligand-Gated Ion Channels

Support: DPI 20140008

Title: Expression of ethanol sensitive glycine receptors in brain regions of the reward system

Authors: *S. S. GALLEGOS, B. MUÑOZ, R. VIVEROS, L. G. AGUAYO
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Abstract: Introduction
Glycine receptors (GlyR) are expressed primarily in spinal cord and brain stem neurons. GlyRs are sensitive to general anesthetics, neurosteroids, Zn^{2+} and ethanol. Recently, GlyRs were also found in other supratentorial regions, but their properties are largely unknown. Mesolimbic regions, such as ventral tegmental area (VTA) and nucleus accumbens (nAc) were also found to express GlyR of a still unidentified molecular nature. This information is of interest because the presence of GlyRs in these areas might be relevant for the rewarding effects of drugs of abuse (i.e. ethanol). The aim of this work was to identify the presence of GlyR in main regions of the reward system (prefrontal cortex, PFC; nucleus Accumbens, nAc; ventral tegmental area, VTA) and to characterize their electrophysiological properties and sensitivity to ethanol.
Results
Using western blot analysis, we detected the GlyR α1 subunit in PFC, VTA and nAc in C57BL/6J mice. We found lower levels of α1 in these three regions than those found in spinal cord and brain stem. These results were corroborated with immunohistochemistry studies done in coronal brain slices (40 μm) containing the regions of interest from adult WT (C57BL/6J), D1-GFP and GlyT2-GFP mice. The confocal microscopy analysis suggests the presence of both synaptic and non-synaptic GlyRs in the three areas. The signal for α1 was higher in VTA than in PFC and nAc, where we found other subunits, possibly α2.
Electrophysiological recordings from acutely dissociated neurons from these three areas showed that most neurons recorded displayed a large current (>500 pA at 1 mM of glycine). Data showed that the currents had different sensitivities in the three cell types. For instance, the glycine concentration-response curve in accumbal neurons was displaced towards the left compared to PFC. Electrophysiological data were analyzed to assess EC_{50} values and it was found that for PFC the EC_{50} was 84 ± 3.3 μM, for nAc 47 ± 6 μM and for VTA the EC_{50} was 44 ± 2.1 μM of glycine. The effects of ethanol were also tested showing different sensitivities to 10-100 mM.
Conclusion

We found the presence of GlyR in three critical mesolimbic areas, and it appears that the receptor conformation and sensitivity to glycine and ethanol are different in these areas. These differences could be relevant for the regulation of the reward system and the rewarding properties of ethanol.
Funding DPI 20140008

Disclosures: **S.S. Gallegos:** None. **B. Muñoz:** None. **R. Viveros:** None. **L.G. Aguayo:** None.

Poster

200. GABAA and Other Ligand-Gated Ion Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 200.22/C10

Topic: B.02. Ligand-Gated Ion Channels

Support: MRC grant MR L021676

Title: Characterizing a 5-HT_3 receptor-ELIC chimera

Authors: *S. C. LUMMIS, K. PRICE
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Abstract: The pentameric ligand-gated ion channel (pLGIC) family encompasses both eukaryotic (e.g. 5-HT_3, nACh, GABA and Gly receptors) and prokaryotic (e.g. ELIC and GLIC) members. The latter have provided many high resolution structures, and more recently have been used to create chimeric receptors allowing details of specific regions of these critical proteins to be understood in more detail. This has not only clarified the sites of actions of various allosteric modulators, but also the importance of the amino acid sequences at regions where the extracellular (ECD) and transmembrane (TMD) domains interact. Here we create a 5-HT_3- ELIC chimera, with the ECD of the mouse 5-HT_3A receptor and the TMD of ELIC (Erwinia ligand gated ion channel) which required altered residues in the Cys-loop and in the C-terminal tail to enable it to function. The resulting protein was expressed in oocytes and function measured using two-electrode voltage clamp. The data revealed the chimera was more sensitive to 5-HT that WT 5-HT_3 receptors (with EC_{50}s of 0.34 μM and 1 μM respectively). It was also more sensitive to the 5-HT_3 agonist m-chlorophenylbiguanide (EC_{50} = 13 nM), which was a weak partial agonist (R_{max}/R_{max}5-HT = 13%), although the potency of the nACh/5-HT_3 receptor agonist varenicline was similar to WT (EC_{50}s = 16μM and 18μM respectively), as was its maximum response (R_{max} /R_{max}5-HT = 40%; WT = 35%)[1]. Conversely the 5-HT_3 receptor antagonists ondansetron and bemsetron were less potent than at WT 5-HT_3 receptors, with IC_{50}s more similar to those in ELIC. The effects of a range of modulators (including ethanol, thymol, and 5-hydroxyindole) were also explored. The data are compared to those from other chimeric and WT receptors, and reveal some unexpected insights into the mechanism of action of agonist,

antagonist and modulators in pLGIC.
[1] Lummis et al. JPET 339:125-131, 2011

Disclosures: S.C. Lummis: None. **K. Price:** None.

Poster

200. GABAA and Other Ligand-Gated Ion Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 200.23/C11

Topic: B.02. Ligand-Gated Ion Channels

Support: GAUK Grant 928517

CSF Grant 16-12695S

CSF Grant P304/12/G069

MEYS Grant LQ1604 NPU II

Czech Technology Agency, Center for development of Original Drugs, Grant TE01020028

Title: Identification of neurosteroids that are able to interact with modulatory sites on P2X receptors

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Abstract: Purinergic P2X receptors (P2X1-7R) are ligand-gated ion channels activated by adenosine triphosphate (ATP). They are widely expressed in a central nervous system, and play role in many physiological and pathophysiological processes, for example in neuropatic pain and psychiatric disorders. The activity of P2XRs is influenced by a variety of allosteric modulators, including neurosteroids. The aim of this study was to identify new neurosteroids that are able to modulate activity of purinergic P2X receptors, and to characterize their specificity and biding site on selected subtypes of P2X receptors. We screened the effect of 82 compounds, synthesized at the Department of Steroidal Inhibitors, Institute of Organic Chemistry and Biochemistry, ASCR, that have not yet been tested with P2XRs. These included sex steroids and neurosteroids previously shown to affect NMDA and GABAA receptors. We also designed and synthesized new analogues. Electrophysiological experiments were performed on recombinant P2X2 and P2X4 receptors expressed in HEK cells and native P2XRs endogenously expressed in neurons and pituitary cells and stimulated with ATP. In addition, we examined the effect of selected

compounds also on GABAAR in neurons and pituitary cells stimulated with GABA. We found that some neurosteroids exhibited P2XR-specific potentiating or inhibitory effect, and some neurosteroids potentiated both PX2R and P2X4R. For example, several testosterone analogues have potentiating effect on ATP-induced currents mediated by P2X2R and P2X4R, and the interactions of testosterone analogues with the P2XRs depend not only on lipophilicity but also on the length of ester moiety at position C-17 on the D-ring. A new class of neurosteroid analogues which possess another structural modifications in the steroid D-ring and which have been recently shown to inhibit NMDA receptor, also modulated P2XRs. Some derivatives of cholic acids, the end products of cholesterol metabolism, are able to modulate differently the PX2R and P2X4R function. These results revealed structural requirements of putative steroid site(s) for proper receptor-mediated interactions that might serve as a guide for synthesis of new molecules. Detailed knowledge about neurosteroid modulatory site is a prerequisite for development of new drugs against P2XR-based disorders.

Disclosures: H. Zemkova: None. **S. Sivcev:** None. **M. Ivetic:** None. **B. Slavikova:** None. **E. Kudova:** None.

Poster

200. GABAA and Other Ligand-Gated Ion Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 200.24/C12

Topic: B.02. Ligand-Gated Ion Channels

Support: Fondecyt 1160851 to GM-C

Fondecyt Postdoctoral Fellowship 3170108 to CFB

Title: Intracellular domain of glycine receptors is an essential domain to confer sensitivity to allosteric modulators

Authors: *C. F. BURGOS[1], M. P. ESPINOZA[1], C. MUÑOZ-MONTESINO[1], A. M. MARILEO[1], V. P. SAN MARTÍN[1], L. G. AGUAYO[1], P.-J. CORRINGER[2], G. E. YÉVENES[1], G. MORAGA-CID[1]
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Abstract: Glycine receptors (GlyRs) are a member of the pLGICs superfamily which play a critical role mediating fast synaptic neurotransmission in the nervous system. Functional GlyRs are pentameric complexes formed by identical or different subunits. Each subunit consist of a large extracellular N-terminal domain (ECD), four membrane spanning helices (TMD) and a large intracellular domain (ICD) connecting the TM3 and TM4. The function of the GlyRs can be modulated by a large number of structurally unrelated modulators. So far, it's largely accepted

that the TMD constitute the primary target for many of these molecules. In the other hand, historically the ICD has been seen as an accessory domain involve only in trafficking and membrane insertion of the receptor. However, in this work we demonstrate that the ICD of the GlyRs is much more than an accessory domain. We investigated the role of the ICD in the modulation of the GlyR using a previously reported chimeric protein, called Lily. Lily was made by the fusion of the ECD of the prokaryotic GLIC receptor with the TMD of human GlyR α_1. In Lily chimera the ICD was originally replaced by a short peptide. Here, we inserted back the complete ICD into Lily chimera (Lily-ICD). Both protein were expressed in BHK cells, yielded robust proton-elicited currents characterized by an EC_{50} for proton activation of $4.1 \pm 0.3 \times 10^{-7}$ M (pH 6.55) for Lily and $4.6 \pm 0.2 \times 10^{-7}$ (pH 6.61) for Lily-ICD, indicating of insertion of the ICD into Lily does not alter the expression and function of Lily-ICD. Moreover, we tested the effects of two largely recognized allosteric modulators of GlyRs. First, we examined the effects of ethanol (100 mM) in Lily and Lily-ICD. Ethanol had weak effects (10 ± 2% of potentiation) in the proton-activated currents in cells expressing Lily. The insertion of the ICD, increased the sensitivity to ethanol (58 ± 3%), similar to the values observed in the GlyR α_1 WT (54 ± 2%). Similarly, we tested the effects of propofol (50µM) and we observed weak effects (75 ± 10%) in Lily, compared with the potentiation observed in Lily-ICD (400 ± 30 %). These values are comparable to that observed in the GlyR α_1 (380 ± 25 % at 50 µM). All together our data suggested a role for the ICD that goes much further that its role in trafficking and membrane insertion. These data showed that the ICD is necessary to confer full sensitivity to allosteric modulators to Lily-ICD, confirming the presence of additional relevant allosteric sites for two recognized GlyR's modulators within the ICD. Therefore, the ICD is a relevant domain in the design of new drugs targeting the GlyRs.

Disclosures: C.F. Burgos: None. **M.P. Espinoza:** None. **C. Muñoz-Montesino:** None. **A.M. Marileo:** None. **V.P. San Martín:** None. **L.G. Aguayo:** None. **P. Corringer:** None. **G.E. Yévenes:** None. **G. Moraga-Cid:** None.

Poster

200. GABAA and Other Ligand-Gated Ion Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 200.25/C13

Topic: B.02. Ligand-Gated Ion Channels

Title: The ionotropic 5-HT3 receptor: A sensitive model for pharmacogenomic differences

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Abstract: 5-HT3 receptors belong to the large family of the cys-loop ligand-gated ion channels and share structural homologies with the neuronal nicotinic acetylcholine receptors. Each receptor is composed of five subunits arranged around the ion conducting pore which is lined by the second transmembrane segment of each monomer. Genes encoding for the 5HT3 are classified as HTR3A-HTR3E. In the simplest form receptors may be composed of five identical 5-HT3A subunits or a combination of 5-HT3A and one of the other four, i.e. 5-HT3B-E. 5HT3 receptors are widely expressed throughout our body and contribute to both central and peripheral processes.
Sequence alignment of the protein sequences of the 5HT3A subunit from different species (human, dog, ferret or rat) reveals some differences which can be thought to impact the functional properties of the receptors. To examine how these receptors might differ in their pharmacological properties, functional studies were conducted using recombinant 5HT3A receptors expressed in Xenopus oocytes from human, dog, ferret and rat for both agonist and antagonists. Moreover, as it was shown that 5HT3A receptors display a cross pharmacology with the 7 nicotinic acetylcholine receptors, effects of the 7 partial agonist EVP6124 was evaluated on the four different species.
Altogether, data presented herein illustrate the similitudes and differences observed between receptors encoded by the HTR3A genes from four species and their impact on pharmacological properties of the corresponding ligand gated ion channels. Pointing out to the importance of careful analysis of the translatability of animal data these experiments are shining a new light on the understanding of the relevance of genetic variants.

Disclosures: **L. Danober:** None. **S. Bertrand:** None. **T. Schaer:** None. **D. Bertrand:** None.

Poster

200. GABAA and Other Ligand-Gated Ion Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 200.26/C14

Topic: B.02. Ligand-Gated Ion Channels

Support: FONDECYT 1141132

FONDECYT 11470842

CONICYT FB0807

CONICYT 21140407

Title: Alkylation of cysteine 132 or cysteine 159 abolished the zinc-induced positive allosteric modulation in rP2X4R but not in rP2X2R

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Abstract: Zinc is a positive allosteric modulator of P2X4R; site directed mutagenesis of cysteine 132 or cysteine 159 revealed their critical role in zinc potentiation. These residues are normally forming the SS3 disulphide bond of P2XR's. In view that SH groups coordinate zinc we hypothesized that zinc reduces the SS3 bond to yield SH groups capable of reacting with alkylating reagents. We ascertained the role of zinc in the alkylation reaction by comparing the chemical modification of SH groups in cysteine 132 and cysteine 159 by N-ethylmaleimide (NEM) or iodoacetamide (IA) in absence and presence of zinc. We used *Xenopus laevis* oocytes microinjected with 5ng of plasmids containing rP2X4R, the double mutant of rP2X4R C132T/C159T or rP2X2R coding sequence and performed two electrode voltage clamp recordings of the ATP-induced currents. In the rP2X4R, 10 μM zinc decreased 4-fold the ATP EC50 from 23.85±3.17 to 5.85±1.29 μM ($P<0.01$). 300 μM NEM per se, did not modify the ATP EC50 (22.44±10.6), nor the zinc-induced potentiation. In contrast, pretreatment with 300 μM NEM plus 10 μM zinc for five minutes, did not alter the ATP EC50 (21.34±3.11 μM) neither the joint ATP plus zinc EC50 (21.98±9.39 μM). The effect of NEM was not reversible. Likewise, a 300 μM IA application for five minutes in presence of zinc abolished the zinc potentiation, effect that was not seen in absence of the metal. Moreover, 300 μM iodoacetate or 300 μM DTNB did not mimic the effect of NEM or IA. The rP2X4R double mutant did not modify the ATP EC50 (32.67±7.27 μM), 10 μM zinc reduced the ATP EC50 to 6.9±1.9 μM ($P<0.05$). 300 μM NEM plus 10 μM zinc did not altered the ATP EC50 (32.85±10.21 μM) but was resistant to NEM alkylation ($P<0.05$), in contrast to the results attained in rP2X4R. As a control, in rP2X2R, the ATP EC50 was decreased by zinc (49.1±6.9 to 11.06±1.6 μM, $P<0.05$); 300 μM NEM did not modify the ATP EC50 (31.63±7.02 μM) nor the zinc-induced potentiation. However, the treatment with 300 μM NEM plus zinc still decreased the ATP EC50 in presence of the metal (7.98±1.52 μM). These results are compatible with our working hypothesis that zinc reduces of the SS3, allowing the alkylation of the respective SH groups in rP2X4R but not in rP2X2. We conclude that zinc coordination with cysteine 132 and/or cysteine 159 is essential for the metal positive allosteric modulation in rP2X4R.

Disclosures: F.A. Peralta: None. **J.P. Huidobro-Toro:** None.

Poster

200. GABAA and Other Ligand-Gated Ion Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 200.27/C15

Topic: B.02. Ligand-Gated Ion Channels

Support: CNRS

LabEx Brain

Université de Bordeaux

Title: New P2X4mCherryIN knockin transgenic mice expressing non-internalized P2X4 receptors revealed alteration in hippocampal plasticity and memory

Authors: *E. BOUE-GRABOT[1], T. DELUC[1], J.-T. POUGNET[1], A. MARTINEZ[1], E. BERTIN[1], E. DOUDNIKOFF[1], E. TOULMÉ[1], A.-E. ALLAIN[2], E. BEZARD[1], S. S. BERTRAND[2], B. BONTEMPI[1], O. NICOLE[1]
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Abstract: Extracellular adenosine triphosphate (ATP) is released by neurons and glia and modulates synaptic transmission and plasticity via activation of ionotropic P2X receptors in the CNS. Importantly, ATP signalling and surface P2X4 receptors (P2X4) are upregulated under neuropathic or neurodegenerative conditions such as Alzheimer's disease (AD) or amyotrophic lateral sclerosis. In pathological conditions, increase of surface expression of P2X4 drives neuropathic pain and may contribute to the synaptic dysfunction observed in AD leading to learning and memory dysfunction. To elucidate the role of P2X4 in the alteration of synaptic plasticity and memory, we generated innovative transgenic knockin P2X4 mice expressing the non-internalized P2X4 gene (P2X4mCherryIN) respectively in excitatory neurons (CaMK2Cre/P2X4mCherryIN) or in all P2X4-expressing cells (CMVCre/P2X4mCherryIN). The Cre/Lox based strategy consisted in the conditional substitution of the internalization motif present within the C-terminal tail of P2X4 by the fluorescent mCherry protein in specific neuronal populations expressing the Cre recombinase. By combining RT-PCR, Western blots, immunofluorescent and electron microscopies from different brain structures or peripheral tissues (macrophages), we show that the expression of P2X4mCherryIN occurs in the expected tissues or cell types for both knockin mice and leads to an increased number of surface P2X4. The primary screen of the behavioral phenotype of CaMKIICre-P2X4mCherryIN, CMVCre-P2X4mCherryIN and control littermates reveals that all transgenic mice are *viable* and normal in size and in terms of locomotor/exploratory activity or anxiety. Using a dedicated test battery (Y-maze, novel object recognition and 8-arm radial maze) enabling to dissect different memory forms and stages of memory processing, our results show that the increase of P2X4 at the surface of neurons impaired the spatial memory formation and retrieval of knockin P2X4mCherryIN mice. We are currently examining if these changes parallel alterations of hippocampal long-term depression and potentiation by field potential recordings of hippocampal neurons in sliced brain tissue.

Disclosures: E. Boue-Grabot: None. **T. Deluc:** None. **J. Pougnet:** None. **A. Martinez:** None. **E. Bertin:** None. **E. Doudnikoff:** None. **E. Toulmé:** None. **A. Allain:** None. **E. Bezard:** None. **S.S. Bertrand:** None. **B. Bontempi:** None. **O. Nicole:** None.

Poster

200. GABAA and Other Ligand-Gated Ion Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 200.28/C16

Topic: B.02. Ligand-Gated Ion Channels

Support: Interuniversity Attraction Pole (IAP – P7/10) from Belgian Science Policy Office (BELSPO)

Title: Loss of the alpha2 subunit of glycine receptors affects the maturation and the development of the glutamatergic input on striatal medium spiny neurons

Authors: *J.-M. RIGO[1], J. COMHAIR[1,2], S. MOLCHANOVA[2], G. MORELLI[1], R. J. HARVEY[3], D. GALL[2], E. PICCART[1], S. SCHIFFMANN[2], B. BRÔNE[1]
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Abstract: Among the many factors that control brain development, spontaneous activity has been shown to be essential for the development and maturation of neuronal populations, hence driving neuronal circuitry development. One important mechanism controlling this spontaneous activity is neurotransmitter-dependent. Glycine receptors containing the alpha2 subunit are highly expressed in the developing brain, where they regulate migration and maturation of the cortical neurons and promote neonatal spontaneous neuronal network activity, needed for the development of synaptic connections. Furthermore, several mutations in the X-linked gene GLRA2, encoding the alpha2 subunit, have been found in boys with autism spectrum disorder, pointing at a possible involvement of glycinergic transmission in the development of cognitive abilities. We have previously shown that medium spiny projection neurons (MSNs) in the dorsal striatum (DS) express tonically active alpha2-containing GlyRs, which stabilize the resting membrane potential and determine the offset of action potential firing. Here, we show that the expression of alpha2 subunits is upregulated in the DS of neonatal mice. In MSNs, evoked glycinergic currents have a higher density in one-week-old mice, compared to adults. A fraction of the neonatal MSNs was spontaneously active, and in Glra2 knockouts, the frequency of spontaneous action potentials in these active cells was reduced. Network formation and maturation in Glra2-KO animals is also affected. Mini-Excitatory Postsynaptic Currents (mEPSCs) are reduced in frequency at postnatal day (P)7 and (P)21 up until adults ages. The complexity of the MSNs dendritic tree and the (total) spine density was not affected at any investigated developmental time points. To further identify the cortico-striatal synapse, biocytin injected MSNs were co-labelled with the presynaptic cortical marker VGLUT1. The number of VGLUT1 colocalized with MSNs dendrites was not affected in the Glra2-KO animals. To explain our initial reduction in mEPSCs, we measured AMPA/NMDA ratios and the release

probability by cortico-striatal stimulation. The AMPA/NMDA ratio was decreased in Glra2-KO animals without additional effects from acutely blocking the glycine receptors with strychnine. Release probability was affected only in the presence of strychnine and was more pronounced in the Glra2-KO animals indicating both a developmental and an acute effect.

Disclosures: **J. Rigo:** None. **J. Comhair:** None. **S. Molchanova:** None. **G. Morelli:** None. **R.J. Harvey:** None. **D. Gall:** None. **E. Piccart:** None. **S. Schiffmann:** None. **B. Brône:** None.

Poster

200. GABAA and Other Ligand-Gated Ion Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 200.29/C17

Topic: B.02. Ligand-Gated Ion Channels

Support: NRF-2014R1A1A2056820

Title: Tricyclic antidepressant amitriptyline inhibits 5-hydroxytryptamine 3 receptors currents in NCB 20 cells

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Abstract: Amitriptyline, one of tricyclic anti-depressant, is widely used to treat depression and neuropathic pain. But its mechanism is still uncertain. Amitriptyline therapeutic range is overlapped with the potential 5-hydroxytryptamine 3 (5-HT_3) receptor therapeutic use including depression and neuropathic pain. In this study, we tested the effect of amitriptyline on 5-HT_3 receptor currents in NCB-20 neuroblastoma cells and find out its blocking mechanism on 5-HT_3 receptor.
Using whole cell voltage clamp method, we compared the currents of 5-HT_3 receptor when 5-HT was applied alone and co-applied with amitriptyline in cultured NCB-20 cells known to express 5-HT_3 receptors. To make it certain the mechanism of the amitriptyline on the 5-HT_3 receptors, we simulated the 5-HT_3 receptor currents using Berkely Madonna software and calculated the rate constant of the each reaction step for the agonist and receptors. The 5-HT_3 receptor currents were inhibited by amitriptyline. Amitriptyline blocked the peak currents in competitive manner. It accelerated the desensitization process of 5-HT_3 receptor with no voltage dependency. Blocking effects of amitriptyline were different depending on its application method. When amitriptyline was applied before 5-HT treatment, the current amplitude continuously increased until to stop the 5-HT treatment. At the co-application of amitriptyline with 5-HT, current rise and decay rapidly. Peak current amplitudes were strongly suppressed in both applications. All macroscopic current we recorded was reproduced by simulation. The results of rate constants

change we obtained were identical with macroscopic current recording.
These results suggest that amitriptyline blocks the 5-HT_3 receptor by close and open states blocking mechanism. Also it acts as a competitive blocker. From this study, we could expand our understanding the pharmacological mechanisms of amitriptyline to relieve the depression and neuropathic pain. Also it suggests 5-HT_3 receptor is a potential target for wide variety of neurologic and psychiatric diseases.

Disclosures: K. Sung: None. **Y. Park:** None. **S. Myeong:** None.

Poster

201. Structural Plasticity: Circuit Function

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 201.01/C18

Topic: B.08. Synaptic Plasticity

Support: This work is supported by a GRF grant from the Research Grant Council of the Hong Kong Special Administrative Region Government (CityU 11100015)

Title: Gene ablation in cerebellar Purkinje cells reduces regenerative capacity of peripheral neuron after injury

Authors: *K. K. SINGH[1], G. KUMAR[1], W. Y. TAM[1], K. M. KWAN[3,4,5], C. H. E. MA[1,2]
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Abstract: Peripheral nervous system (PNS), unlike the central nervous system, is capable of regrowth albeit at a slow rate. The regenerative capacity of PNS depends on the severity and anatomic location of the injury. Cerebellum is the fine movement coordination center for motor function. Purkinje cell (PC) is one of the major neurons in the cerebellum and the sole output neuron for fine-tuning motor activity. However, how cortical synaptic plasticity contributes to functional recovery after injury remains largely unknown. Recently, a conditional knockout mouse ablating a transcription factor expression specifically in mature PCs is generated without showing any loss of PCs. In the present study, we demonstrated that motor functional recovery was delayed in the mutant mice after sciatic nerve injury in the PNS. Functional synapse formation was measured by electromyography recording at the distal muscle. Reduced compound muscle action potential was observed only in the mutant mice months after peripheral nerve injury (PNI). The number of re-innervated neuromuscular junction was significantly reduced in the mutant mice. All these results indicate that genetic ablation of transcription factor in PCs leads to reduced regenerative capacity of injured peripheral neurons and motor functional

recovery after PNI. Knowledge obtained from current study provides further insight into the development of neuroprosthetics and neurorehabilitation strategies for treating traumatic PNI.

Disclosures: K.K. Singh: None. **G. Kumar:** None. **W.Y. Tam:** None. **K.M. Kwan:** None. **C.H.E. Ma:** None.

Poster

201. Structural Plasticity: Circuit Function

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 201.02/C19

Topic: B.08. Synaptic Plasticity

Title: The structural & functional reorganization of neuro-glio-vascular complexes of the perifocal zones in focal damage of the human neocortex

Authors: *V. AKULININ[1], A. MYTSIK[2], A. STEPANOV[2], D. AVDEEV[2], S. STEPANOV[2], A. SERGEEV[2]
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Abstract: The study of structural and functional reorganization of neuro-glio-vascular complexes (NGVC) of the perifocal zones in focal damage of the human neocortex is an important task of neuromorphology. In this research, using histological (Nissl staining, hematoxylin eosin), immunohistochemical neurons (NeuN, NSE, Calbindin D28k, NPY), synapses (synaptophysin p38), glial cells (GFAP) and DNA staining of cell nuclei (DAPI), and electron microscopy verification methods. Human neocortex biopsy tissues were obtained from patients during operational removal of the brain tumor performed at the Omsk State Med. Univ. with the approval of the Ethical Committee. The focal damage of the human neocortex were investigated in patients, who had a surgery for traumatic brain injury (n=5, biopsy) and brain tumor (n=25, biopsy). Five patients, died from accidental causes and served as controls. Morphometric analysis was performed using ImageJ 1.48 program. For statistical analysis we used nonparametric tests (Friedman ANOVA, Mann-Whitney, Wilcoxon, frequency table, cluster analysis and multidimensional scaling). In the perifocal zone, signs of brain swelling, necrosis, apoptosis, reactive and reparative changes in the structural components of NGVC were revealed. The content of reactively altered neurons was 15-75% (95% CI, Nissl staining), hyperchromic cells with different degrees of dehydration prevailed. In comparison with the control, the total number density of neurons (NeuN, DAPI) decreased by 10.5-45.6% (95% CI). Pyramidal neurons were more damaged. The surviving neurons were characterized by increased expression of NSE, hypertrophy of axosomatic, axodendritic and axospines synapses, complication of the spatial organization of the neuropil (p38). The glial cell content increased 2.5-fold (DAPI, GFAP), a large number of satellite cells appeared, and single active microglial cells were noted. Reorganization of NGVC was accompanied by the appearance of microvessels

with numerous branched processes of pericytes, complication of the form of basal membranes, activation of transcytosis processes (large number of caves, smooth and clathrin vesicles) in pericytes and endothelial cells. All this indicated the damage and death in the perifocal zone of a significant part of the neurons and activation of the surviving neurons. Increase of the transfer through the blood-brain barrier of macromolecules, intensive metabolic processes aimed at the sanation of the nervous tissue, activation of angiogenesis, reorganization of NGVC and inter-neuronal relationships due to reparative neuroplasticity.

Disclosures: V. Akulinin: None. **A. Mytsik:** None. **A. Stepanov:** None. **D. Avdeev:** None. **S. Stepanov:** None. **A. Sergeev:** None.

Poster

201. Structural Plasticity: Circuit Function

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 201.03/C20

Topic: B.08. Synaptic Plasticity

Support: CIHR grant MOP-79411

Louise and Alan Edwards Foundation

Title: Role of microglia in structural plasticity of touch circuitry in neuropathic pain

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Abstract: INTRODUCTION: Injury or disease affecting the peripheral or central nervous systems often results in the development of chronic neuropathic pain. This can result in long-lasting pain and sensory abnormalities such as pain in response to innocuous mechanical stimulation (mechanical allodynia). One of the proposed mechanisms underlying mechanical allodynia is selective loss of inhibitory synapses on the central terminals of normally innocuous touch primary afferents (low-threshold mechanoreceptors - LTMRs). This study focuses on morphological changes in inhibitory control of two subpopulations of LTMRs, C-LTMRs and A-LTMRs, and aims to find what mechanism underlies these selective changes, in a rat model of neuropathic pain. We hypothesize that neuropathic pain is maintained by spinal cord disinhibition mediated by selective loss of synapses between LTMRs and GABAergic inhibitory neurons resulting in mechanical allodynia, and this selective loss is mediated by the activity of microglia. METHODS: Male and female rats underwent cuff surgery and split into minocycline (to suppress microglial activation) and vehicle treated groups. Mechanical allodynia was assessed weekly with the von Frey test. At three weeks post-surgery, animals were perfused for

confocal or ultrastructural immunocytochemistry using markers for C- and A-LTMRs, inhibitory neurons and microglia. The number of inhibitory appositions on dorsal horn neurons and synapses on LTMR terminals was quantified with confocal and electron microscopy, respectively. RESULTS: Following nerve injury, there was a reduction in the number LTMR central terminals, and a loss of inhibitory synapses in those that remained. LTMR terminals showed signs of degeneration and microglia profiles were observed to partially or completely surround these degenerating terminals. Cuff animals chronically treated with minocycline compared to vehicle treated animals showed reduced mechanical allodynia and microgliosis. Minocycline treatment reduced the loss of inhibitory appositions on dorsal horn neurons and of inhibitory synapses on LTMR terminals. This study shows that microglia contribute to mechanical allodynia by controlling a selective synaptic removal in the spinal dorsal horn in a model of neuropathic pain.

Disclosures: **N. Yousefpour:** None. **M. Aparicio:** None. **A. Ribeiro-da-Silva:** None.

Poster

201. Structural Plasticity: Circuit Function

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 201.04/C21

Topic: B.08. Synaptic Plasticity

Support: NIH Grant 1R21MH109779-01

Title: Differences between juvenile and adult fear memory capabilities: The role of IP3/MAP kinase activation and trafficking of glua2 into mature spines

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Abstract: It is well known that young organisms do not maintain memories as long as adults, but the mechanisms for this ontogenetic difference are unknown. Our overall research program is to identify the behavioral and molecular mechanisms of these ontogenetic differences. This work is significant because, even though young animals forget more rapidly than adults, early learning and especially traumatic experiences can have consequences that last a lifetime. The fear experience has a significant impact on the brain. In some cases a fear experience can create a lasting memory.
We have shown that the elevated pedestal stress in adult Sprague Dawley rats produces a fear-based reorganization resulting in a significant increase in mushroom spines within the hippocampus in as short as 2h. Here we demonstrate that 1h pedestal stress also produces a long-

lasting behavioral change in rodent behavior indicative of a lasting fear memory. Groups of Sprague Dawley rats were assigned to either pedestal stress (1h) or no stress control (home cage). All animals were placed in an open field at the base of a 6x6 sq inch pedestal (4ft high). The animals were allowed to explore this novel environment for 5 min. Half the subjects were then placed on this 4ft pedestal for 1h, control subjects were placed in their home cage following the initial exploration. All the animals were returned for this open field environment for 5 min either 1d or 7d following the initial exposure. All behavioral video recordings were analyzed for rodent exploration time (sec), time in a freeze posture (sec), and number of rears. The results show that during the initial exposure to the novel context, there were no differences between groups for any of the measurements: exploration, freezing or number of rears ($p>0.05$). For the 1d re-exposure test, compared to controls, the stress group shows a significant reduction in both number of rears, and exploration time with a concomitant significant increase in freezing time. For the 7d re-exposure, the stress group shows a significant decrease in exploration time (sec) and a significant increase in freezing time but not differences in number of rears between conditions. These results illustrate the longevity of this fear-based memory in adults. Spine analyses will be conducted to provide insight into the consolidation of this fear memory across adults and juvenile rats. We predict that in adults, but not juveniles, this fear memory will increase the expression of mushroom spines in the hippocampus that contain a significant increase in AMPA – GluA2 subunit expression providing insight into the ontogenic differences in fear memory consolidation.

Disclosures: **S. Sanay:** None. **R.M. Zanca:** None. **H.N. Shair:** None. **P.A. Serrano:** None.

Poster

201. Structural Plasticity: Circuit Function

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 201.05/C22

Topic: B.08. Synaptic Plasticity

Support: ZIA NS00300213

Title: The role of complement signaling in olfactory map plasticity

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Abstract: The olfactory system depends upon organizational maps that develop and persist despite continuous neuronal turnover and plasticity. From the nose, olfactory sensory neurons (OSNs), residing in the olfactory epithelium (OE), send axons to the surface of the olfactory bulb (OB), where they converge into odorant receptor (OR)-specific “glomeruli.” As older OSNs die

they are replaced throughout life, indicating that new axons are constantly innervating the bulb to find their appropriate glomeruli. Two isofunctional glomeruli are formed for each OR and are then connected through the “intrabulbar map”, mediated by tufted cells. While it is known that this map organization is activity dependent, the cellular and molecular mechanisms that underlie glomerular and intrabulbar circuitry maintenance are unknown. Studies have shown that microglia and complement molecules are important for the developmental refinement of circuitry within the visual system, thus we asked whether they played a role in the maintenance of the glomerular and intrabulbar maps. Our findings first revealed that microglia engulf OSN axons in addition to the synaptic terminals of tufted cells both in the glomerular and intrabulbar maps. We then used Complement 3 (C3) and Complement Receptor 3 (CR3) knockout mice to investigate if C3 mediated microglia pruning was necessary for proper map establishment and maintenance. Our results demonstrate that both glomerular and intrabulbar map refinement are significantly impeded when C3 signaling is disrupted, thus establishing microglia and the C3/CR3 pathway as necessary for the homeostatic maintenance of the olfactory maps. We further present the olfactory system as a novel platform to study the role of glia in plasticity and regeneration.

Disclosures: K. Lehmann: None. **A.N. Wood:** None. **B.A. Stevens:** None. **L. Belluscio:** None.

Poster

201. Structural Plasticity: Circuit Function

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 201.06/C23

Topic: B.08. Synaptic Plasticity

Title: Morphometric plasticity of neuron somata and alterations in satellite glial cells of paravaginal ganglia in pregnant and primiparous rabbits

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Abstract: The pelvic plexus supplies most of the autonomic innervation that receives the lower urogenital tract in vertebrates. The estrogenic status has been associated with plastic changes involving pelvic neurons. Glial cells are considered to play an important role in neuronal function and survival by modulating the properties of synapses. We aimed to determine structural plasticity linked to the size of neuronal somata and satellite glial cells (SGC) of paravaginal ganglia. Rabbits were allocated into nulliparous (N), pregnant (G), and primiparous

after three (P3) and twenty days (P20) post-delivery. All groups was evaluated the neuronal soma area; the percentage of immunoreactive (ir) of neurons anti-aromatase, anti- androgen receptors (AR) and the number of SGCs per neuron. There was a decrease in the neuronal soma size for the G group, which was associated with a high number of axon initial segment and no aromatase-ir expression in SGC. The correlation between number of SGC per neuron and neuronal soma area decreased in G and P3 groups. Moreover, there was a lowest percentage of axon initial segment AR-ir in P20 group, with a regular soma size and similar number of SGCs per neuron as N group. Present findings show that pregnancy modulate the soma size of neurons in paravaginal ganglia, likely affecting the participation of the SGC and the axon initial segment.

Disclosures: L.G. Hernandez aragon: None. **E. Cuevas-Romero:** None. **M. Martínez-Gómez:** None. **A. Ortega:** None. **F. Castelan:** None.

Poster

201. Structural Plasticity: Circuit Function

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 201.07/C24

Topic: B.08. Synaptic Plasticity

Support: NIH Grant P30GM103398-05

NIH RO1DA040965

Title: Exposure to a high-fat diet alters perineuronal nets in the prefrontal cortex

Authors: *P. M. DINGESS[1], E. T. JORGENSEN[1], J. H. HARKNESS[3], M. SLAKER[4], B. A. SORG[5], C. R. FERRARIO[6], T. E. BROWN[2]
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Abstract: A key factor in the development of obesity is the overconsumption of palatable high-fat food, which elicits structural plasticity within the reward circuitry of the brain. Our previous work demonstrated that both short- and long-term exposure to a diet high in fat reduces dendritic spine density on excitatory pyramidal cells of the infralimbic prefrontal cortex (IL-PFC). What remains unclear is how high-fat diets alters inhibitory cells of the PFC, which have been shown to play a key modulatory role in excitatory cell firing. Of particular interest to our lab is the role of perineuronal nets (PNNs) in mediating experience-dependent plasticity. PNNs are specialized extracellular matrix structures that surround, primarily, the soma and proximal neurites of inhibitory parvalbumin-containing interneurons in the cortex. PNNs contribute to synaptic

stabilization, provide protection from oxidative stress, and help regulate the ionic microenvironment within cells. We set out to determine whether exposure to a high-fat diet (60% by kilocalorie) would alter the presence and/or intensity of PNNs in the PFC and whether or not selectively bred obesity-prone (OP) and obesity-resistant (OR) rat strains would be more susceptible and invulnerable, respectively, to any observed diet-induced changes. To test this, we placed rats on one of three dietary conditions: *ad libitum* chow, *ad libitum* high-fat, or restricted high-fat for three weeks and subsequently quantified PNN density and intensity in the IL-PFC, prelimbic prefrontal cortex (PL-PFC), and orbitofrontal cortex (OFC). Our results demonstrate that fat exposure induces a significant reduction in PNN intensity in both the PL-PFC and OFC and a decrease in PNN density in the OFC. Interestingly, no changes were observed in the IL-PFC, suggesting that high-fat consumption may alter excitatory and inhibitory structures in a regionally specific manner. Ultimately, the observed diet-induced structural adaptations may contribute to maladaptive food-seeking behavior and the development of obesity.

Disclosures: P.M. Dingess: None. **E.T. Jorgensen:** None. **J.H. Harkness:** None. **M. Slaker:** None. **B.A. Sorg:** None. **C.R. Ferrario:** None. **T.E. Brown:** None.

Poster

201. Structural Plasticity: Circuit Function

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 201.08/C25

Topic: B.08. Synaptic Plasticity

Support: NIH Grant SC1DA 034995

NIH Grant 1R21MH109779-01

Title: The role of ampar trafficking and phosphorylation during pavlovian reward conditioning and extinction

Authors: *R. ZANCA[1,2], R. CAAMANO-TUBIO[3], J. A. AVILA[1,2], P. A. SERRANO[1,2], A. R. DELAMATER[3,2]
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Abstract: Appetitive Pavlovian Conditioning (PC) is a model used to investigate appetitive-reward based learning. Very little is known about the molecular mechanisms in the brain underlying Appetitive PC and extinction. Previous work has revealed that the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAr) subunit GluA1 is preferentially trafficked in the hippocampus shortly after spatial-memory acquisition. Furthermore, AMPAr subunit GluA3 is preferentially trafficked in the lateral amygdala during fear-memory

consolidation. Additionally, phosphorylated GluA1 (pS845) has shown to promote AMPAr at the synapse and LTP induction, whereas phosphorylated GluA2 (pS880) has shown to induce internalization and recycling of GluA2-containing AMPArs. Thus, we hypothesized that Appetitive PC could also mediate differential AMPAr subunit trafficking in the Basolateral Amygdala (BLA) and other brain regions. The present study analyzed expression of molecular markers via western blotting in the BLA, Nucleus Accumbens (NAc) and Dorsal Striatum (DS); 3 brain regions that play pivotal roles in PC. Markers analyzed include: AMPAr subunits GluA1(total), pS845, GluA2 (total), pS880, GluA3(total) and pS880 + pS891. Analyzing these markers can reveal synaptic plasticity changes that occur as a result of Appetitive PC. Rats were trained on a Pavlovian magazine approach-conditioning task in which a short duration auditory stimulus was paired with delivery of a food pellet. Following 8 sessions of conditioning, rats either underwent 5 days of extinction training in which the tone CS occurred without food reward (Extinction), or were exposed to the experimental context without any scheduled events (No-Extinction). A third group of rats (Random) were trained on a truly random control contingency procedure in which a tone CS and food pellet US presentations occurred randomly in time within each acquisition session. Results from this study showed clear behavioral differences in the test day with the No-Extinction group displaying more conditioned magazine approach responses to the tone CS than either of the other two groups. Western blots revealed GluA1 (total) is elevated in our Extinction group in the BLA and NAc. GluA2 (total) is elevated in both our Extinction and No-Extinction group in all 3 brain regions. GluA3 (total), pS845, and pS880 + pS891 are elevated in our No-Extinction group in the DS and BLA. Our current data reveal that appetitive PC mediates the differential trafficking and phosphorylation of AMPAr subunits in different parts of the brain, suggesting that plasticity in these regions could be pivotal to Appetitive PC learning and extinction.

Disclosures: **R. Zanca:** None. **R. Caamano-Tubio:** None. **J.A. Avila:** None. **P.A. Serrano:** None. **A.R. Delamater:** None.

Poster

201. Structural Plasticity: Circuit Function

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 201.09/C26

Topic: B.08. Synaptic Plasticity

Support: NIH R01EY014074-19

Title: Abnormal retina specific segregation at the dLGN of flailer mice - A dominant negative myosin 5a mutant mice

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Abstract: Flailer mice express 2 WT copies of the +end actin motor protein, the dimer, Myosin Va and also express two copies of a *mutant myo5a* lacking sequences encoding the distal region of the motor lever arm and the ATP hydrolyzing end-feet (Jones et al., 2000). Flailer show a variety of abnormal behaviors such as: early seizures, an abnormal gait, repetitive, stereotyped, full-body grooming, anxiety, and poor spatial memory. Animals and people homozygous for mutant MyosinVa throughout their bodies die shortly after birth. Flailer is an exception, it lives and breeds normally, because its' mutation is expressed only in brain. The mutation resulted from a spontaneous recombination, in frame, between the upstream brain-specific promoter for *gnb5 and* the truncated *myo5a* (Jones et al 2000). Flailer, visual cortical neurons have abnormally high AMPAR miniature current frequencies and eAMPA/eNMDA ratios significantly larger than the WT_{FLR} strain. They also lack NMDA-dependent LTD at layer 4 to 2/3 synapses although NMDA-LTP is normal (Yoshii et al 2013). In developing rodent dorsal lateral geniculate nucleus (dLGN) the ipsilateral input arrives later than the contralateral input (Godement et al., 1984) and there is a competition between the left and right eye axons (Huberman et al., 2008). We hypothesized that if the retinogeniculate pathway of Flailer mice also lacked LTD, the ipsilateral eye axons should be unable to terminate in their normal "island-like" region of dLGN because the earlier innervating contralateral inputs could not undergo LTD. Here we report that when both eyes of Flr pups are differentially labeled with CTB (555, 647) they show an abnormally small ipsilateral zone with a higher percentage of overlap, while the contralateral projection occupies a larger territory. C1q, a component of the complement pathway involved in synapse elimination (Stevens et al 2007), is also down regulated in Flr mice. These results are all consistent with the result that NMDAR LTD is also defective in the dLGN of Flr and prevents displacement of early contralateral inputs by the later arriving axons.

Disclosures: S. Pandian: None. **J. Zhao:** None. **M. Constantine-Paton:** None.

Poster

201. Structural Plasticity: Circuit Function

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 201.10/C27

Topic: B.08. Synaptic Plasticity

Support: European Research Council (ERC)

Agence Nationale de la Recherche (ANR)

Fondation Recherche Médicale (FRM)

NARSAD independent investigator grant

Title: Synaptic changes upon removal of extracellular perineuronal nets in adult visual cortex

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Abstract: The maturation of sensory processing undergoes a critical period (CP), during which cortical neural circuits are sculpted and changed by experience. The closure of CP is paralleled by the accumulation of extracellular perineuronal nets (PNN) around parvalbumin (PV)-positive, fast-spiking interneurons. The degradation of these nets in adult animals was shown to reopen the structural plasticity typical of the CP, but absent during adulthood. Although the mechanisms underlying CP have been studied, the functional aspects linking PNNs to activity-dependent plasticity remain obscure. We aimed at defining *i)* the neurophysiological properties of PV cells in layer 4 of primary visual cortex (V1) during the establishment of the CP, and *ii)* how these properties are altered by PNN accumulation. PV cells were compared to their glutamatergic counterparts, the regular spiking (RS) spiny-stellate neurons. We found a robust age-dependent increase of input-output firing relationships in both cell types, with no overall change in their passive electrical properties. Importantly, we found that *in vivo* PNN removal in V1 in adult mice did not affect the action potential properties and firing dynamics. Importantly, PNN removal increased excitatory and inhibitory transmission selectively onto PV cells, recapitulating younger, pre-CP states. In addition, triggering plasticity *in vivo* by monocular deprivation specifically boosted the increase of glutamatergic transmission onto PV interneurons. Interestingly, paired recordings in layer 4 of V1 showed no changes of inhibitory unitary connections in the presence and absences of PNNs. We found that PNN removal increases the recruitment of PV cells by optogenetic activation of thalamocortical fibers leading to an increase of feed-forward inhibition onto PV and RS cells. Importantly, PNN removal caused a reduction of the slope of the contrast sensitivity curve measured in vivo, indicating a higher recruitment of inhibition. In conclusion, we found that PNN removal in adult visual cortex increases the specific recruitment of PV interneurons by thalamic fibers and this effect is amplified by a sensory deprivation. Increased PV cell recruitment results in a neuron-specific alteration of the E/I balance both *in vitro* and *in vivo*. These experiments shed light on the basic mechanisms underlying cortical plasticity, and its reopening through PNN removal.

Disclosures: **G. Faini:** None. **C. Deleuze:** None. **S. Landi:** None. **A. Aguirre:** None. **T. Pizzorusso:** None. **G. Ratto:** None. **A. Bacci:** None.

Poster

201. Structural Plasticity: Circuit Function

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 201.11/C28

Topic: B.08. Synaptic Plasticity

Support: NRF Grant 2016M3C7A1914123

NRF Grant 2015R1C1A1A02036851

Yonsei Challenge of 2016-22-0109

Title: Focused ultrasound increases vesicular zinc and concomitant adult hippocampal neurogenesis

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Abstract: Introduction: Transcranial focused ultrasound (FUS) has gained attention for its potential application as a method to locally open the blood-brain barrier (BBB) and facilitate drug delivery into the brain parenchyma. It has been demonstrated that FUS-mediated BBB opening induces an increase in hippocampal neurogenesis in adult rodents. However, the mechanism underlying FUS-induced neurogenesis is unclear. Recent evidence suggests that zinc is a central actor in regulating stem cell proliferation and neurogenesis in the adult brain. Here we speculate that vesicular zinc may relate to the increased hippocampal neurogenesis after focused ultrasound sonication. **Materials and Methods:** The present study utilized adult male Sprague-Dawley rats (2-3 months, 250-300 g). Rats were sonicated using a single-element transducer (frequency 0.5 MHz) with microbubble. The acoustic parameters used for each sonication are: pressure amplitude 0.3 MPa, pulse length 10 ms, burst repetition frequency 1 Hz, and a duration of 120 s. BrdU was intraperitoneally injected 2 times per day for 4 consecutive days starting 24 hours after FUS sonication. Histological examination was performed at 5 or 21 days after FUS sonication. **Results:** We found that the number of $BrdU^+$ and DCX^+ cells were significantly increased in the FUS-treated dentate gyrus (DG) following 5 days of FUS sonication, compared to the contralateral untreated DG. Zinc transporter 3 (ZnT3), a transporter of zinc into synaptic vesicles, was also seen to increase in the DG at 5 days after FUS sonication. Furthermore, the total number of $NeuN^+/BrdU^+$ cells in FUS-treated DG was significantly increased at 21 days after FUS sonication, compared to the untreated DG. **Conclusion:** The present study demonstrates that increased vesicular zinc by FUS induces adult hippocampal

neurogenesis. Therefore, this study suggests that vesicular zinc may be involved in FUS-induced neurogenesis.

Disclosures: **J. Shin:** None. **B. Choi:** None. **C. Kong:** None. **S. Lee:** None. **J. Chang:** None. **W. Chang:** None. **S. Suh:** None.

Poster

201. Structural Plasticity: Circuit Function

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 201.12/C29

Topic: B.08. Synaptic Plasticity

Support: NRF Grant 2016M3C7A1914123

NRF Grant 2015R1C1A1A02036851

NRF Grant 2016R1D1A3B03932649

Title: Improvements in memory after focused ultrasound are associated with changes in hippocampal cholinergic activity and neurogenesis

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Abstract: Introduction: Alzheimer's disease is characterized pathologically by neurofibrillary tangles, amyloid plaques, gliosis, synaptic loss and cholinergic deficits. Recently, cell proliferation and neurogenesis was reported to have increased when the blood brain barrier (BBB) was disrupted by Focused ultrasound (FUS) with microbubbles. Previously, we have demonstrated that the cholinergic cell decreases in 192 IgG-saporin rat model, and that decrease in cholinergic cell is associated to decrease in cognitive behavior. The purpose of this study was to determine if the learning and memory abilities of the 192 IgG-saporin rat model are improved by FUS.
Materials and Methods: Animals were divided into the four groups: Sham group (PBS injection), Lesion group (saporin injection), FUS-3 and FUS-10 groups (After 3 and 10 days after saporin injection, FUS treatment). Sprague-Dawley rats (200-250g) were injected bilaterally with 192 IgG-saporin into the ventricle. Rats were sonicated using a single-element transducer (frequency 0.5 MHz) with microbubble. The acoustic parameters used for each sonication are: pressure amplitude 0.3 MPa, pulse length 10 ms, burst repetition frequency 1 Hz, and a duration of 120 s. To confirm cell proliferation, BrdU was intraperitoneally injected 2 times per day for 4

consecutive days starting 24 hours after FUS sonication. Two weeks after IgG-saporin administration, spatial memory was tested with the Morris water maze training for 5 days and the final test was performed after 3 days afterwards. Immediately after behavioral testing, rats were sacrificed and immunohistochemistry was performed.
Results: In the water maze test, the FUS groups had a higher number of crossing times and staying time in the platform zone than the lesion group. Also, the FUS-3 group was higher than for the FUS-10 group. We confirmed that the amounts of DCX^+, $NeuN^+$, and $BrdU^+$ were different between the FUS group and the lesion group.
Conclusion: Our results suggest that FUS sonication facilitates recovery of memory and learning abilities in cholinergic deficits rat model. Moreover, the results suggest that neurogenesis is correlated with the mechanism of cognitive behavior recovery.

Disclosures: C. Kong: None. **J. Shin:** None. **J. Lee:** None. **C. Koh:** None. **M. Yoon:** None. **Y. Na:** None. **J. Chang:** None. **W. Chang:** None.

Poster

201. Structural Plasticity: Circuit Function

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 201.13/C30

Topic: B.08. Synaptic Plasticity

Support: CABMC Grant UD140069ID

KRISS Grant 2016-31-0970

Title: Circuit plasticity reconstruction pain modeling (cprp): New method inducing hypersensitivity in rat

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Abstract: Introduction: Neuropathic pain occurs from abnormal sensitivity in the central nervous system. The mechanism of hypersensitivity has been barely known. However, it has been reported that one of the reasons of hypersensitivity is neural plasticity change in the neural circuit. Long term potentiation (LTP) enhances connections between circuits and this plasticity change causes mechanical allodynia. In this study, we proposed a new pain model by changing neural plasticity and we evaluated the model successiveness via Von Frey test and immunohistochemistry. **Materials and Methods:** We performed CPRP surgery using Sprague Dawaley rats (180 g - 200 g) under pentobarbital anesthesia. A reagent mixture of 2 mM NMDA

and 0.6 mM Ro 25-6981 was injected into their right rostral agranular insular cortex (RAIC). Sham groups were only injected with PBS in the same target region. Then, an electrode was inserted in the lateral edge of the contralateral hind paw and electrical stimulations (350 uA, 100 Hz) were delivered for 3 hours under anesthesia. We injected lidocaine into the ipsilateral hind paw to diminish unnecessary sensory input. After recovery, rats underwent Von Frey filament test for evaluate of withdrawal thresholds of both hind paws. Three weeks after the CPRP surgery, we confirmed the neural plasticity change through immunohistochemistry. **Result:** In Von Frey test, the withdrawal threshold value was reduced by 94% ± 2%, compared with the pre-operation values in both hind paws. Post-operation threshold values stayed low from post day 1 to post day 21, which indicates that the mechanical allodynia appeared after CPRP surgery. Moreover, the amount of decreasing threshold value was significantly different from the values of the sham group. Around the injection area, we confirmed the presence of PSA-NCAM antibody positive stains which is widely used as an adult plasticity changing marker. **Discussion:** We hypothesized that the electrical stimulation of the hind paw evoked pre-synaptic activation and that the NMDA/Ro 225 reagents enhanced post-synaptic response in order to induce LTP in the insular cortex which is a high-plasticity area in the brain and a main part of pain matrix. Based on this hypothetical situation, hyper sensitization appears in the insular cortex which can be confirmed by the presence of allodynia symptoms. In conclusion, we propose this method as a new neuropathic pain model that results in plasticity change with a fast processing time and no muscle injury.

Disclosures: M. Yoon: None. **C. Koh:** None. **J. Lee:** None. **J. Shin:** None. **C. Kong:** None. **H. Jung:** None. **J. Chang:** None.

Poster

201. Structural Plasticity: Circuit Function

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 201.14/C31

Topic: B.08. Synaptic Plasticity

Support: CABMC UD140069ID

KRISS 2016-31-0970

Title: Right dorsolateral prefrontal cortex stimulation reduces mechanical allodynia in neuropathic pain model

Authors: *C. KOH[1], *C. KOH[3], M.-S. YOON[1,2], J. SHIN[1,2], C. KONG[1], J. LEE[1,2], W. CHANG[1], H. JUNG[1], J. CHANG[1,2]
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Abstract: Introduction: Neuropathic pain initiated from primary injury or dysfunction of nervous system, and cause difficulty for patients in leading ordinary lives. Many clinical trials have been developed for relief of these severe pain. However, neuropathic pain is still challenging to treat for various limitations such as drug resistance, invasiveness and effectiveness. As an alternative, epidural stimulation such as motor cortex stimulation (MCS) has emerged, which is semi-invasive and less risky. However, most of pain controlling studies have been only focused on MCS and still approximately 50% of pharmacoresistant neuropathic patients may benefit from this trial. To enhance the therapeutic effect of epidural stimulation, other possible areas should be studied. In this paper, we present the effect of electrical stimulation of right dorsolateral prefrontal cortex (rdPFC) in neuropathic pain rats.
Materials and Methods: Neuropathic pain was induced in Sprague-Dawley rats (180g-200g) using spared nerve injury (SNI) modeling method. After 2 weeks from the surgery, two screw type surface electrodes were implanted on the rdPFC area through burr holes and firmly fixed with dental cement under pentobarbital anesthesia (intraperitoneal injection, 50 mg/Kg). After recovery, the electrical stimulation (450 uA, 130 Hz) was delivered to rdPFC using STG8004. Tactile allodynia was measured to verify the effect of rdPFC stimulation.
Result: rdPFC stimulation was found to modulate mechanical allodynia in neuropathic pain in rats. The withdrawal threshold was increased from pre- (0.4 gram force) to post stimulation (8 gram force). In addition, sustained stimulation effect was observed after one set of stimulation.
Discussion: rdPFC is a functional structure which has been known as involving management of cognitive process and planning. However, rdPFC has an additional important function: monitoring sensory-motor incongruities which can be one axis of complex neuropathic pain mechanism. We hypothesized that stimulations in rdPFC can reduce the neuropathic pain and proved the effectiveness. As a result, rdPFC can be an attractive target for studying pain relief mechanism and treatment.

Disclosures: C. Koh: None. **C. Koh:** None. **M. Yoon:** None. **J. Shin:** None. **C. Kong:** None. **J. Lee:** None. **W. Chang:** None. **H. Jung:** None. **J. Chang:** None.

Poster

201. Structural Plasticity: Circuit Function

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 201.15/C32

Topic: B.08. Synaptic Plasticity

Title: Function of schizophrenia risk gene dysbindin in stress induced anxiety and aggression

Authors: *Q. GU
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Abstract: Schizophrenia is a serious psychiatric disorder which affects how people cognition, emotion and behavior. It has 1% prevalence in the population. The etiology of schizophrenia has both genetic and environmental components. However, it is not clear whether schizophrenia risk genes also confer vulnerability to environmental factors. Sandy mice are mutant mice null for the schizophrenia risk gene dysbindin-1. They have working memory impairment but do not exhibit anxiety or abnormal social behavior. Here we tested whether sandy mice are vulnerable to traumatic stress by shocking with 14 strong electric-shocks in variable intervals during an 85-min period. One week after foot-shock, we tested the mice for locomotion, anxiety, social interaction, aggressive behavior and depression. We found that stressed sandy mice are anxious and aggressive. Because amygdala is a structure which is involved in anxiety, emotion and aggressive behavior, we hypothesize that dysbindin is involved in the stress response of the amygdala. To test this hypothesis, we use electrophysiology, calcium imaging and optogenetics to study the synaptic function and neuronal circuit in amygdala, aiming to uncover the cellular mechanism underlying the behavior changes induced by traumatic stress.

Disclosures: Q. Gu: None.

Poster

201. Structural Plasticity: Circuit Function

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 201.16/DP02/C33 (Dynamic Poster)

Topic: B.08. Synaptic Plasticity

Support: KAKEN-15K01834

KAKEN-16H01494

KAKEN-16H01600

Title: Biphasic change in water diffusion MRI signals in the hippocampus of the rat brains following training of the Barnes maze task across the successive 2-days and 6-days sessions

Authors: *M. ABE[1], Y. TAKANO[2], T. A. HIGUCHI, 960-1295[3], R. RYOKE[4], S. OHARA[6], Y. TAKI[7], R. KAWASHIMA[5]
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Sci., Sendai, Japan; [7]Dept. of Radiology and Nuclear Medicine, Inst. of Development, Aging and Cancer, Tohoku Univ., Sendai, Japan

Abstract: Recent studies revealed biphasic stages of the morphological plasticity in neural tissue of the brain, representing formation and elimination of the structural elements, as learning has progressed over multiple days. Water diffusion-weighted magnetic resonance imaging (DW-MRI) techniques can work as a probe to estimate microscopic morphological change in neural tissue. We examined if learning tasks would elicit biphasic change in water diffusion in the early and late phase of learning. We had rats (Long-evans, 7 weeks, male) trained the Barns maze task over the 2-days (n = 10) or 6-days session (n = 14). We had control groups who were not engaged in the task and kept housed in the cage during the same period of time (n = 10 and n = 12 for 2-days and 6-days, respectively). We acquired DW imaging of the brain 1 day before the beginning of or 1 day after the end of the training session. T2-weighted imaging was also acquired for co-registration of the DW images to anatomical template. We compared mean water diffusivity between the two time points in the whole brain. Preprocessing and statics were performed with use of the distributed softwares, SPM 12 and FSL (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/; https://fsl.fmrib.ox.ac.uk/fsl/fslwiki). We hypothesized that the 2-days and 6-days training session would change water diffusion in opposite directions in the hippocampus, a critical region for spatial learning. Since sample size was small, threshold was set at uncorrected $p = 0.05$ for the tentative purpose of displaying brain mapping.

Rats under the 2-days and 6 days training conditions showed improvements in performance when compared between mean performance at the first and final training day (paired t test, $p < 0.001$ for both). Improvements showed bigger in the 6-days than the 2-days condition (two sample t test, $p = 0.004$).

Imaging results showed increased and decreased change in water diffusion in the hippocampus after end of the 2-days and 6-days training session, respectively. Notably, in the 6-days training, rats exhibiting a greater learning showed a bigger increase in water diffusion (simple regression analysis, $R^2 = 0.36$, $p = 0.03$). The present results suggested biphasic change in water diffusion in the hippocampus in the early and late phase of learning. It is possible that biphasic change in water diffusion might reflect learning-dependent progressive stages of the morphological plasticity occurring in the hippocampus.

Disclosures: **M. Abe:** None. **Y. Takano:** None. **T.A. Higuchi:** None. **R. Ryoke:** None. **S. Ohara:** None. **Y. Taki:** None. **R. Kawashima:** None.

Poster

202. Neuronal Firing Properties and Regulation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 202.01/C34

Topic: B.09. Physiological Properties of Neurons

Support: NS027881

Title: Orexin receptor activation in serotonergic (5-HT) dorsal raphe (DR) neurons induces a novel slow afterhyperpolarization (sAHP) that results from the Ca^{2+}-dependent closure of cation channels

Authors: *M. ISHIBASHI, C. S. LEONARD
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Abstract: Serotonergic (5-HT) dorsal raphe (DR) neurons regulate numerous brain functions including sleep-wake states, circadian phase, reward and mood. Moreover, orexin receptor signaling at 5-HT DR neurons appears critical in the sleep disorder narcolepsy, which emerges following the loss of orexin signaling. This suggests that the orexin –mediated changes in 5-HT DR neuron firing plays an important role in regulating the expression of normal waking. In trying to better understand how orexin influences the firing of these neurons, we recently reported that in addition to producing a slow depolarization, orexin-A also strongly enhances the post-spike afterhyperpolarization (orexin-enhanced afterhyperpolarization; oeAHP) which alters spike encoding by increasing spike frequency adaptation. Mechanistically we found that the oeAHP involved two distinct components that required Ca^{2+} influx. The first was of medium-duration (tau ~ 0.5s) and involved apamin-sensitive SK Ca^{2+}-activated K^+ channels. The second was of longer duration (tau ~ 5s), was apamin-insensitive (termed the ai-oeAHP) and appeared similar to a slow AHP (sAHP). In this study we used whole-cell patch clamp recordings and Ca^{2+} imaging in mouse brain slices to investigate the mechanisms and function of this ai-oeAHP. Surprisingly, we found that the ai-oeAHP was not attenuated by a cesium-based patch solution as expected for a K^+ currents, but rather was blocked by substituting NMDG for Na^+ in the ACSF or by application of flufenamic acid (FFA), both of which attenuated the orexin-induced inward current. Moreover, we found that the increase in baseline membrane conductance produced by orexin-A was reduced during the ai-oeAHP suggesting that the ai-oeAHP was mediated by a transient, Ca^{2+}-dependent closure of the cation channels activated by orexin. Interestingly, while blocking SK channels with apamin greatly increased excitability, orexin-A still produced a reduction in the steady-state repetitive firing suggesting that the ai-oeAHP functions to promote spike-frequency adaptation despite its novel mechanism. These results suggest that ai-oeAHP is a novel type of Ca^{2+}-dependent sAHP that is conditionally expressed following orexin-activation of non-selective cation channels. Collectively, these findings suggest that orexin, which is released during active waking, alters the temporal firing properties of 5-HT DR neurons to reduce spike encoding of tonic inputs without attenuating the encoding of transient inputs. The loss of orexin in narcolepsy would be expected to degrade this signal processing which may contribute to the emergence of the narcolepsy phenotype.

Disclosures: M. Ishibashi: None. **C.S. Leonard:** None.

Poster

202. Neuronal Firing Properties and Regulation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 202.02/C35

Topic: B.09. Physiological Properties of Neurons

Support: NIH grant R01 NS027781

Title: Alpha-1 adrenergic receptor excitation of serotonergic (5-HT) dorsal raphe (DR) neurons increases membrane noise, the late afterhyperpolarization (AHP), spike frequency adaptation and has a subtractive effect on firing gain

Authors: *N. E. MOLINA[1], M. ISHIBASHI[2], C. S. LEONARD[3]
[1]Physiol., New York Med. Col., Valhalla, NY; [3]Dept Physiol, [2]New York Med. Coll, Valhalla, NY

Abstract: Serotonergic (5-HT) dorsal raphe (DR) neurons regulate numerous brain functions including sleep-wake states, circadian phase, reward, mood and are implicated in major psychiatric disorders. They receive convergent excitatory input from orexin (OX) and norepinephrine (NE) containing afferents that act via OX1/OX2 and alpha-1 adrenergic receptors, respectively. But how these receptors influence the encoding of inputs into the firing of action potentials is not well understood. In this study, we used whole-cell patch clamp recordings from DR neurons in mouse brain slices to examine the effect of phenylephrine (PE), an alpha-1 agonist, on several attributes of the spike encoding process. As expected, from our recent OX studies, PE application (3 uM) produced a slow depolarization with a large broad-band increase in membrane current noise, consistent with activating “noisy” cation channels. Furthermore, like OX, PE enhanced a late AHP by increasing its amplitude (Control: -6.71 ± 0.84 mV; PE: -9.93 ± 1.11 mV; n = 10; p = 0.001) and greatly prolonging its duration (20-80% recovery in Control: 0.32 ± 0.06 s; PE: 1.95 ± 0.34 s; n = 10; p < 0.001). This AHP change resulted in decreased steady-state, but not initial firing rate, over a broad range of driving currents. We next examined a possible function of the membrane current noise produced by PE. Although noise can be a detriment to system performance, it can also be useful. For example, previous work in neocortical pyramidal neurons has shown that random synaptic noise can multiplicatively modulate the firing gain (initial slope of the steady-state frequency - current curve), especially in neurons having large, slow AHPs. We therefore tested whether the increased noise and AHP produced by PE also produced multiplicative changes to the firing gain of DR neurons. We found that while the slope of the frequency-current curve changed little (Control: 3.84± 0.35 sps/100pA; PE: 4.35 ± 0.37 sps/100pA; p < 0.05), the offset (measured as the x-intercept) changed substantially (Control: -73.4 ± 9.80 pA; n = 10; p < 0.001; PE: -11.4 ± 5.92 pA; n=10) in response to PE. This suggests that PE induces a subtractive but not

multiplicative change in the steady-state firing gain of 5-HT DR neurons over the range of driving currents tested. Collectively, these data suggest that both PE and OX, which are released during the waking state, “tune” the temporal responsiveness of 5-HT DR neurons. This change would preserve encoding of rapidly varying inputs, like those related to transient behavioral events, while producing a subtractive reduction in responses to slowly varying inputs.

Disclosures: **N.E. Molina:** None. **M. Ishibashi:** None. **C.S. Leonard:** None.

Poster

202. Neuronal Firing Properties and Regulation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 202.03/C36

Topic: B.09. Physiological Properties of Neurons

Title: Novel description of the large conductance Ca^{2+}-modulated K^+ current, BK, during an action potential from suprachiasmatic nucleus neurons

Authors: *J. R. CLAY
Physiol., NIH, Rockville, MD

Abstract: The contribution of the large conductance, Ca^{2+}-modulated, voltage gated K^+ channel current, I_{BK}, to the total current during an action potential (AP) from suprachiasmatic nucleus (SCN) neurons is described using a novel computational approach. An experimental recording of an AP and the corresponding AP-clamp recording of I_{BK} from an SCN neuron (Jackson, et al. *J Neurosci* 24:7985, 2004) were both digitized. The AP data set was applied computationally to a kinetic model of I_{BK} that was based on results from the *mslo* BK channel clone heterologously expressed in *Xenopus* oocytes (Cui, et al. *J Gen Physiol* 109:647, 1997). This computational AP-clamp procedure was recently described (Clay, *J Neurophysiol* 114:707, 2015). The I_{BK} model result during an AP was compared with the AP-clamp recording of I_{BK}. The comparison suggests that a change in the intracellular Ca^{2+} concentration does not have an immediate effect on BK channel kinetics. Rather, a delay of a few milliseconds is involved before the effect fully occurs. The implication of this result for models of the AP for neurons in which BK channels are present is that an additional time dependent process will be required in the models, a process that describes the time dependence of the development of a change in Ca_i^{2+} on BK channel kinetics.

Disclosures: **J.R. Clay:** None.

Poster

202. Neuronal Firing Properties and Regulation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 202.04/C37

Topic: B.09. Physiological Properties of Neurons

Title: The effect of neural orientation on action potential generation elicited by transcranial magnetic stimulation:a computational study

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Abstract: Transcranial magnetic stimulation (TMS) has great potential both as a noninvasive therapeutic for cognitive, neurological and affective disorders and as a scientific tool to answer basic questions about brain function. However, the effect of TMS at the level of single neurons is not well understood. Stimulation is achieved by discharging a capacitor to pass a brief electric current through a magnetic coil, which produces a brief, high-intensity magnetic field, which in turn induces an electric field. The induced electric field causes current to flow in the axial direction of somata, dendrites and axons; current flow across the thin plasma membrane directly induced by the electric field is usually neglected (Rattay, Neuroscience 89:335, 1999). We attempted to replicate the previous computational work of Pashut et al. (PLoS Computational Biology 7: e1002022, 2011) modeling the effect of TMS on a rat cortical pyramidal neuron in 2D (the difference in the field in the direction toward the coil was considered negligible). They implemented the activating function approximation of the effect of an external electric field on a neuron in the simulation package NEURON in the following way: 1) The spatial derivative of the projection of the electric field onto the unit vector in the axial direction gives an estimate of the instantaneous current flowing in the axial direction at a given point on a neurite. 2) The difference in “extra” axial current induced by the field flowing at two different points on a neurite gives the “extra” current that charges the membrane between those two points. The previous 2D results depended upon several errors, including an error in the spatial component of the field, in the topology of the axon and in the units of the axial current. Moreover, the boundary condition of no induced axial current at the tips of the neurites (Joucla and Yerte, J Physiol 106:146, 2012) was not honored, and we found that the tip currents are much greater than currents induced in segments without tips. After correcting for these errors, we were able to evoke action potentials with a reasonable potential across the capacitor of 2.5 kV. We also showed that the orientation of the neurites in the field clearly affects the action potential threshold. Next we will modify the code to take into account the sinks and sources introduced by branch points. This improved NEURON model of TMS should be useful in determining the effects of morphology on the response to TMS.

Disclosures: **D. Elcin:** None. **R.A. Tikidji-Hamburyan:** None. **C.C. Canavier:** None.

Poster

202. Neuronal Firing Properties and Regulation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 202.05/C38

Topic: B.09. Physiological Properties of Neurons

Support: KTIA_NAP_13-2014-0018

NVKP_16-1-2016-0016

Title: Frequency-dependent regulation of intrinsic excitability and spiking resonance by voltage-gated currents

Authors: *A. SZÜCS[1,2], A. RÁTKAI[2], K. SCHLETT[2], R. HUERTA[3]
[1]UCSD, La Jolla, CA; [2]Dept. of Physiol. and Neurobio., Eotvos Lorand Univ., Budapest, Hungary; [3]BioCircuits Inst., Univ. of California San Diego, La Jolla, CA

Abstract: The generation of action potentials reflects a complex interplay between the synaptic inputs and the voltage-dependent membrane currents of the postsynaptic neuron. A multitude of neuron types have been shown to exhibit some form of subthreshold resonance that potentially allows them to respond to synaptic inputs in a frequency-selective manner. Membrane impedance as determined by analysis of subthreshold voltage responses under oscillatory current waveforms is considered as a key indicator of resonant properties. However, it is not well understood how the regulation of subthreshold resonance by voltage-dependent currents translates to firing output under more naturalistic conditions such as synaptic bombardment. In the present study we developed computational models of hippocampal and striatal neurons and performed dynamic clamp experiments to examine how specific voltage-gated currents regulate excitability and firing under simulated, frequency-modulated synaptic inputs. The model simulations revealed that the impact of voltage-gated currents in regulating the firing output is strongly frequency-dependent and mostly affecting the synaptic integration at theta-frequencies. Notably, robust frequency-dependent regulation of intrinsic excitability can be found even when the particular neuron model phenotype exhibits no signs of subthreshold membrane resonance. We validated the model predictions using simulated synaptic bombardment and concurrent biophysical manipulation of cultured hippocampal pyramidal neurons using the dynamic clamp technique. In agreement with the model, the insertion of a computer-generated inwardly rectifying K-current reduced the intrinsic excitability of hippocampal neurons most effectively under theta frequencies. Our findings show that resonant-type regulation of intrinsic excitability is more common and more elaborate than anticipated from conventional analysis of subthreshold membrane resonance.

Disclosures: **A. Szücs:** None. **A. Rátkai:** None. **K. Schlett:** None. **R. Huerta:** None.

Poster

202. Neuronal Firing Properties and Regulation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 202.06/C39

Topic: B.09. Physiological Properties of Neurons

Support: RSBO

Title: Decreases of extracellular calcium elicit sustained firing in axons of primary afferents through $Na_v1.6$ channels

Authors: J. GIRAUD[1], P. C. MORQUETTE[3], B. BRÉANT[4], M. COUILLARD-LAROCQUE[2], D. VERDIER[5], *A. KOLTA[6]
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Abstract: Pain is usually associated to activity of small diameter primary afferents, but changes of excitability of large diameter sensory afferent fibers also occur after nerve injury. These afferents have subthreshold membrane oscillations (SMO) from which firing normally emerges. In neuropathic pain models, the amplitude of SMOs increases and leads to abnormal ectopic firing. Similar changes in intrinsic electrical properties are observed in mesencephalic trigeminal (NVmes) cells innervating muscle spindle afferents (MSA) of the jaw closing muscles in a chronic muscle pain model. The SMOs, in these neurons rely on a persistent sodium current (I_{NaP}). Interestingly, blocking I_{NaP} with riluzole reduces pain behavior for at least 3 weeks after application. Ectopic discharges could therefore represent a target for therapy, but the site at which they are generated remains unclear. Our previous work has shown that I_{NaP}-mediated firing is exquisitely sensitive to extracellular Ca^{2+} decreases. Thus, to identify and localize the sodium channels underlying these SMOs and ectopic discharges, we used local applications of the Ca^{2+} chelator BAPTA with whole-cell patch-clamp recordings, confocal imaging and immunohistochemistry methods on mice brain slices. We measured the effects of localised BAPTA applications along the dye-labelled axon at a distance from 0 to 300 μm from the soma and calculated a normalized BAPTA index, which indicates the number of action potentials evoked depending on the duration of BAPTA application. We found that restricted $[Ca^{2+}]_e$ decreases near the soma have no effect on either SMO or firing (n=8), whereas applications on the axon between 40 and 120 μm from the soma promoted SMO and sustained firing (n=13). Interestingly, the BAPTA index was maximal in a precise axonal compartment between 60 and 80 μm (n=6), where immunostaining confirmed an enrichment of $Na_v1.6$ (n=1). Furthermore,

bath application of 4,9-anhydrotetrodotoxin, a highly selective blocker of $Na_v1.6$ channels, reversibly abolished evoked SMO and firing (n=10). The SMO and the ectopic discharges persisted in presence of synaptic blockers (n=3), which suggest that this region could be an important site of regulation for these cells and could be critical in the development of ectopic activities. Because S100ß, an astrocytic Ca^{2+} binding protein was found around this precise axon segment in immunostainings (n=1), we hypothesize that astrocytes may play a key role in discharge initiation by regulating the electrical properties of NVmes cells through $Na_v1.6$. Our next goal is to determine the role of astrocytes in changes of excitability of MSA in the chronic muscle pain model.

Disclosures: J. Giraud: None. **P.C. Morquette:** None. **B. Bréant:** None. **M. Couillard-Larocque:** None. **D. Verdier:** None. **A. Kolta:** None.

Poster

202. Neuronal Firing Properties and Regulation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 202.07/C40

Topic: B.09. Physiological Properties of Neurons

Support: ERC - INTERIMPACT

Title: Rhythmic persistent firing of neurogliaform interneurons in the human and rodent neocortex

Authors: *M. RÓZSA[1], M. TÓTH[1], G. OLÁH[1], J. BAKA[1], P. BARZÓ[2], G. TAMÁS[1]
[1]MTA-SZTE Res. Group For Cortical Microcircuits, Szeged, Hungary; [2]Dept. of Neurosurg., Univ. of Szeged, Szeged, Hungary

Abstract: Persistent firing is a form of activity-induced ectopic action potential generation which has been recorded in several GABAergic interneuron classes from the hippocampus and the neocortex of rodents in vitro and in vivo. In order to assess potential species specific aspects of persistent firing, we performed whole cell patch clamp recordings of layer 1 interneurons in rat and human neocortical slices in submerged recording chamber. Interneurons in layer 1 of the human neocortex were capable of establishing persistent firing induced by the same paradigm used in rodents. In addition, we detected episodes of persistent firing alternating with silent periods rhythmically in the frequency range of slow oscillations (0.5 - 2 Hz) in identified human neurogliaform cells. This bistable persistent firing state was absent in human and rodent non-neurogliaform interneurons remaining silent following a single persistent firing episode. Furthermore, we show that rodent neurogliaform cells are also capable of rhythmic persistent firing but only in dual superfusion recording chambers, presumably due to a more physiological

environment. We hypothesize that rhythmic persistent firing in neurogliaform cells might contribute to the generation of slow oscillations in the rodent and human neocortex.

Disclosures: **M. Rózsa:** None. **M. Tóth:** None. **G. Oláh:** None. **J. Baka:** None. **P. Barzó:** None. **G. Tamás:** None.

Poster

202. Neuronal Firing Properties and Regulation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 202.08/C41

Topic: B.09. Physiological Properties of Neurons

Support: Craig H. Neilsen Foundation

Title: Excitability differences and ionic currents in mouse neurons of major pelvic ganglion

Authors: *M. L. GRAY, C. KYI, D. SCHULZ
Univ. of Missouri, Columbia, MO

Abstract: Autonomic bladder-innervating neurons of the major pelvic ganglion (MPG) in the mouse can be classified by whether they display two major types of excitability in response to depolarizing current. The first type, called phasic neurons, constitute up to 70% of these neurons, and fire 1-3 spikes before rapidly adapting to current injection. The second type, called tonic cells, continuously spike faster in proportion with increasing current injection. Interestingly, the dog cardiac autonomic ganglia also displays similar neuron firing types. Despite these robust differences, little is known about their ionic mechanism. As these neurons are the final outputs to the bladder, understanding the reasons for these differences are important for understanding micturition circuitry and lays a foundation for studying how and if these properties are changed in pathological states such as spinal cord injury and diabetes.
In this study, we characterize the firing properties and passive properties of male mouse MPG neurons in current clamp, and attempt to determine the reason for these underlying differences by dissecting ionic currents with a combination of single electrode voltage clamp (SEVC) and channel blockers.
Consistent with previous reports we find 67.7 ± 42.2% of neurons display the phasic phenotype with the remainder displaying tonic spiking. In contrast to previous reports in female mice, that these cell types do not differ in input resistance (R_{IN}) (but consistent with findings in cardiac ganglion of dog), our preliminary data suggest that input resistance of phasic is lower than that of tonic neurons in male mice. Consistent with this, we find rheobase larger for phasic than tonic cells. Firing frequency plotted as a function of rheobase (RB) demonstrates that phasic cells have near flat FI curves while tonic cells are linear up until 5 RB and then plateau with increasing current injection. Preliminary SEVC data suggests phasic cells have greater steady state high

threshold potassium currents (I_{HTK}) compared to tonic cells, while tonic cells have relatively depolarized $V_{1/2}$ inactivation.
Our results are suggestive of previously unreported differences in passive properties of these cell types that may shed light on characterizing these differences in firing rate. Further, limited data is suggestive of an enhanced steady state potassium current in phasic neurons, however, further study is needed to confirm its identity as a delayed rectifier. These data suggest that excitability differences of these cell types can in part be explained by passive properties and a slow potassium current.

Disclosures: M.L. Gray: None. **C. Kyi:** None. **D. Schulz:** None.

Poster

202. Neuronal Firing Properties and Regulation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 202.09/C42

Topic: B.09. Physiological Properties of Neurons

Support: NIH Grant 1R01EB014641

NIH Grant 1R21EY026438-01

Title: Electric field confinement and control of spreading depression

Authors: *A. J. WHALEN[1], H. KADJI[2], M. DAHLEM[4], B. J. GLUCKMAN[2], S. J. SCHIFF[3]
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Abstract: Spreading depression is a large-scale pathological network phenomenon related to migraine, stroke, ischemia and traumatic brain injury. Once initiated, spreading depression propagates across grey matter mainly through the diffusion of potassium via extra and intracellular processes, which collapses the resting membrane voltage gradient of adjacent cells leading to transient inactivation and cellular swelling in its wake, and is difficult to block pharmacologically as the propagation is independent of synapses. Here we present the suppression and confinement of spreading depression utilizing externally applied transcortical DC electric fields and simultaneous epifluorescence and intrinsic optical imaging in brain slices. We experimentally observe the electric field induced forcing of spreading depression propagation to locations in cortex outside of the normal propagation path whereby further propagation is confined and arrested even after field termination. Our experiments also show that the opposite electric field polarity will produce an increase in propagation velocity and a confinement of the wave to the normal propagation path, and that potassium sensitive dye fluorescence is strongly coincident with the intrinsic optical signal during spreading depression.

The results could guide the design of new medical devices targeting sufferers of migraine headaches with a non-invasive and locally enabled method of treatment and prevention.

Disclosures: A.J. Whalen: None. **H. Kadji:** None. **M. Dahlem:** None. **B.J. Gluckman:** None. **S.J. Schiff:** None.

Poster

202. Neuronal Firing Properties and Regulation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 202.10/C43

Topic: B.09. Physiological Properties of Neurons

Support: Wellcome Trust Neural Dynamics

Title: Biophysical maturation of the action potential waveform

Authors: *F. H. INKPEN[1], N. F. LEPORA[2], M. C. ASHBY[1]
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Abstract: The developing neuron experiences rapid changes in the first few postnatal weeks, adapting its electrical activity, morphology and synaptic connectivity. Action potentials drive the patterns of neurotransmitter release that underpin neuronal communication and plasticity, and also control calcium influx, influencing gene expression. Therefore, changes to the waveform of the action potential over the course of development may have a wide-ranging and profound influence on neuronal structure and function. We assessed the postnatal development of the action potential waveform and neuronal membrane passive dynamics via whole cell current clamp electrophysiology in layer 4 stellate cells of the mouse somatosensory cortex, taking recordings in slices from mice aged from 3 to 12 postnatal days. Action potentials were triggered via the application of a long depolarising current step, whilst passive dynamics were triggered by injecting a short (1ms) current. We show that postnatal neuronal maturation is associated with large increases in the height and speed of individual action potentials. Passive membrane dynamics are also observed to mature, with analysis via a two-compartment model of exponential decay revealing an unexpectedly fast passive current sink in some cells. Intracellular labelling and subsequent imaging of Neurobiotin and dextran-conjugated Alexa546 dyes exposed gap junctions as a potential cause of these dynamics. The effect of gap junction-coupling on neuronal excitability during postnatal development is examined, with potential implications for the regulation of neural networks. By fitting computational conductance-based Hodgkin-Huxley style models to current-clamp electrophysiological data, the underlying biophysics behind the subtleties of the action potential shape can be revealed. For computational models to accurately reflect the complexity of the changing biophysics, model-optimisation techniques are needed.

We developed a computationally efficient analytical method of multiple-parameter optimisation of this model of active neuron dynamics. Prior to fitting to data, optimisation is reduced to a simple linear sum in which a residual current error is minimised, resulting in a smooth multi-parameter landscape. Optimised multi-parameter models should have increased robustness to noise, facilitating multiple channel neuron modelling, to return predictions of the ion conductance channel populations and cell membrane properties that drive maturation of neuronal excitability.

Disclosures: F.H. Inkpen: None. **N.F. Lepora:** None. **M.C. Ashby:** None.

Poster

202. Neuronal Firing Properties and Regulation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 202.11/C44

Topic: B.09. Physiological Properties of Neurons

Support: "973" of China 2014CB943002

NSFC of China U1301225

NSFC of China 31529003

NSFC of China 31671083

Title: Kv1.1 functions as a regulator blocking $Na_v1.6$ rather than a K^+ channel inducing outward current in ventral cochlear nucleus

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Abstract: Voltage-gated potassium (KV) channels are important for the nervous system function, especially Kv1.1 subunits. The function of Kv1.1 is mainly known as a K^+ channel although some proteins are reported to co-localize with Kv1.1 subunits from immunofluroreaction. However, it is unknown if Kv1.1 function as a regulator for some proteins rather than the K^+ channel. In auditory system, the bush cells (BC) in ventral cochlear nucleus (VCN) discharge single spike time-coding the information of a stimulus, and play a unique role in auditory information processing. Kv1.1 is thought to be the key protein to form single discharge in bush cells, but it is unexplored if it functions as a K^+ channel. In developing mice, the bush cells discharged multiply to singly from P7 to P21, and its Kv1.1 increased gradually to a plateau. Accordingly, the threshold of spike discharging increased, its latency decreased and the membrane resistance and the reaction time constants reduced. When Kv1.1 channels blocked by a-DTX, the bush cells of adult animal discharged in single action potential mode to multiple,

and the characteristics of membrane potential as the above changed just oppositely to those for development. Kv1.1 channel induces an outward current of K^+. The results were contrast to the function of crescent Kv1.1 channel as outward current of K^+. It could be interpreted as that the Kv1.1 channel might not work as an outward current of K^+, but a regulator of Na^+ channel. Immunohistochemistry experiments showed that the Kv1.1 channels were conjugated with the voltage-gated sodium ($Na_v1.6$) channels axon initial segment. $Na_v1.6$ channel could be regulated by Kv1.1 subunits. When Kv1.1 channel was blocked with antagonist a-DTX first, the bush cells discharged in single action potential mode to multiple, this effect could be rescued by antagonist of $Na_v1.6$ channel, Riluzole (3μm). However, with $Na_v1.6$ channel of the bush cells blocked by Riluzole first, the effect of a-DTX did not present any more. Therefore, this study reveals a new action mechanism of Kv1.1, that is, Kv1.1 functions as a regulator blocking $Na_v1.6$ rather than a K^+ channel inducing outward current in VCN.

Disclosures: **M. Fu:** None. **W. Zhong:** None. **Z. Xiao:** None.

Poster

202. Neuronal Firing Properties and Regulation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 202.12/C45

Topic: B.09. Physiological Properties of Neurons

Title: Selective boosting of burst firing by L-type calcium channels in lateral substantia nigra dopamine neurons

Authors: *J. SHIN[1], C. A. PALADINI[2], J. ROEPER[1]
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Abstract: Burst firing of dopamine (DA) midbrain neurons signal unexpected rewards, reward-predicting cues or initiation of voluntary movement. Recent studies support the notion that this functional diversity in burst signaling is associated with the heterogeneous nature of DA midbrain neurons and their distinct axonal projections. To extend our understanding of the region-specific biophysical mechanisms underlying burst discharges, we used both synaptic stimulation of excitatory inputs as well as the real-time dynamic-clamp approach injecting modelled NMDA-receptor-mediated conductances in identified DA neurons across the entire medial-lateral extend of the substantia nigra in brain slices from adult 3 month-old C57Bl6N mice. Synaptic as well as simulated NMDA-receptor conductances both lead to significantly higher maximal burst discharge rates in lateral SN DA neurons compared to medial SN DA neurons (synaptic stimulation: lateral, 16.7 ± 8.5 Hz, n=9, medial, 5.3 ± 2.2 Hz, n=8, p=0.002; dynamic clamp: lateral, 61.9 ± 18.7 Hz, n=23, medial, 37.6 ± 15.9 Hz, n=17, p=0.0003). Pharmacological experiments revealed that this enhanced burst excitability of lateral SN DA

neurons was completely suppressed by inhibition of L-type calcium channels (preferentially Cav 1.3 by 300 nM isradipine), while burst excitability of medial SN DA neurons was not affected by isradipine. In contrast, inhibition of calcium-activated small conductance potassium (SK) channels significantly enhanced burst excitability in medial SN DA neurons but without an effect on evoked bursting in lateral SN DA neurons. Thus, we demonstrate that SK and L-type calcium channels are differentially engaged during burst firing in DA neurons across the mediolateral axis of the SN - either boosting or attenuating burst excitability. We currently study the functional and pathophysiological implication of this differential burst control in distinct SN DA subpopulations in the context of Parkinson Disease.

Disclosures: **J. Shin:** None. **C.A. Paladini:** None. **J. Roeper:** None.

Poster

202. Neuronal Firing Properties and Regulation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 202.13/C46

Topic: B.09. Physiological Properties of Neurons

Title: Neuroinflammation-hypoxia breaks the excitatory-inhibitory balance in neural networks

Authors: *Y.-S. YANG, S. SON, J.-C. RAH
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Abstract: Neuroinflammation and hypoxia share an interdependent relationship. Blood-brain barrier changes by neuroinflammation leads to hypoxia, which then exacerbate inflammation. Previous studies predict that inflammatory responses would enhance neuronal excitability and excitatory synaptic transmission, whereas lines of evidence show the effect of ischemic hypoxia would be the opposite. However, direct effect of combined inflammation and hypoxia on synaptic transmission and neuronal excitability has not been studied thoroughly. In this study, we measured neuronal responses to hypoxia and an inflammatory stimulus. We found drastic reduction of EPSC amplitude in Schaffer collateral synapses previously observed. We reasoned the reduced synaptic transmission to presynaptic release efficiency based on (1)reduced mEPSC frequency and (2)slower short-term depression. We did not find any evidence of affecting postsynaptic strength. Neither mEPSC amplitude nor $EPSC_{AMPAR}$-to-$EPSC_{NMDAR}$ ratio. In terms of intrinsic properties, hyperpolarization of resting membrane potentials (RMPs), decreased input resistant (R_{in}) and action potential (AP) frequency were observed by the combined insults. Upon reperfusion, on the other hand, we found dramatic rebound activity including significant depolarization and increased AP frequency, which may be a major cause of excitotoxicity during reoxygenation after a period of hypoxia. We found the changes of AP frequencies can be attributed to the hyperpolarization-activated cation current (Ih), at least in part. Our results

suggest that net effect of hypoxia and various neuroinflammatory brain diseases on neural circuit is to skew the balance of excitation-inhibition toward excitation and Ih channel should be tested as a potential drug target.

Disclosures: **Y. Yang:** None. **S. Son:** None. **J. Rah:** None.

Poster

202. Neuronal Firing Properties and Regulation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 202.14/C47

Topic: B.09. Physiological Properties of Neurons

Support: NIMH RC2MH090011-02

California Institute of Regenerative Medicine (CIRM) training grants

California Bipolar Foundation

Title: The difference between activity and function: Utilizing mouse models and hiPSCs for elucidating the electrophysiology of bipolar disorder

Authors: *C. D. PERNIA[1], R. C. O'DONNELL[2], B. TOBE[2], A. WINQUIST[2], Y. GOSHIMA[4], E. Y. SNYDER[3]
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Abstract: Bipolar disorder (BD) is a neuropsychiatric disease that impacts 2.6% of the adult population, and is characterized by oscillations in depressive and manic behavior. BD is the most fatal of the psychiatric diseases due to a high suicide rate, and little is known regarding its underlying pathology. Currently there is no therapy that is both safe and efficacious for treating BD, which is a critical unmet need. Recent discoveries utilizing transgenic mouse models have demonstrated collapsin response mediator protein-2 (CRMP2) plays an integral role in BD's molecular pathology, but how CRMP2 mediates BD has yet to be elucidated. Employing CRMP2 transgenic mice as models for BD, we have discovered CRMP2 activity impacts neuronal electrophysiology, structure, and proteomics. Interestingly, many of the aberrations found in the transgenic CRMP2 neurons superficially appear counter-intuitive, but under further examination expose the complexity of how neuronal circuits function. Specifically, BD-like transgenic CRMP2 neurons appear to have hyperactive calcium activity, while having less neuronal-network signaling. Collectively, these works begin to illuminate long sought-after insights in BD pathology, and offer new targets for future BD therapeutics to be designed for.

Disclosures: **C.D. Pernia:** None. **R.C. O'Donnell:** None. **B. Tobe:** None. **A. Winquist:** None. **Y. Goshima:** None. **E.Y. Snyder:** None.

Poster

202. Neuronal Firing Properties and Regulation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 202.15/C48

Topic: B.09. Physiological Properties of Neurons

Support: 973 Program 2013CB835100

NSFC 31070935

CAS XDB02050200

Title: Emergence of conserved firing patterns of reverberatory activity in neuronal networks through activity-dependent synaptic plasticity

Authors: *F. XU, D. SHI, P. LAU, G. BI
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Abstract: It is generally believed that the brain retains information as reverberatory activity in interconnected neuronal circuits termed the cell assemblies, which are formed through activity-induced synaptic plasticity. However, direct test of this hypothesis has been lacking due to the vast complexity of in vivo circuits. Using simultaneous patch-clamp recording and high-speed calcium imaging, we found that brief stimulation in networks of cultured hippocampal neurons could evoke persistent reverberatory activity with conserved spatiotemporal patterns at ~5-millisecond precision. Paired-pulse stimulation of a nascent network induced emergence of reverberation, which was accompanied by enhanced neuronal recruitment and overall synaptic potentiation, and required active N-methyl-D-aspartate (NMDA) receptors. During the emergence, reverberatory firing patterns got consolidated and stabilized. With in silico simulations, we also demonstrated the emergence of reverberatory firing patterns could be resulted from spike-timing dependent plasticity mechanisms. These results demonstrate the basic principle of how interconnected neurons self-organize through synaptic plasticity to form reverberatory cell assemblies, which may store information in their robust spatiotemporal dynamics.

Disclosures: **F. Xu:** None. **D. Shi:** None. **P. Lau:** None. **G. Bi:** None.

Poster

202. Neuronal Firing Properties and Regulation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 202.16/C49

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH NS083319

Title: Differences in potassium channel gating properties have little effect on spike propagation in an unmyelinated axon

Authors: N. DAUR[1], F. NADIM[2], *D. M. BUCHER[3]
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Abstract: Axons can have complex membrane excitability and show history-dependent changes in conduction velocity, which potentially change the temporal code. We have previously described changes in conduction delay in the pyloric dilator (PD) neuron in the stomatogastric nervous system of the lobster. Spike conduction delay in the peripheral axon of this rhythmically active motor neuron is dependent on mean activity. Repeated bursting hyperpolarizes the axon with a time constant of several minutes and increases delay. The variability of delay increases substantially with the increase in mean delay, so that delay can vary ~30% within a single burst. Experimental results and computer models show that the hyperpolarization is due to the Na^+/K^+ pump, and balanced by a hyperpolarization-activated inward current (I_h). The main determinant of spike velocity during repetitive activity is the gating state of the fast Na^+ channel. Other ionic mechanisms affect delay indirectly through the impact they have on the membrane potential trajectory, which in turn affects the gating state of the Na^+ channel. The slow time scale changes governed by the interaction of the pump and I_h explain the increase in mean delay, but the faster time scale changes in delay over a single burst should also depend on K^+ currents, particularly on how the activation of those currents overlaps with the Na^+ current and affects voltage trajectory. We show that the PD axons expresses both a delayed rectifier (I_{Kd}) blocked by TEA, and an A-type (I_A) current blocked by 4-AP. These currents show similar magnitude, but I_A has a lower threshold, activates much more rapidly, and inactivates almost completely. Total block of I_{Kd} leads to repetitive spiking in response to a single electrical stimulus. Total block of I_A eliminates activity-dependent increases in spike duration but does not lead to repetitive firing. Despite these substantial differences, the effects of partial pharmacological block of either current on spike propagation delay are similar. We delivered trains of stimuli to the PD axon, either with a *Poisson*-like temporal structure, or mimicking realistic bursting activity, and measured conduction delay in peripheral nerves. Partial block of either I_{Kd} or I_A increases both mean delay and variability of delay, both at the beginning of stimulation, and after several minutes of

activity. This suggests that the effect K^+ currents have on Na^+ current trajectory are robust to substantial differences in their gating properties. This may have important implications for many systems, as multiple types of K^+ channels with different gating properties are commonly found in axons.

Disclosures: **N. Daur:** None. **F. Nadim:** None. **D.M. Bucher:** None.

Poster

202. Neuronal Firing Properties and Regulation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 202.17/C50

Topic: B.09. Physiological Properties of Neurons

Support: Henry and Marilyn Taub Foundation

Parkinson's Disease Foundation

Zuckerman gift for Normal Brain Aging

Title: Glutamate stimulation leads to down-regulation of ATF4/CREB2

Authors: *F. AMAR[1], J. LIU[1], C. CORONA[1], E. GRAEFF[2], L. GREENE[1], M. SHELANSKI[1]
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Abstract: Activating transcription factor 4 (ATF4/CREB2), in addition to its well-studied role in stress responses, has also been proposed to play other important physiologic functions in the nervous system including regulation of learning and memory. Studies have suggested that ATF4 may play either positive or negative roles in memory processes. In our experiments, directly reducing neuronal ATF4 levels by lentiviral-mediated shRNA knockdown *in vitro* and *in vivo* has suggested a positive role for ATF4 in neuronal plasticity and memory. Yet, outside of the phospho-eIF2α-dependent stress response pathway, there is little information about how ATF4 levels are regulated in neurons. Based on the idea that synaptic plasticity is the underlying molecular mechanism for learning and memory and that synaptic plasticity starts with synaptic activation, we hypothesized that ATF4 expression is modulated by synaptic activity. Given that glutamate is the major fast excitatory neurotransmitter; is involved in almost all CNS functions, especially in cortical and hippocampal regions; and that substantial evidence has implicated glutamate receptors in learning and memory, we investigated whether glutamate stimulation modulates ATF4**.** Using cultured hippocampal and cortical neurons we found that short-term (30 sec to 1 min) glutamate stimulation rapidly induces downregulation of ATF4 protein. Immunostaining revealed that this was apparent in distal processes within 15 min and by 2 h in nuclei. Glutamate-induced ATF4 depletion was blocked by ionotropic glutamate receptor (NMDA) antagonists AP5 and MK801, but not by ionotropic or metabotropic glutamate receptor

antagonists. Selective short-term activation of NMDA receptors also downregulated ATF4 levels. The actions of glutamate on ATF4 required extracellular calcium and did not appear due to enhanced proteosomal degradation of ATF4. Finally, glutamate treatment also reduced ATF4 expression in acute brain slices, an environment in which neuronal connectivity is better preserved than dissociated culture. Together our findings indicate that glutamatergic NMDA receptor activation rapidly depletes ATF4 protein levels. These observations support the hypothesis that neuronal activity regulates ATF4 levels which in turn affects synaptic plasticity and memory.

Disclosures: F. Amar: None. **J. Liu:** None. **C. Corona:** None. **E. Graeff:** None. **L. Greene:** None. **M. Shelanski:** None.

Poster

202. Neuronal Firing Properties and Regulation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 202.18/C51

Topic: B.09. Physiological Properties of Neurons

Support: the Henry and Marilyn Taub Foundation

Parkinson's Disease Foundation

Zuckerman gift for normal brain aging

Title: ATF4 modulates neuronal excitability by regulating GABAB receptors trafficking

Authors: *C. CORONA, J. LIU, S. PASINI, F. AMAR, L. A. GREENE, M. L. SHELANSKI
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Abstract: Activating Transcription Factor 4 (ATF4) is a member of the ATF/cAMP responsive element binding protein (CREB) family described to be involved in learning and memory. In this regard, we previously reported that specific hippocampal ATF4 down-regulation induces deficits in synaptic plasticity and memory accompanied by a reduction in glutamatergic functionality. Here we extend our studies to address the role of ATF4 in neuronal excitability. Our electrophysiological data, obtained after long-term knockdown of ATF4 levels in cultured rat hippocampal neurons by shATF4-lentiviral infection, show that ATF4 down-regulation significantly increases the frequency of spontaneous action potentials. Metabotropic $GABA_B$ receptors ($GABA_BRs$) are among many neuromodulatory receptors that can effectively influence the firing rate of neurons. We therefore next queried whether modulating ATF4 levels would in turn influence the functionality of $GABA_BRs$. We found that knocking down ATF4 results in a significant reduction of $GABA_BRs$-induced GIRK-currents. Furthermore, western immunoblotting revealed that reducing ATF4 levels significantly decreases the expression of

membrane-exposed, but not total, R1a and R1b types of $GABA_BRs$, thus supporting the idea that ATF4 contributes to regulation of $GABA_BR$ trafficking. Of note, the effects of ATF4 down-regulation described above depend on its transcriptional capability, since they are rescued by transcriptionally active, but not by transcriptionally-inactive shRNA-resistant ATF4. To elaborate the mechanism that leads to increased firing and decreased $GABA_BR$ trafficking following ATF4 knockdown, we examined Rho GTPase Cell Division Cycle 42 (Cdc42), whose expression we previously reported to be dependent on ATF4 transcriptional activity. Specific down-regulation of Cdc42 phenocopied the effects of ATF4 knockdown on these properties. In conclusion, our data favor a model in which ATF4, by regulating the expression of Cdc42, affects the trafficking of $GABA_BRs$, in turn modulating the excitability properties of neurons.

Disclosures: **C. Corona:** None. **J. Liu:** None. **S. Pasini:** None. **F. Amar:** None. **L.A. Greene:** None. **M.L. Shelanski:** None.

Poster

202. Neuronal Firing Properties and Regulation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 202.19/C52

Topic: B.09. Physiological Properties of Neurons

Support: KAKENHI 15K08673

Title: Inhibitory action of beta-thujaplicin on compound action potentials in frog sciatic nerve fibers

Authors: N. MAGORI, T. FUJITA, R. SUZUKI, C. WANG, F. YANG, *E. KUMAMOTO
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Abstract: β-Thujaplicin (hinokitiol), a natural tropolone derivative contained in *Chamaecyparis taiwanensis*, has various actions, such as apoptosis inhibition, insecticidal, antifungal, antitumor, antibacterial, antiinflammatory and cytotoxic activities. However, it has not been examined yet how β-thujaplicin affects nerve conduction. We have previously reported that various plant-derived compounds inhibit fast-conducting compound action potentials (CAPs) recorded from frog sciatic nerve fibers. This inhibition was dependent on a chemical structure of the compounds. For example, an efficacy sequence of plant-derived compounds for the CAP inhibitions was phenols (carvacrol, thymol, eugenol and carveol) ≥ aldehydes (citral and citronellal) ≥ esters (linalyl acetate, geranyl acetate and bornyl acetate) ≥ alcohols (citronellol, geraniol, linalool, borneol, α-terpineol and menthol) ≥ ketones ((+)-pulegone, carvone and menthone) > oxides (rose oxide, 1,8-cineole and 1,4-cineole) >> hydrocarbons (*p*-cymene, myrcene and limonene), except for a ketone camphor that was less effective than oxides. In order to reveal whether β-thujaplicin inhibits CAPs and if so what chemical structure of β-thujaplicin

is important in this inhibition, we examined the effects of β-thujaplicin and its related natural compounds on CAPs by applying the air gap method to the frog sciatic nerve. β-Thujaplicin concentration-dependently reduced the peak amplitude of the CAP with a half-maximal inhibitory concentration (IC_{50}) value of 0.57 mM in a partially reversible manner. A threshold to elicit CAPs was increased by β-thujaplicin. A stereoisomer of β-thujaplicin, γ-thujaplicin, also inhibited CAPs with the IC_{50} of 0.48 mM, a value similar to that of β-thujaplicin. On the other hand, tropolone, which lacks the isopropyl group of β-thujaplicin, had no effects on CAPs. Moreover, CAPs were unaffected by kojic acid and guaiazulene. Biosol, which has isopropyl and hydroxyl groups bound to its six-membered ring, reduced CAP peak amplitude with an IC_{50} of 0.58 mM, a value comparable to that of β-thujaplicin. These results indicate that β-thujaplicin inhibits CAPs, possibly through an interaction among the functional groups (isopropyl, carbonyl and hydroxyl groups) bound to its seven-membered ring.
This result may be consistent with the previous observation that plant-derived phenols, aldehydes, esters, alcohols and ketones inhibit CAPs more effectively than the other compounds. It is suggested that β-thujaplicin has an ability to inhibit nerve conduction. This could contribute to at least a part of the pharmacological actions of β-thujaplicin.

Disclosures: **N. Magori:** None. **T. Fujita:** None. **R. Suzuki:** None. **C. Wang:** None. **F. Yang:** None. **E. Kumamoto:** None.

Poster

202. Neuronal Firing Properties and Regulation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 202.20/C53

Topic: B.09. Physiological Properties of Neurons

Support: KAKENHI 15K08673

Title: Non-steroidal anti-inflammatory drugs inhibit compound action potentials in frog sciatic nerve fibers

Authors: R. SUZUKI[1], T. FUJITA[1], K. MIZUTA[2,1], N. MAGORI[1], C. WANG[1], F. YANG[1], *M. ISHIMATSU[3], E. KUMAMOTO[1]
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Abstract: Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit the synthesis of prostaglandins from arachidonic acid by inhibiting the cyclooxygenase enzyme, resulting in anti-inflammation, antinociception and pyretolysis. Although NSAIDs are reported to inhibit nerve conduction, this inhibition has not been throughly examined yet. Nerve conduction inhibition could contribute to at least a part of antinociception produced by analgesic and its adjuvants. We have previously reported the inhibitory effects of a variety of drugs involved in antinociception

on fast-conducting and voltage-gated Na^+-channel blocker tetrodotoxin-sensitive compound action potentials (CAPs) recorded from the frog sciatic nerve. For example, local anesthetics, α_2-adrenoceptor agonists, anticonvulsants and antidepressants inhibited the CAPs. The aim of the present study was to reveal how various types of NSAID affect frog sciatic nerve CAPs. The experiments were performed by applying the air-gap method to the frog sciatic nerve. Soaking the frog sciatic nerve for 20 min with an acetic acid-based NSAID diclofenac reduced the peak amplitude of the CAP in a partially reversible manner. This diclofenac activity was concentration-dependent with an IC_{50} value of 0.94 mM. A similar CAP amplitude reduction was produced by other acetic acid-based NSAIDs, indomethacin and etodolac (the extent of the inhibition at 1 mM: some 40 % and 15 %, respectively), except for sulindac at 1 mM which had no effects on CAPs. Another acetic acid-based NSAID, acemetacin, which is metabolized to indomethacin in the body, at 0.5 mM produced a CAP amplitude reduction of about 30 %. With respect to other types of NSAID, a fenamic acid-based NSAID tolfenamic acid, which is similar in chemical structure to diclofenac, reduced CAP amplitude with an IC_{50} value of 0.36 mM. On the other hand, CAPs were almost unaffected by a salicylic acid-based NSAID aspirin (1 mM), propionic acid-based NSAIDs (ketoprofen, ibuprofen, naproxen and loxoprofen; each 1 mM) and an enolic acid-based NSAID meloxicam (0.5 mM). These results indicate that NSAIDs inhibit CAPs in a manner dependent on their chemical structures. The diclofenac's IC_{50} value was similar to those of maprotiline, lidocaine and cocaine (0.95, 0.74 and 0.80 mM, respectively), while the tolfenamic acid's one was close to those of duloxetine, lamotrigine, carbamazepine, dexmedetomidine, ropivacaine and levobupivacaine (0.39, 0.44, 0.50, 0.40, 0.34 and 0.23 mM, respectively). At least a part of antinociception produced by NSAIDs used as a dematological drug to alleviate pain may be attributed to a nerve conduction inhibition produced by the drugs.

Disclosures: **R. Suzuki:** None. **T. Fujita:** None. **K. Mizuta:** None. **N. Magori:** None. **C. Wang:** None. **F. Yang:** None. **M. Ishimatsu:** None. **E. Kumamoto:** None.

Poster

202. Neuronal Firing Properties and Regulation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 202.21/C54

Topic: B.09. Physiological Properties of Neurons

Support: Carleton University Startup funds

CIHR MFE-115462

Title: Plasticity of developmentally regulated postinhibitory rebound depolarization enhances precision of spike timing in developing midbrain neurons

Authors: *H. SUN
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Abstract: Precise spike timing in auditory neurons permits them to encode important temporal features of sounds. Certain neurons in the auditory lower brainstem have a remarkable capacity of firing that is precisely locked to a particular phase of a tone. These neurons have anatomical and biophysical specializations that enable them to fire action potentials with a precision of tens of microseconds. In the auditory midbrain inferior colliculus (IC), neurons analyze temporal features of sounds and are tuned to temporal parameters of sounds by integrating excitatory and inhibitory inputs in a special time window. One striking biophysical property of IC neurons is the rebound depolarization that is produced following membrane hyperpolarization. The rebound has been proposed to play a critical role in the selection of sounds with special temporal features. To understand how the rebound is involved in spike timing, I made whole-cell patch clamp recordings from IC neurons in brain slices of young rodents at P9-21. Rebound was encountered in 19/42 (45.2%) neurons at P9-11, 15/23 (65.2%) neurons at P12-13 and 68/93 (73.1%) neurons at P14-21. I further investigated the precision of spike timing by measuring jitter when the neurons were repetitively depolarized with pre-hyperpolarization. With pre-hyperpolarization, the precision of timing of the 1st spike was substantially improved (without pre-hyperpolarization: the jitter was 2.5±0.5 ms; with prehyperpolarization: the jitter was 0.5±0.1 ms; $P<0.01$, n=20). The rebound and associated spikes were completely abolished by the T-type Ca2+ channel antagonist, mibefradil. During mibefradil, in response to repetitive depolarization following membrane hyperpolarization the neuron produced 1st spike that showed a significant larger jitter (5.0±1.2 ms) than that in control bath solution (0.7±0.5 ms, n=6). Interestingly, the rebound was potentiated by 1-2 preceding rebounds within a few hundred milliseconds. The 1st spike generated on the potentiated rebound was more precise than that on the non-potentiated rebound. Furthermore, the rebound potentiation was blocked by adding calcium chelator, BAPTA, into the cell. These results suggest that the postinhibitory rebound mediated by T-type Ca2+ channel promotes spike precision in IC neurons. The rebound potentiation and precise spikes may be induced by increasing the intracellular calcium level. The precision of spike timing enhanced by postinhibitory rebound can be one of the mechanisms for processing specific temporal features of acoustic signals.

Disclosures: H. Sun: None.

Poster

203. Epilepsy: Channels - Ion channels and receptors

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 203.01/C55

Topic: B.11. Epilepsy

Support: Postdoctoral Training Fellowship, American Epilepsy Society and Wishes for Elliott Foundation

NIH Grant NS34774

Title: Impaired action potential initiation and propagation shape cortical network dysfunction following loss of the voltage-gated sodium channel $Na_v1.6$

Authors: *C. D. MAKINSON, T. N. WEERAKKODY, J. R. HUGUENARD
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Abstract: The voltage gated sodium channel $Na_v1.6$ strongly modulates neuronal excitability and is important for initiating and propagating action potentials. Gain-of-function mutations in the $Na_v1.6$ gene (*SCN8A*) can cause severe epileptic encephalopathy, whereas loss-of-function mutations in this channel are associated with reduced convulsive seizure susceptibility. However, loss of $Na_v1.6$ function is also associated with cognitive impairment in humans and mice. These phenotypes indicate that loss of $Na_v1.6$ function has a dynamic and complex role in the cortex. We used a mouse model for $Na_v1.6$ loss-of-function to probe cortical dynamics. First, we evoked local field potentials (LFP) along the cortical column in sensorimotor cortex and performed current source density (CSD) analysis to identify major synaptic current sinks and sources. We found no difference in either current sources or sinks at baseline in $Na_v1.6$ hemizogous knockout compared to wild-type (WT). However, once the cortical network was rendered hyperactive by partial blockade of $GABA_A$ receptors with gabazine (200 nM), superficial layer sinks were enhanced in WT but not $Na_v1.6$-deficient slices, indicating that reduced $Na_v1.6$ impairs the ability of the network to engage hyperactive modes. Next, to understand the mechanisms underlying altered cortical circuit function with $Na_v1.6$ deficiency, we performed patch-clamp analysis of intrinsic excitability in inhibitory parvalbumin (PV) and excitatory pyramidal neurons. Action potential generation was impaired in both cell types, with lower AP amplitudes, and slower rates of rise, while propagation, as measured by time delays between different components of fractionated spikes, was more strongly affected in PV interneurons than pyramidal cells. We then assessed synaptic inhibition by expressing channelrhodopsin-2 in cortical inhibitory cells while measuring post-synaptic inhibitory responses in other inhibitory cells and in excitatory cells. We found robust reductions in the amplitude of responses onto both excitatory and inhibitory cells. We speculate that, under conditions that promote hyperexcitability in $Na_v1.6$-deficient cortical circuits (e.g. seizures), disinhibition by reduced inhibitory-to-inhibitory cell activity overcomes reductions in inhibitory-to-excitatory cell activity such that network control can be maintained.
These studies reveal that loss of $Na_v1.6$ leads to profound impairments in cortical network excitability that surprisingly do not lead to seizure or hyperactivity; we speculate that this is due to reduced cortical excitatory cell output and reduced inhibitory-to-inhibitory cell synaptic inhibition.

Disclosures: C.D. Makinson: None. **T.N. Weerakkody:** None. **J.R. Huguenard:** None.

Poster

203. Epilepsy: Channels - Ion channels and receptors

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 203.02/C56

Topic: B.11. Epilepsy

Support: NIH/NINDS NS087068

NIH/NINDS NS096246

American Epilepsy Society Seed Grant

AHA Predoctoral Fellowship 15PRE25310013

Title: Mitochondrial Ca^{2+} uniporter (MCO) knockout (KO) protects against neural network hyperexcitability and seizures

Authors: *J. RYSTED[1], Z. LIN[1], A. GNANASEKARAN[1], B. PURNELL[2], K. DAYTON[2], E. ANDERSON[1], G. WALTERS[1], L. SHUTOV[1], G. F. BUCHANAN[2], Y. M. USACHEV[1]
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Abstract: During neuronal activity, mitochondria buffer cytosolic Ca^{2+} that is subsequently released back to the cytosol. This mitochondrial Ca^{2+} cycling shapes Ca^{2+} signaling and regulates processes such as neurotransmission, gene expression, excitability and cell survival. Critical for mitochondrial buffering is the protein CCDC109A, also known as the mitochondrial Ca^{2+} uniporter (MCU), the pore forming subunit of a greater Ca^{2+} transport complex that allows Ca^{2+} uptake into mitochondria. Previously, we have shown that MCU knockout (KO) significantly alters cytosolic and mitochondrial Ca^{2+} signaling in peripheral and central neurons. Using MCU KO mice and Ca^{2+} imaging we investigated neuronal network excitability *in vitro* using two convulsants, the $GABA_A$ receptor antagonist, bicuculline and an inhibitor of A-type voltage-gated K^+ channels, 4-Aminopyridine (4-AP). Both convulsants (0.2-4 μM for bicuculline and 0.5-10 μM for 4-AP) induced prominent oscillations in intracellular Ca^{2+} concentration ($[Ca^{2+}]_{cyt}$) in wild type (WT) cultured hippocampal neurons (12-16 DIV). These $[Ca^{2+}]_{cyt}$ oscillations are known to be driven by bursts of action potentials and synaptic activity, and are synchronized throughout the neuronal network. We found that hippocampal neurons from MCU KO mice were highly resistant to the induction of $[Ca^{2+}]_{cyt}$ oscillations by both convulsants. Given that epileptiform activity *in vitro* was inhibited by MCU KO, we hypothesized that MCU KO mice would be more resistant to seizures. To test this hypothesis, we compared the susceptibility of WT and MCU KO mice to electroshock-induced seizures. We found that WT mice developed maximal tonic hind limb extension seizures with a threshold of 9 +/- 1 mA. In contrast, stimulations up to 30 mA failed to induce maximal seizures in MCU KO mice.

Interestingly, a broad panel of behavioral testing failed to detect any sensory, motor or cognitive deficits in MCU KO mice. Patch-clamp examination of synaptic activity showed that frequency of glutamate AMPA receptor-mediated miniature EPSCs significantly decreased whereas frequency of $GABA_A$ receptor-mediated miniature IPSCs significantly increased in MCU KO hippocampal neurons compared to that from WT mice. Our research suggests that MCU regulates neural network (hyper)excitability and identify MCU as a potential new therapeutic target for the treatment of epilepsy and seizures.

Disclosures: **J. Rysted:** None. **Z. Lin:** None. **A. Gnanasekaran:** None. **B. Purnell:** None. **K. Dayton:** None. **E. Anderson:** None. **G. Walters:** None. **L. Shutov:** None. **G.F. Buchanan:** None. **Y.M. Usachev:** None.

Poster

203. Epilepsy: Channels - Ion channels and receptors

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 203.03/C57

Topic: B.11. Epilepsy

Support: NIH Grant R25NS070695

Title: Analysis of KCNT1 mutation in epilepsy

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Abstract: Epileptic encephalopathies (EEs) are severe, infantile-onset epilepsies characterized by medically-refractory, pleomorphic seizures and early developmental arrest. Malignant migrating partial epilepsy of infancy (MMPEI) is a type of EE, classified by its electroclinical presentation of a diffusely abnormal electroencephalogram (EEG) with independent, multifocal seizures and severe motor, cognitive, and social disability. Up to 40-50% of cases of MMPEI are attributable to missense, gain-of-function mutations within the KCNT1 gene encoding Slack, a sodium-activated potassium channel. Quinidine has been reported as a uniquely efficacious anticonvulsant, suggesting that targeting neuronal excitability in EE is therapeutically beneficial, yet its use is limited by non-specific channel block in the brain and heart.
This project seeks to delineate the molecular mechanisms governing gain-of-function of Slack channels in a mammalian heterologous expression system. Using CHO cells transiently expressing wild-type Slack channels as well as novel, de novo patient-derived KCNT1 mutations, we have identified a biophysical signature of a gain-of-function Slack conductance. Automated electrophysiology will be used to further screen a limited panel of potassium channel blockers and quinidine-like compounds to identify selective and potent blockers of Slack

channels for use in additional experiments as well as potential therapies for MMPEI. We hypothesize that altered Slack channel kinetics will result in increased persistent potassium current, rendering mutant channels differentially sensitive to open channel blockers. In neurons, this gain-of-function is likely to dampen excitability and inhibit high-frequency firing. Taken together, these studies will broaden our understanding of the molecular and cellular mechanisms by which KCNT1 mutations contribute to pathogenesis of severe childhood epilepsy. By identifying the mechanism of 'overactive' Slack channels and developing a select panel of drugs which block its gain-of-function, we hope to identify a more precise approach to treating patients with KCNT1 mutations.

Disclosures: T.S. Gertler: None. **A.L. George, Jr:** None.

Poster

203. Epilepsy: Channels - Ion channels and receptors

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 203.04/C58

Topic: B.11. Epilepsy

Title: iPSC-derived neurons harboring a known epilepsy mutation display known and novel electrophysiological phenotypes

Authors: *K. P. MANGAN[1], I. H. QURAISHI[2], Y. ZHANG[3], E. ENGHOFER[1], C. KANNEMEIER[1], M. MCLACHLAN[1], B. MELINE[1], C. MCMAHON[1], E. JONES[1], L. K. KACZMAREK[3]
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Abstract: Epilepsy is a disturbance in the electrical activity of the brain manifested via countless etiologies. 65 million individuals suffer from epilepsy and one-third of these individuals live with uncontrollable seizures because no known pharmacological treatment works for them. A portion of this population is accounted for by single-gene epilepsy disorders resulting from mutations within sodium, potassium or inhibitory channels. For example, the Slack gene (KCNT1) encodes a sodium-activated potassium channel that is very widely expressed in the brain. Mutations in this KCNT1 gene in humans presents with autosomal-dominant nocturnal frontal lobe epilepsy (ADNFLE), a disease marked by brief, but violent, seizures during sleep and devastating effects on intellectual function. Advances in personalized medicine is crucial for these types of diseases.
Central to this vision is induced pluripotent stem (iPS) cell technology, which provides a platform to expand our understanding of how single-gene mutations result in disease states. This approach illustrates and leverages the "disease-in-a-dish" iPSC-technology into phenotypic screening and drug development.

We have engineered and generated human cortical neurons harboring the *KCNT1* {P924L} single-gene mutations, as well as the isogenic wild-type control match. This ability provides unprecedented access to *in vitro* models of all-types of neurological disorders. Here we present functional data, via patch-clamp and multi-electrode array (MEA) electrophysiological techniques, illustrating the known 'gain-of-function' ionotropic cellular-level fingerprint, which has previously been linked to this mutation, along with newly-discovered neural-network level hyper-active phenotypes. We further show multiple examples that selective pharmacology can reverse these observed phenotypes. Collectively, our results illustrate how human iPS cells can be model disease states and be leveraged in the personal medicine space.

Disclosures: K.P. Mangan: A. Employment/Salary (full or part-time):; Cellular Dynamics International. **I.H. Quraishi:** None. **Y. Zhang:** None. **E. Enghofer:** A. Employment/Salary (full or part-time):; Cellular Dynamics International. **C. Kannemeier:** A. Employment/Salary (full or part-time):; Cellular Dynamics International. **M. McLachlan:** A. Employment/Salary (full or part-time):; Cellular Dynamics International. **B. Meline:** A. Employment/Salary (full or part-time):; Cellular Dynamics International. **C. McMahon:** A. Employment/Salary (full or part-time):; Cellular Dynamics International. **E. Jones:** A. Employment/Salary (full or part-time):; Cellular Dynamics International. **L.K. Kaczmarek:** None.

Poster

203. Epilepsy: Channels - Ion channels and receptors

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 203.05/C59

Topic: B.11. Epilepsy

Support: NIH NINDS 082635

Title: Copy number variation of GABRA1 and GABRG2 is associated with severe epilepsy and optical atrophy

Authors: Q. ZHANG[1], C. GIBSON[3], Z. LI[2], K. BOYD[2], H. DONG[2], S. GUTTI[2], M. J. GALLAGHER[4], T. S. REX[2], *J.-Q. KANG[5]
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Abstract: Mutations in $GABA_A$ receptor subunit genes are frequently associated with epilepsy and different mutations in different $GABA_A$ receptor subunit genes are associated with different epilepsy syndromes. Particularly, mutations in *GABRA1* have been associated with childhood absence seizures to juvenile myoclonic seizures while the mutations in *GABRG2* have been associated with a spectrum of seizures ranging from mild childhood absence or febrile seizures to

generalized epilepsy with febrile seizures plus (GEFS+) to Dravet syndrome. In this study, we report a novel case of copy number variation, double deletion of *GABRA1* and *GABRG2*. The patient with double deletion of *GABRA1* and *GABRG2*, had seizures with fever starting at 9 months old and had some grand mal seizures and primarily occipital seizures in adulthood. The patient had optic atrophy and was legally blind. We have modeled the disease condition in vitro with human recombinant $GABA_A$ receptors and in vivo by generating $Gabra1^{+/-}/Gabrg2^{+/-}$ double knockout in C57BL/6J background. The double knockout mice had abnormal ictal discharges in EEGs which had longer duration and increased occurrence compared with the $Gabra1^{+/-}$ *or* $Gabrg2^{+/-}$ mice. The double knockout mice also had abnormal electroretinogram (ERG) by showing reduced a_{max} and b_{max} as well as reduced amplitude in the oscillatory potentials. Biochemistry and immunohistochemistry indicated a global reduction of α1, γ2 as well as β2 subunits in the brain except cerebellum. The double knockout $Gabra1^{+/-}/Gabrg2^{+/-}$ mice recapitulate the feature phenotypes in patients. Future work will focus on identifying the effective drugs to improve the outcome for patients. (Acknowledgements: The work is supported by research grants from CURE, Dravet Syndrome Foundation and NIH NINDS 082635 to KJQ)

Disclosures: Q. Zhang: None. **C. Gibson:** None. **Z. Li:** None. **K. Boyd:** None. **H. Dong:** None. **S. Gutti:** None. **M.J. Gallagher:** None. **T.S. Rex:** None. **J. Kang:** None.

Poster

203. Epilepsy: Channels - Ion channels and receptors

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 203.06/C60

Topic: B.11. Epilepsy

Support: NIH NINDS R01 NS094186

NIH NINDS R01 NS025704

Title: Diminished excitability of 5-HT3aR-expressing GABAergic interneurons but no pro-epileptic effects caused by selective deletion of Nav1.1 channels in a mouse model of Dravet Syndrome

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Abstract: Dravet Syndrome (DS) is a childhood-onset epileptic disorder caused by dominant loss-of-function mutations in the voltage-gated sodium channel Nav1.1. We previously demonstrated that global deletion of Nav1.1 impairs excitability of hippocampal and neocortical GABAergic interneurons and causes DS phenotypes in C57BL/6J mice, including epilepsy, premature death, hyperactivity, cognitive deficit, and autistic-like behaviors. Selective

haploinsufficiency of Nav1.1 in parvalbumin (PV)-expressing interneurons or somatostatin (SST)-expressing interneurons diminishes the excitability of interneurons in brain slices and reduces the threshold for thermally-induced seizures in mice, although premature deaths do not occur. Selective haploinsufficiency of Nav1.1 in PV interneurons causes an autistic-like phenotype in mice, without hyperactivity, while selective haploinsufficiency of Nav1.1 in SST interneurons causes hyperactivity without an autistic-like phenotype. These findings suggest that the individual components of the DS phenotype could result from deficits in different neural circuits, which can be dissected using genetic techniques. Here we investigate the physiological effects of Nav1.1 haploinsufficiency in GABAergic interneurons expressing the serotonin 5-HT3A receptor (Htr), the third major class of neocortical interneuron. Htr interneurons are heterogeneous in morphology and electrophysiology. We find that selective haploinsufficiency of Nav1.1 in Htr interneurons increases action potential threshold and rheobase substantially in two sub-classes of Htr interneurons: late-spiking and burst-firing/non-adapting. Intrinsic excitability is more modestly diminished in three other subclasses of Htr interneurons: irregular-spiking, regular-spiking, and fast-adapting. The relative proportion of the five different Htr interneuron subclasses is similar between wild-type and Htr-Nav1.1 haploinsufficient mice. Haploinsufficiency in Htr neurons does not reduce the threshold for thermally-induced seizures, and mice with this mutation do not die prematurely, suggesting that they do not have frequent spontaneous generalized tonic-clonic seizures. These results show that haploinsufficiency of Nav1.1 in Htr interneurons has more modest effects on electrical excitability than in PV or SST interneurons. Consistent with these physiological results, deficiency of Nav1.1 in Htr interneurons is not sufficient to cause pro-epileptic effects or premature death in DS mice, in contrast to our results with PV and SST interneurons.

Disclosures: A.D. Williams: None. **C.S. Cheah:** None. **W.A. Catterall:** None. **J.C. Oakley:** None.

Poster

203. Epilepsy: Channels - Ion channels and receptors

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 203.07/C61

Topic: B.11. Epilepsy

Support: AES/DSF Postdoctoral Fellowship

Title: Deconstructing thalamic circuits to treat seizures in Dravet syndrome

Authors: *S. L. MAKINSON[1], A. P. CLEMENTE[1,2], B. HIGASHIKUBO[1], B. DELORD[3], J. T. PAZ[1,4]
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Abstract: Dravet syndrome (DS) is a severe epileptic encephalopathy with a high incidence of mortality. There is no cure for DS, and current treatments cause major side effects. Approximately 70% of patients with DS have a loss-of-function mutation in one allele of the sodium-channel gene SCN1A. Although most evidence so far supports hippocampal and neocortical abnormalities in DS seizures, the thalamus might also be pathological as it expresses high levels of Scn1a in inhibitory neurons within the thalamic reticular nucleus (TRN). Moreover, the thalamus is strategically positioned to regulate seizure circuits in DS due to its extensive and vital interconnections with cortical seizure circuits. With a well-established mouse model of DS and recordings of thalamic oscillations in vitro, we found that the somatosensory thalamic circuit is hyperexcitable. Intracellular electrophysiology and computational modeling revealed that this hyperexcitability can be explained by the abnormal rebound burst firing and the altered afterhyperpolarization (AHP) in TRN neurons from DS mice. Moreover, pharmacological enhancement of the AHP normalizes thalamic oscillations from DS mice. We also found that TRN and thalamocortical (TC) cells fire high-frequency bursts of action potentials in phase with electrocorticographic spikes during spontaneous convulsive and non-convulsive seizures in DS mice. To test the hypothesis that rhythmic bursting in the thalamus facilitates seizure expression in DS, we used activation of stable step function opsins in the somatosensory thalamus to manipulate the mode of TC neuron firing. Indeed, unilateral disruption of TC neuron bursting in the ventral basal thalamus was sufficient to interrupt non-convulsive seizures in DS mice. Together, these data reveal pathological synchronous activity in the thalamus in DS and highlight a novel pathway to regulate thalamic activity in DS. This work may also provide new insight into the therapeutic potential of targeting the thalamus to treat seizures in DS and direct our future efforts in determining whether targeting the thalamus can also prevent behavioral deficits and/or Sudden Unexpected Death in Epilepsy in DS.

Disclosures: S.L. Makinson: None. **A.P. Clemente:** None. **B. Higashikubo:** None. **B. Delord:** None. **J.T. Paz:** None.

Poster

203. Epilepsy: Channels - Ion channels and receptors

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 203.08/C62

Topic: B.11. Epilepsy

Support: NIH Grant NS073981

NIH Grant MH110887

Title: Loss of KCNQ2/3 from interneurons leads to increase interneuron population and network activity in the immature forbrain

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Abstract: By controlling neuronal excitability, potassium channels have emerged as indispensable players in normal brain function. KCNQ2/3 channels, in particular, have arisen as critical regulators of neonatal brain excitability, with *KCNQ2* and *KCNQ3* loss-of-function (LOF) pathogenic variants being continuously identified in patients with severe forms of neonatal and infantile epileptic encephalopathy. However, the mechanisms by which KCNQ2/3 LOF variants lead to hyperexcitability are not fully known. Importantly, it's currently unknown whether loss of *Kcnq2/3* function alters interneuron activity early in development. Here, we used genetics, electrophysiology, and mesoscale calcium imaging ex vivo, to examine whether loss of KCNQ2/3 activity from interneurons using *VGAT-Cre; Kcnq2^{f}/3^{f};GCamp5* mice increase network excitability in P4-P5 forebrain. We found that in the presence of the pro-convulsive potassium channel blocker 4-AP ablation of Kcnq2/3 channels from interneurons leads to elevated synchronized interneuron population activity in CA3 region of the hippocampus and entorhinal cortex as well as prolongation of local field potentials measured simultaneously to calcium imaging in the CA3 region of the hippocampus. Together our data show that loss-of-function of KCNQ2/3 channels from interneurons increases network excitability of the immature forebrain circuits, revealing a new and unexpected function of KCNQ2/3 channels in interneuron physiology and immature brain.

Disclosures: B. Hou: None. **H. Soh:** None. **A. Tzingounis:** None.

Poster

203. Epilepsy: Channels - Ion channels and receptors

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 203.09/C63

Topic: B.11. Epilepsy

Support: NIH Grant NS083009

NIH Grant NS032387

NIH Grant HD059967

CART Pilot Grant

Title: Cell type-specific defects in sodium channel functions in an isogenic human iPSC model of genetic epilepsy with febrile seizures plus

Authors: *Y. XIE[1], N. NG[1], O. SAFRINA[1], S. KONOPLESKI[1], A. STOVER[2], K. ESS[3], A. GEORGE[4], D. O'DOWD[1]
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Abstract: Over 1200 mutations in the *SCN1A* gene, encoding the alpha subunit of the $Na_v1.1$ voltage-gated sodium channel, have been identified and are associated with a wide range of epileptic disorders including genetic epilepsy with febrile seizures plus (GEFS+). How specific *SCN1A* mutations affect sodium channel function in their native environment is not well understood. To address this question we are examining the functional properties of neurons differentiated from three human iPSC lines: 1) patient with K1270T *SCN1A* mutation (GEFS+ sibling), 2) control (unaffected sibling), and 3) isogenic mutant generated by CRISPR/Cas9 editing of the control line. We patterned iPSCs into neural progenitors that were plated onto astroglial feeder layers for neuronal differentiation. Electrophysiological analysis of the inhibitory neurons at D21-24 post plating showed a decrease in evoked firing frequency, a more depolarized action potential (AP) threshold, a lower AP amplitude and a larger AP half width in patient and isogenic mutant lines compared to the control line. In contrast, the excitatory neurons in all three lines had similar evoked firing properties with the exception of a lower AP amplitude in the patient line. To investigate the underlying changes in sodium channel function, we are now evaluating the sodium current density, kinetics, and voltage dependence, in both excitatory and inhibitory neurons in the 3 iPSC lines. RT-PCR is being used to compare the relative expression of *SCN1A* between the iPSC-derived neurons from 3 lines. This isogenic iPSC model will be beneficial to deciphering the links between *SCN1A* mutations and the impact on epileptic disorders, facilitating the development of personalized anti-epileptic medicine and improved therapies.

Disclosures: Y. Xie: None. **N. Ng:** None. **O. Safrina:** None. **S. Konopleski:** None. **A. Stover:** None. **K. Ess:** None. **A. George:** None. **D. O'Dowd:** None.

Poster

203. Epilepsy: Channels - Ion channels and receptors

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 203.10/D1

Topic: B.11. Epilepsy

Support: F74

Title: Inhibition of thrombin receptor 1 attenuates upregulation of persistent sodium current after status epilepticus in young rats

Authors: *O. ISAEVA[1,2], O. LUNKO[3], O. NETSYK[3], M. SEMENIKHINA[3], L. AL KURY[4], V. SYDORENKO[3], G. HOLMES[2], O. KRISHTAL[3]
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Abstract: The mechanisms underlying the epileptogenic process after status epilepticus (SE) remains obscure. It has been recently shown that downregulation of the major thrombin receptor in the brain, protease-activated receptor 1 (PAR1), confers a significant antiepileptogenic effect in Li+-pilocarpine model of SE. However, involved signaling pathways are unclear. Many studies on the different CNS regions consistently demonstrate that the tetrodotoxin-sensitive persistent Na+ current (INap) became upregulated shortly after SE, implying its possible involvement in the formation of hyperexcitable neuronal networks through the modulation of intrinsic neuronal bursting activity. As INap properties can be influenced by PAR1 activation, here we tested the hypothesis that downregulation of PAR1 may interfere with an epileptogenic process by counteracting the SE-induced alteration of sodium channel properties. Li+-pilocarpine model of SE in young rats, extracellular field potential recordings from hippocampal slice preparation and whole-cell voltage clamp recordings from acutely dissociated pyramidal CA1 neurons were utilized in these studies. We showed that repetitive injection of PAR1 antagonist, SCH 79797, during the first ten days after SE resulted in a reduction in the probability of inducing epileptiform activity in the response to a low-Mg2+ solution in hippocampal slice preparation. Moreover, the INap density recorded in hippocampal CA1 pyramidal cells at 13-15 days after SE was significantly increased and PAR1 inhibition restores INap density to the control level. These findings reveal that PAR1 involved in the perturbation of sodium channel properties after SE providing the new molecular mechanism of epilepsy development.

Disclosures: O. Isaeva: None. **O. Lunko:** None. **O. Netsyk:** None. **M. Semenikhina:** None. **L. Al Kury:** None. **V. Sydorenko:** None. **G. Holmes:** None. **O. Krishtal:** None.

Poster

204. Epilepsy: In Vivo and Behavior - Identifying and Targeting Seizure Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 204.01/D2

Topic: B.11. Epilepsy

Support: National Natural Science Foundation of China (81673413)

Natural Science Foundation of Jiangsu Province (BK20141335)

the Specialized Research Fund for the Doctoral Program of Higher Education (20130092120043)

the Fundamental Research Funds for the Central Universities and the Scientific Research Foundation of State Education Ministry for the Returned Overseas Chinese Scholars (No. 311)

Title: Neuronal nitric oxide synthase contributes to PTZ kindling-induced cognitive impairment and depressive-like behavior by activation of hippocampal endoplasmic reticulum stress

Authors: *X. ZHU
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Abstract: Epilepsy is a chronic neurological disease which is usually associated with psychiatric comorbidities. Depression and cognition impairment are considered to be the most common psychiatric comorbidities in epilepsy patients. However, the specific contribution of epilepsy made to these psychiatric comorbidities remains largely unknown. Here we use pentylenetetrazole (PTZ) kindling, a chronic epilepsy model, to identify neuronal nitric oxide synthase (nNOS) as a signaling molecule triggering PTZ kindling-induced cognitive impairment and depressive-like behavior. We further found that nNOS acts through peroxynitrite, an important member of reactive nitrogen species, to trigger hippocampal endoplasmic reticulum (ER) stress, which consequently causes cognition deficit and depressive-like behavior in PTZ-kindled mice. Our findings thus define a specific mechanism for chronic epilepsy-induced cognitive impairment and depressive-like behavior, and identify a potential therapeutic target for psychiatric comorbidities in chronic epilepsy patients.

Disclosures: X. Zhu: None.

Poster

204. Epilepsy: In Vivo and Behavior - Identifying and Targeting Seizure Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 204.02/D3

Topic: B.11. Epilepsy

Support: SFI SIRG1725

Title: Phenobarbital treated neonatal mice present worse neurodevelopmental outcomes independent of brain injury

Authors: *S. QUINLAN, N. RODRIGUEZ-ALVAREZ, E. JIMENEZ-MATEOS
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Abstract: Phenobarbital, as recommended by the WHO [1], is currently the most common first line therapy for the treatment of neonatal seizures. This recommendation is based on the acceptance that neonatal seizures are harmful to the developing brain and require rapid treatment.

However it is also acknowledges that this recommendation is based on very-low-quality evidence, with it being effective in only 50% of neonatal-seizures. It is also known that anti-seizure drugs (ASD) given at this critical period may have long lasting consequences [2]. **Aim:** To evaluate the complex spectrum of effects of the ASD, phenobarbital on acute neonatal seizures, behavioural outcomes and seizure threshold later in life. **Methods:** In mice, the first postnatal week approximately corresponds to the neonatal period in humans. We examined the effects of phenobarbital treatment in P7 mice subject to hypoxia induced seizures, on electroencephalopathy (EEG), behaviour and susceptibility to kanic-acid challenge in adulthood. Motor and anxiety-like behaviours were assessed by using the open field test and light/dark box transition task. The threshold for seizure activity in adult mice was assessed by analysing EEG recording of mice injected with a sub-threshold dose of the pro-convulsant Kanic Acid (15mg/kg). **Results:** We found that when PB was given immediately after hypoxia induced seizures, EEG power was reduced, however not to control levels. We also saw a significant reduction in weight gain in the first 72 h after hypoxia and PB administration. Neonatal mice who were treated with phenobarbital and/or subject to hypoxia displayed increased anxiety-like behaviours later in life. Moreover mice which were subject to hypoxia and treated with phenobarbital showed greater susceptibility to KA induced seizures, compared to those who were not treated. **Conclusions:** These data suggest that phenobarbital may have a short-term seizure reduction capability, but it has long-term effects by inducing a subset of behavioural alterations, along with a decreased threshold for seizure activity later in life

Disclosures: **S. Quinlan:** None. **N. Rodriguez-Alvarez:** None. **E. Jimenez-Mateos:** None.

Poster

204. Epilepsy: In Vivo and Behavior - Identifying and Targeting Seizure Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 204.03/D4

Topic: B.11. Epilepsy

Support: NIH Grant R01NS065783

Title: Effect of epilepsy-associated panic disorder on depression

Authors: *S. MEDEL-MATUS, D. SHIN, R. SANKAR, A. MAZARATI
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Abstract: Anxiety is one of the most common comorbidities of epilepsy. In persons with epilepsy, this condition may exacerbate depression, creating a multiple-morbidity state. According to epidemiological findings these patients present with various types of anxiety. Yet, the most examined type is generalized anxiety disorder (GAD). Particularly, panic disorder (PD) is even more frequent than GAD. However, there have been no attempts to study comorbidity

between epilepsy and PD. The goal of this study was to assess how induction of epilepsy-associated PD affects each condition separately, and its role on depression. Fifty days old male Wistar rats (n=8 per group) were subjected to electrical stimulations of basolateral amygdala (BLA, 3x/day) and/or dorsal periaqueductal gray (DPAG, 2x/day) over 7 days, in order to create persistent epileptic state and PD susceptibility, respectively. Prior to, and 24 hours after this procedure, we examined the ictogenesis by identifying afterdischarge threshold (ADT) and duration (ADD), and predisposition to panic attacks (PA) by detecting the threshold of electrical stimuli required for producing panic-like response. One day after completion of the stimulations, the rats were examined in forced swimming test (FST) and saccharin preference test (SPT) to characterize states of despair/hopelessness and anhedonia, respectively. We used sham rats as controls (n=8). BLA+DPAG stimulation increased seizure severity by reducing the ADT (fold vs baseline: 0.08±0.02; control 0.95±0.02, $p<0.0001$) and prolonging the ADD (fold vs baseline: 2.34±0.16; control 1.04±0.09, $p<0.0001$); also decreased the threshold to PA behaviors [exophthalmus (0.10±0.02 mA; control 0.28±0.06 mA, $p<0.05$), immobility (0.15±0.02 mA; control 0.33±0.07 mA, $p<0.05$), running (0.33±0.06 mA; control 0.71±0.07 mA, $p<0.05$), jumping (0.36±0.06 mA; control 0.85±0.07 mA, $p<0.0001$)]. In addition, the BLA+DPAG stimulation extended the immobility time on FST (161.5±6.0 s; control 71.0±6.1 s, $p<0.0001$), and reduced the saccharin preference (58.1±5.9%; control 94.9±2.6%, $p<0.01$). The effect of the stimulation of these two areas was worse compared to each one separately. Results suggest a synergistic effect of the joint induction of epilepsy and PD that contributes to depression development. This protocol could be used as the basis for a new model of comorbidity.

Disclosures: **S. Medel-Matus:** None. **D. Shin:** None. **R. Sankar:** None. **A. Mazarati:** None.

Poster

204. Epilepsy: In Vivo and Behavior - Identifying and Targeting Seizure Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 204.04/D5

Topic: B.11. Epilepsy

Title: P2X7 receptor antagonism lowers the innate seizure threshold possibly through inhibition of Interleukin-1β release

Authors: *S. S. DUTTA, J. HEWETT
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Abstract: Interleukin-1β (IL-1β) is a well-characterized cytokine of the innate and adaptive immune systems and is an important mediator in the communication between the peripheral immune and central nervous systems (CNS). Within the CNS, while it contributes to the pathogenesis of various neuroinflammatory and neurodegenerative maladies, it can also modulate physiological functions under normal conditions. In this regard, IL-1β protein is

expressed constitutively at low levels in the normal brain, including in the hypothalamus and hippocampus, where it appears to modulate sleep and hormone secretion as well as learning and memory, respectively. Thus, IL-1β is a neuromodulator in both the dysfunctional and normal CNS. IL-1β has been implicated as a neuromodulator of seizures, the defining feature of the brain disorder, epilepsy. However, the nature of its role remains controversial. Of particular relevance to this study, we showed previously that the incidence of acute convulsive seizures was increased in mice in which IL-1β signaling was disrupted genetically via inactivation of genes coding for either the signaling receptor or ligand. This provides compelling evidence to support the premise that constitutive production of IL-1β functions as an endogenous neuromodulator in the normal brain to suppress excessive neuronal excitatory. Much remains unknown about the regulation of IL-1β in the normal CNS. Herein, we examined the role of the purinergic receptor P_2X_7R, which has been implicated in the release of IL-1β under neuroinflammatory conditions. We hypothesize that P2X7R is necessary for constitutive IL-1β release in the normal brain and thereby contributes to maintenance of the innate seizure threshold. This possibility was tested using JNJ-47965567 (JNJ), a selective antagonist of P2X7R. We found that the severity of seizures and incidence of convulsions were increased in mice pretreated with JNJ relative to vehicle-treated controls. The latency to convulsions was also reduced in JNJ-treated mice. These results are consistent with the notion that P2X7R contributes to maintenance of the innate seizure threshold and, together with results from mice lacking IL-1β signaling, suggest that this may be via IL-1β release.

Disclosures: S.S. Dutta: None. **J. Hewett:** None.

Poster

204. Epilepsy: In Vivo and Behavior - Identifying and Targeting Seizure Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 204.05/D6

Topic: B.11. Epilepsy

Support: European Union's Seventh Framework Programme (FP7) under grant agreement 602102 (EPITARGET)

Dr. Pavel Klein

Title: Development of new multitargeted antiepileptogenic drug combinations: tolerability in nonepileptic and post-status epilepticus mice

Authors: *L. WELZEL, F. TWELE, K. TÖLLNER, W. LÖSCHER
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Abstract: The development of symptomatic epilepsies, including temporal lobe epilepsy (TLE), can be induced by a variety of brain insults, such as status epilepticus (SE), traumatic brain injury, stroke or infections. Following a brain insult, diverse functional and structural brain alterations, such as neuronal hyperexcitability, neurodegeneration and inflammation, can occur (epileptogenesis). The latent period, defined as the interval between the initiating brain insult and the appearance of the first spontaneous, recurrent seizures (SRS), would be an ideal time point for a preventive (= antiepileptogenic) treatment. Antiepileptogenesis in patients at risk is a major unmet clinical need. Due to the multiple mechanisms involved in epileptogenesis, the development of multitargeted drug combinations ("network pharmacology"), using clinically approved drugs for rapid translation into clinical trials, was proposed. Based on the variety of epileptogenic brain alterations we selected drugs with promising mechanisms or already known disease-modifying effects (e.g. reduction of severity of SRS in preclinical studies when given as a monotherapy). We used an algorithm, based on the drug development phases in humans, which we have recently reported (KLEE et al., 2015) for testing the following rationally chosen drug combinations: A) levetiracetam + alpha-tocopherol, B) levetiracetam + deferoxamine + melatonin, C) levetiracetam + deferoxamine + celecoxib, D) levetiracetam + deferoxamine + gabapentin + fingolimod, E) levetiracetam + gabapentin + topiramate. As a first step (phase I), we tested the tolerability in naïve mice. Male NMRI-mice were treated with one of the drug combinations two times daily over three days. Tolerability was evaluated using a large test battery including an Irwin screen and a rotarod test, which were performed up to four times daily over four days. All five drug combinations tested in naive mice were relatively well tolerated and are currently being evaluated for tolerability in post-SE mice (phase IIa). In these studies, we induce the SE by intrahippocampal kainate injection the day before we start the drug treatment. The evaluation of the tolerability of drug combinations is critical to prevent toxicity in subsequent phases of drug testing by eliminating problematic drug combinations. As a next step the drug combinations can then be evaluated for antiepileptogenic efficacy in the intrahippocampal kainate mouse model in larger groups of mice (phase IIb) and, if effective, in a rat model of post-SE TLE (phase IIc). We thank Dr. Pavel Klein for proposing the drug combinations.

Disclosures: **L. Welzel:** None. **F. Twele:** None. **K. Töllner:** None. **W. Löscher:** None.

Poster

204. Epilepsy: In Vivo and Behavior - Identifying and Targeting Seizure Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 204.06/D7

Topic: B.11. Epilepsy

Support: SIP 20141344

SIP 20151476

SIP20171334

Title: Neuropharmacological screening of chiral and non-chiral thaidomide analogues containing phthalimide moiety in mice

Authors: *C. CAMPOS RODRIGUEZ[1,2], J. G. TRUJILLO FERRARA[3], A. ALVAREZ GUERRA[4], I. M. CUMBRES VARGAS[1], R. OLSSON[2], E. RAMIREZ-SAN JUAN[5]
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Abstract: Thalidomide was the first synthetized phthalimide and has now a days a wide range of demonstrated pharmacological effects. Phthalimides are the most studied heterocyclic compounds due to their substantial number of biology applications and chemist synthesis. That's the reason of studying phthalimides *N*-substituted, which are molecules with interesting chemical structure that gives the derivatives important biological properties. Here, non-chiral (phthaloyl glycine: TGLY; *ortho*-(phenyl)-isoindolin-1,3-dione: OFI; *para*-(phenyl)-isoindolin-1,3-dione: PFI) and chiral phthalimides (phthaloyl-*S*-glutamate; S-TGLU; phthaloyl-*R*-glutamate: R-TGLU; phthaloyl-*S*-aspartate: S-TASP, phthaloyl-*R*-aspartate: R-TASP) were synthetized and the sedative, anxiolytic and anticonvulsant effect were tested. Groups of 12 CD1 male mice (25 - 30 g) were formed randomly for all the experiments. All the drugs were suspended in phosphate buffer solution (pH=7) with carboxymethylcellulose 0.5 % and administered to the animals intraperitoneally in different doses: 100, 316, 562.3 mg/kg. During the development of the experiments, S-TGLU, S-TASP and R-TASP have shown important results, so more experimental groups were added (237.1, 421.7 mg/kg doses). To evaluate the sedative and anxiolytic profile, the open field and the elevated plus maze (EPM) test were employed. For the anticonvulsant activity, the compounds effects were proved against pentylenetetrazol (PTZ; 90 mg/kg) and 4-aminopyridine (4-AP; 10 mg/kg). For the PTZ and 4-AP assays, a positive control for anti-seizure activity was included (sodium valproate; SVP 300 or 400 mg/kg respectively). The non-chiral tested compounds diminish the locomotor activity: OFI 562.3 mg/kg dose and PFI at 316 and 562.3 mg/kg suggest that they have a sedative effect, whereas the chiral compounds have some excitatory effects: S-TGLU and R-TGLU increased the activity with all the tested doses (100, 316, 562.3 mg/kg), while S-TASP just showed this effect with 316 and 562.3 mg/kg. None of the compounds have activity in the EPM and PTZ induced seizures models. When the compounds were tested in the 4-AP induced seizures model, S-TGLU 237.1, 316, 421.7 mg/kg doses have protected the animals of convulsions and death, also S-TASP and R-TASP protected mice of convulsions and death at 316 mg/kg dose. The results suggest that the chiral compounds have a non-competitive NMDA antagonist profile, while the non-chiral have sedative properties.

Disclosures: **C. Campos Rodriguez:** None. **J.G. Trujillo Ferrara:** None. **A. Alvarez Guerra:** None. **I.M. Cumbres Vargas:** None. **R. Olsson:** None. **E. Ramirez-San Juan:** None.

Poster

204. Epilepsy: In Vivo and Behavior - Identifying and Targeting Seizure Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 204.07/D8

Topic: B.11. Epilepsy

Title: Real-time measurements of brain acetylcholinesterase activity following nerve agent exposure in the guinea pig

Authors: C. E. KAROLENKO[1], J. L. WINKLER[1], *J. W. SKOVIRA[2]
[1]Neurosci., USAMRICD, Aberdeen Proving Ground, MD; [2]US Army Med. Res. Inst. of Chem. Def., Aber Prov Grd, MD

Abstract: Traditionally, measurements of the enzyme acetylcholinesterase (AChE) are collected from blood or tissue samples at varying time points after nerve agent exposure or are measured post-mortem. These sampling paradigms require multiple groups of animals to be used for each time point and yield results that are limited in temporal resolution (minutes to hours between samples for a complete time course). Here we utilize a microdialysis technique to measure the activity of AChE in the brain continuously in real time. This method allows for a complete time course of measurements to be taken from each animal, which reduces animal use and variability. One week prior to the experiment guinea pigs were surgically prepared to record brain electrical activity and implanted with a guide cannula. On the day of the experiment a microdialysis probe with 8 mm of exposed membrane was inserted either horizontally or vertically into a guide cannula to establish a sampling surface covering the cortex. Acetylthiocholine was then perfused through the probe, and the returning dialysate was mixed with Ellman's reagent before passing through a flow cell where measurements were taken using a spectrometer. Unexposed control animals were used to determine normal AChE activity in the sampling area and to optimize the concentration of acetylthiocholine in the dialysate. Experimental animals were administered atropine sulfate (1.0 mg/kg) intramuscularly (IM) 10 min prior to receiving the nerve agent GB or VX (1.0 LD_{50} - 1.6 LD_{50}) subcutaneously. AChE activity was continuously measured for 4 hr after nerve agent exposure. The results show that consistent measurements of brain AChE activity can be obtained using this technique.

Disclosures: **C.E. Karolenko:** None. **J.L. Winkler:** None. **J.W. Skovira:** None.

Poster

204. Epilepsy: In Vivo and Behavior - Identifying and Targeting Seizure Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 204.08/D9

Topic: B.11. Epilepsy

Support: IBS-R015-D1

Title: Deep brain stimulation to anterior thalamic nucleus affects the EEG patterns of pilocarpine-induced chronic temporal lobe epilepsy model

Authors: *S. BAE[1,2], E. BAEG[1], H. LIM[1,3], Y.-M. SHON[4], M. SUH[1,2]
[1]Ctr. for Neurosci. Imaging Research, IBS, Suwon, Korea, Republic of; [2]Dept. of Biomed. Engin., [3]Dept. of Biol. Sci., Sungkyunkwan Univ., Suwon, Korea, Republic of; [4]Dept. of Neurol., Samsung Med. Center, Sungkyunkwan Univ. Sch. of Med., Seoul, Korea, Republic of

Abstract: Many animal and human studies performing electrical stimulation in specific brain regions showed reduction in seizure frequencies. Anterior thalamic nucleus (ATN), which has extensive frontal and temporal cortical projections, has been considered as one of the important regions to modulate seizure activities. In spite of promising clinical outcome, how deep brain stimulation (DBS) to ATN regulates epilepsy is poorly understood. Here, we investigated the effects of DBS to the unilateral ATN on electroencephalography (EEG) patterns of the pilocarpine-induced temporal lobe epilepsy (TLE) mouse model. The epilepsy model was made by an injection of pilocarpine (260-280mg/kg) into C57/bl6 mice. Open field test (OFT) were performed to evaluate the degree of epilepsy. After the 2~3 weeks of pilocarpine injection, EEG of the frontal cortex was bilaterally recorded consecutive 12 hours for the confirmation of TLE. The mice exhibited several seizures in 12 hours were chosen to be implanted with a DBS electrode in ATN. They moved more distance than control mice ($P<0.01$) in OFT. After two-week recovery period, the animals underwent a second 12-hour EEG recordings with or without DBS. When DBS at 130 Hz frequency was delivered, the numbers of seizure were significantly decreased during the recording session. In particular, FFT analysis of EEG revealed that there was a peak at theta frequency (~5Hz) in TLE models, whereas when DBS was delivered the peak was disappeared. No peak at 5 Hz was found in normal control group. Our results suggest that DBS into the ATN significantly affects the hyperexcitability of TLE model and reduces both the number of seizures and the peaks at low frequency of EEG. Further study is needed to understand the exact mechanism of DBS in modulating epileptic network.

Disclosures: S. Bae: None. **E. Baeg:** None. **H. Lim:** None. **Y. Shon:** None. **M. Suh:** None.

Poster

204. Epilepsy: In Vivo and Behavior - Identifying and Targeting Seizure Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 204.09/D10

Topic: B.11. Epilepsy

Support: NIH Grant 1K08NS069783

NIH Grant 1R01NS094399

Michigan Brain Initiative Working Group

NIH Grant 1K01ES026839

Title: Characterization of chemical biomarkers in a novel *In vivo* model of ictogenesis

Authors: *H. LUNA-MUNGUIA[1,2], A. G. ZESTOS[3], S. GLISKE[2], R. T. KENNEDY[3], W. C. STACEY[2]
[1]Inst. de Neurobiologia UNAM, Queretaro, Mexico; [2]Neurol., [3]Chem., Univ. of Michigan, Ann Arbor, MI

Abstract: Purpose. Epilepsy is a common neurological disorder in which the random nature of seizures poses difficult research challenges. We recently developed a novel *in vivo* model of ictogenesis, allowing experimental modulation of the risk of temporal lobe seizures. In the present study, we used this model to search for biochemical changes associated with increased seizure risk. **Methods.** Male Sprague-Dawley rats with i.p. pilocarpine were prepared to generate Epileptic (n=15) and Control (n=15) animals. A cannula implanted into *nucleus reuniens* was used for local KCl or PBS injection while another cannula was implanted into left hippocampus for microdialysis experiments. During intracerebral microdialysis experiments, KCl or PBS were injected (120 mM or 1X, respectively; 0.1 µl/min over 5 min) into the *reuniens* of freely moving rats, a process recently shown to increase the risk of seizures up to three-fold. This injection was a total of 9 times, with 15 min between injections, comprising 180 min. Dialysates were collected before (6 collections), during (27 coll) and after (4 coll) KCl or PBS injections, derivatized immediately, and analyzed by liquid chromatography-mass spectrometry (LC-MS) to assess the extracellular concentrations of 24 different neurotransmitters. **Results.** The majority of Epileptic animals had seizures during the KCl injections. The LC-MS analysis revealed that pilocarpine produced significant differences in baseline levels of several neurotransmitters: decreased levels of adenosine, GABA, HVA, 3-MT, and 5-HT, and increased levels of choline, glutamate, phenylalanine, and tyrosine. During the KCl injection into *reuniens*, there was an additional significant change from baseline in several neurotransmitters, particularly showing a clear trend of increasing dopamine and decreasing 3-MT for the duration of the injections. Both

the difference in baseline concentrations (between animals with and without pilocarpine-induced seizures) and the difference during the KCl injection showed complex interactions between multiple neurotransmitters, an effect that we quantified using stepwise logistic regression. **Conclusion.** Our results are the first to show how the pilocarpine model alters the basal hippocampal extracellular concentrations of 24 neurotransmitters. In addition, we report that several are altered during a time period of increased seizure risk. These neurotransmitters, and the interaction between them, are candidates for future experiments investigating the basic mechanisms of ictogenesis, search for biomarkers associated with that risk, and potentially develop and optimize more effective antiseizure therapies.

Disclosures: H. Luna-Munguia: None. **A.G. Zestos:** None. **S. Gliske:** None. **R.T. Kennedy:** None. **W.C. Stacey:** None.

Poster

204. Epilepsy: In Vivo and Behavior - Identifying and Targeting Seizure Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 204.10/D11

Topic: B.11. Epilepsy

Support: NSFC31100786

China 2013CB835100

Title: Interference of TRPV1 function altered the susceptibility of PTZ-induced seizure

Authors: *R. MAO, Y. JIA, L. XU
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Abstract: Transient receptor potential vanilloid 1 (TRPV1) is widely distributed in the central nervous system (CNS) including hippocampus, and regulates the balance of excitation and inhibition in CNS, which imply its important role in epilepsy. We used both pharmacological manipulations and transgenic mice to disturb the function of TRPV1 and then studied the effects of these alterations on the susceptibility of pentylenetetrazol (PTZ)-induced seizures. Our results showed that systemic administration of TRPV1 agonist capsaicin (CAP, 40 mg/kg) directly induced tonic-clonic seizures (TCS) without PTZ induction. The severity of seizure was increased in lower doses of CAP groups (5 and 10 mg/kg), although the latency to TCS was delayed. On the other hand, systemic administration of TRPV1 antagonist capsazepine (CPZ, 0.05 and 0.5 mg/kg) and TRPV1 knockout mice exhibited delayed latency to TCS and reduced mortality. Furthermore, hippocampal administration of CPZ (10 and 33 nmol/μL/side) was firstly reported to increase the latency to TCS, decrease the maximal grade of seizure and mortality. It is worth noting that decreased susceptibility of PTZ-induced seizures was observed in

hippocampal TRPV1 overexpression mice and hippocampal CAP administration (33 nmol/μL/side), which is opposite from
results of systemic agonist CAP. Our findings suggest that the systemic administration of TRPV1 antagonist may be a novel therapeutic target for epilepsy, and alteration of hippocampal TRPV1 function exerts a critical role in seizure susceptibility.

Disclosures: R. Mao: None. **Y. Jia:** None. **L. Xu:** None.

Poster

205. Epilepsy: Human Studies - Seizure Analysis and Modelling

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 205.01/D12

Topic: B.11. Epilepsy

Title: Neural activity model of hemodynamic response during absence seizures

Authors: *J. RYU[1], Y. CHEN[1], S. BRAUN[1], J. N. GUO[1], H. BLUMENFELD[1,2,3]
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Abstract: Childhood absence epilepsy (CAE) is a relative common disorder among children with epilepsy, characterized by 3-4 Hz spike and wave discharges (SWD) on EEG. The seizures vary in severity of behavioral impairment, ranging from a complete unconscious state and withdrawal from tasks to brief staring and relatively spared performance on tasks. Based on correlation analysis, we previously have shown three networks on fMRI during absence seizures: the default mode network (DMN), task positive network (TPN) and the sensorimotor thalamic network (SMT). Furthermore, we found a widespread larger fMRI amplitude in cortical and subcortical regions for seizures with impaired behavioral responsiveness compared to seizures with spared responsiveness. However, the mechanisms of absence seizures are still poorly understood, including the relationship between behavioral impairment and seizure duration, hemodynamic responses, and neural activity during seizures. A complicating factor is that the blood oxygen-level dependent (BOLD) fMRI signal change is not directly related to neuronal activity as measured by EEG. In particular, it has been shown that the boxcar approximation for the neural activity is inadequate in predicting BOLD activity in many brain regions during absence seizures using the canonical hemodynamic response function (HRF). Using a large fMRI data set from the Yale Childhood Epilepsy Project (1032 seizures in 39 patients) and physiological data from animal models, we created a physiologically realistic model of the electrical activity before/during/after SWD. We then used convolution to fit the model to the BOLD activity data and to estimate underlying neuronal electrical activity in different brain regions. We found strikingly different activity patterns and different relationships with seizure duration in different networks. DMN and TPN showed striking early gradual increases many tens

of seconds prior to SWD onset, which were proportional to subsequent SWD duration. In addition, DMN and TPN showed large decreases which persisted for more than 20s after SWD offset, also related to the duration of the preceding SWD episode. None of the changes outside the SMT network could be explained by a simple boxcar model of electrical activity, suggesting that much more complicated changes occur both before and after SWD, which may determine physiological severity in these regions. This approach provides fundamental new insights into absence seizure pathophysiology which may help guide novel treatments for this disorder.

Disclosures: J. Ryu: None. **Y. Chen:** None. **S. Braun:** None. **J.N. Guo:** None. **H. Blumenfeld:** None.

Poster

205. Epilepsy: Human Studies - Seizure Analysis and Modelling

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 205.02/D13

Topic: B.11. Epilepsy

Support: Swebillius Grant

Title: Evaluating the feasibility of automated responsiveness testing in epilepsy (ARTiE)

Authors: *N. SALEEM[1], C. ARENCIBIA[1], Z. SHEIKH[1], T. LIAO[1], L. GOBER[1], R. KHOZEIN[1], L. HIRSCH[1,2,3], H. BLUMENFELD[1,2,3]
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Abstract: Behavioral evaluation of patients during seizures is crucial for clinical decision-making. Information about patient responsiveness during seizures guides decisions about accurate diagnosis, driving safety, seizure localization, and assessment of the severity of seizures for presurgical evaluation. However, objective evaluation of epileptic behavior obtained through inpatient or outpatient video/EEG monitoring presents limitations because testing of responsiveness during seizures relies on bedside availability of trained hospital personnel or family members. In our most recent analysis of this type of behavioral testing in the Yale Comprehensive Epilepsy Center Inpatient Monitoring Unit, we found that questions or commands asked during seizures were highly inconsistent, with testing being performed only 50% of the time during seizures, and often by nonmedical personnel. Our lab has built an "Automatic Responsiveness Testing in Epilepsy" (ARTiE) system to improve the reliability and consistency of behavioral testing during seizures. ARTiE consists of a series of video-recorded behavioral tasks that is automatically triggered in the patient's room upon computerized seizure detection or by event button press. Videos are presented on a flat screen all-in-one PC which can be wall-mounted or free-standing. We have recently introduced ARTiE into routine clinical use on the Yale inpatient epilepsy monitoring unit and initial experience has demonstrated useful

clinical evaluation during seizures which has augmented the testing normally performed by human personnel. ARTiE behavioral testing was used in 26 seizures in 15 patients and successful behavioral evaluation was obtained in 26 of 26 seizures (100%). Testing was initiated immediately after seizure onset in all cases and continued into the postictal period. Nursing staff have found ARTiE to be helpful in the clinical setting and well-integrated with the patient care work flow. With continued testing using ARTiE, we hope to further gather more valuable information for clinical decision-making and on the response of patients to ARTiE in the epilepsy monitoring unit, and ultimately to improve the clinical evaluation of these patients.

Disclosures: **N. Saleem:** None. **C. Arencibia:** None. **Z. Sheikh:** None. **T. Liao:** None. **L. Gober:** None. **R. Khozein:** None. **L. Hirsch:** None. **H. Blumenfeld:** None.

Poster

205. Epilepsy: Human Studies - Seizure Analysis and Modelling

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 205.03/D14

Topic: B.11. Epilepsy

Support: James G. Hirsch M.D., Endowed Medical Student Research Fellowship

Yale University School of Medicine Medical Student Research Fellowship

National Institutes of Health-NHLBI Medical Student Research Fellowship

Title: Impaired consciousness in frontal lobe seizures: Quantitative analysis of intracranial electroencephalography

Authors: *C. A. ARENCIBIA[1], R. GEBRE[1], M. DHAKAR[1], E. GROVER[1], I. QURAISHI[1], E. STERNBERG[1], I. GEORGE[1], A. SIVARAJU[1], J. BONITO[1], H. P. ZAVERI[1], L. GOBER[1], S. GHOSHAL[1], P. FAROOQUE[1], L. HIRSCH[1], J. GERRARD[1,2], D. SPENCER[1,2], S. AHAMMAD[1], H. BLUMENFELD[1,2,3]
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Abstract: One major morbidity of seizures is the loss of consciousness, and understanding the mechanisms by which this occurs can have a major impact on epilepsy patient care. Previous investigation of consciousness in focal epilepsy has emphasized mainly temporal lobe seizures, where increased delta frequency slowing in widespread brain regions is associated with impaired consciousness. We were interested in determining whether frontal lobe seizures with impaired consciousness would similarly have widespread increases in delta activity, or whether they might also have changes in other frequency bands. Therefore, we investigated a cohort of 14 patients and 26 frontal lobe seizures (65% with impaired consciousness) from the Yale Comprehensive Epilepsy Center. We included patients that were undergoing intracranial EEG monitoring for

surgical evaluation with frontal lobe onset confirmed by intracranial EEG. Each patient's EEG was analyzed from 30 second prior to seizure onset to 120 second after seizure onset by a Fast Fourier Transform with 1 second non-overlapping segments. The EEG signal power was calculated for the delta (0.5 to <4 Hz), theta (4 to <8 Hz), alpha (8 to 13 Hz), beta (>13 to <25 Hz), and gamma (25-50 Hz) frequency bands. The fractional change of the power was then calculated as (EEG power - Baseline Power) / Baseline Power. Baseline was defined as 30 second prior to onset until seizure onset. The data were organized by ipsilateral and contralateral localizations to seizure onset. All statistics were two tailed unpaired t-tests with Holm-Bonferroni correction. We found that frontal lobe seizures with impaired consciousness had significantly greater power in all frequency ranges both ipsilateral and contralateral to seizure onset compared to frontal lobe seizures with spared consciousness ($p<0.05$). The one region which showed relatively small differences between seizures with impaired vs. spared consciousness was the medial frontal lobe ipsilateral to the side of seizure onset. Seizure duration, in contrast, was not significantly different for frontal lobe seizures with impaired vs. spared consciousness. Our data suggest that there is a less selective mechanism in play for frontal lobe seizures causing impairment than that shown in temporal lobe seizures. Unlike temporal lobe seizures where decreased subcortical arousal may produce cortical slow waves, frontal lobe seizures appear to impair consciousness due to direct spread of ictal activity in many frequency bands to widespread brain networks. With further investigation, we hope these findings may help guide improved treatments aimed at preventing loss of consciousness in frontal lobe seizures.

Disclosures: C.A. Arencibia: None. **R. Gebre:** None. **M. Dhakar:** None. **E. Grover:** None. **I. Quraishi:** None. **E. Sternberg:** None. **I. George:** None. **A. Sivaraju:** None. **J. Bonito:** None. **H.P. Zaveri:** None. **L. Gober:** None. **S. Ghoshal:** None. **P. Farooque:** None. **L. Hirsch:** None. **J. Gerrard:** None. **D. Spencer:** None. **S. Ahammad:** None. **H. Blumenfeld:** None.

Poster

205. Epilepsy: Human Studies - Seizure Analysis and Modelling

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 205.04/D15

Topic: B.11. Epilepsy

Support: Swiss National Science Foundation grant # 168437

Title: Diverse mechanisms for ictal loss of consciousness: A comparison of intracranial recordings during complex partial and secondarily generalized seizures

Authors: *E. JUAN[1], T. BUGNON[1], G. FINDLAY[1], R. VERHAGEN[1], A. MENSEN[1], C. A. SCHEVON[2], O. DEVINSKY[3], R. MAGANTI[1], G. TONONI[4], H. BLUMENFELD[5], M. BOLY[1]
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Comprehensive Epilepsy-Sleep Inst., New York, NY; [4]Univ. of Wisconsin Madison, Madison, WI; [5]Dept. of Neurol., Yale Univ. Sch. of Med., New Haven, CT

Abstract: Introduction: Loss of consciousness (LOC) during seizures is a major source of injury and decreased quality of life in patients with epilepsy. Previous studies suggest that LOC during complex partial seizures (CPS) might be related to the presence of sleep-like rhythms in extra-temporal cortex. However, the exact pattern of activity present during secondarily generalized tonico-clonic seizures (GTC) - which are accompanied by deeper LOC - remains unknown to date. Here we compared intracranial EEG activity during CPS and GTC, with a particular emphasis on quantifying high frequency activity in the high-gamma range (80-150 Hz), and beta (15-25 HZ)/delta (1-4Hz) ratio, which may help to detect respectively actively seizing cortex and sleep-like cortical activity. Methods: 11 CPS and 10 GTC from 10 mesial temporal lobe epilepsy patients were included. After rejecting noisy epochs and channels, we computed power spectrum for each channel during baseline (60 seconds before seizure onset) and ictal period (from seizure onset to seizure offset). Power spectrum data were then pooled within frontal, temporal and parietal regions. Changes in EEG power between baseline and ictal periods were assessed in delta to high-gamma frequencies (1-4 Hz to 80-150 Hz ranges). T-tests compared baseline and ictal periods within GTC and CPS, and between GTC and CPS. P values were corrected for multiple comparisons using false discovery rate. Results When comparing baseline to ictal activity during CPS, we found a significant high-gamma band increase only in temporal lobe regions (4-fold increase, $p < 0.005$). Interestingly, beta/delta ratio also significantly increased in temporal regions (11-fold increase, $p < 0.001$) while it was reduced in parietal regions during CPS. When comparing baseline to ictal activity during GTC, we found a significant increase in high-gamma band for all brain regions (15-17 fold increase, $p < 0.005$). A significant increase in beta/delta ratio was also found during GTC in frontal and parietal regions (6-9 fold increase, $p < 0.001$). A direct comparison between GTC and CPS showed significantly higher high-gamma power and beta/delta ratio during GTCs in extra-temporal regions. Discussion. During CPS, high-gamma activity and increased beta/delta ratio were restricted to the temporal lobe, while extra-temporal cortex showed sleep-like activity. In contrast, GTC were accompanied by a widespread increase in high-gamma activity and beta/delta ratio in the whole cortex. The widespread increase in hyper-synchronous activity in extra-temporal regions during GTC might be associated with deeper LOC than the sleep-like activity observed in CPS.

Disclosures: E. Juan: None. **T. Bugnon:** None. **G. Findlay:** None. **R. Verhagen:** None. **A. Mensen:** None. **C.A. Schevon:** None. **O. Devinsky:** None. **R. Maganti:** None. **G. Tononi:** None. **H. Blumenfeld:** None. **M. Boly:** None.

Poster

205. Epilepsy: Human Studies - Seizure Analysis and Modelling

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 205.05/D16

Topic: B.11. Epilepsy

Support: Nederlandse Organisatie voor Wetenschappelijk Onderzoek

NINDS 1R03NS096379

Title: Neural correlates of loss of consciousness in simple versus complex partial seizures: A high-density EEG study

Authors: *R. Y. VERHAGEN[1,2], G. FINDLAY[2], B. JONES[2], E. JUAN[2], T. BUGNON[2], A. MENSEN[2], H. BLUMENFELD[3], G. TONONI[2], R. MAGANTI[2], M. BOLY[2]
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Abstract: Introduction: Mechanisms of loss of consciousness (LOC) during epileptic seizures are not yet fully understood. In the present study we used high density (HD-)EEG to compare topographical changes in EEG oscillatory activity during simple partial seizures (SPS, without loss of consciousness) and complex partial seizures (CPS, where consciousness is impaired) in order to identify neurophysiological signatures of seizure-induced LOC.
Methods: Patients with focal epilepsy were recruited at the Epilepsy Monitoring Unit of University of Wisconsin-Madison and divided into two groups depending on seizure type: CPS (n = 7, mean age 40 ± SD 13, 3 females; focus location in bilateral temporal: n =1, R temporal: n = 3; L temporal n = 2; R occipital: n = 1) and SPS (n = 5, mean age 45 ± SD 12, 3 females; focus locations in R temporal: n = 2; L temporal: n = 1; R occipital: n = 1; L fronto-temporal: n = 1). HD-EEG data during 15 CPS and 9 SPS was filtered between 0.3 and 50 Hz, and noisy epochs and bad channels were visually rejected. EEG power spectrums in the delta, theta, alpha, sigma and beta bands (1-4; 4-8; 8-12; 12-15 and 15-25 Hz) as well as beta/delta power ratio were compared between baseline (60 second before seizure onset) and ictal periods (from seizure onset to seizure offset). Quantitative power changes between baseline and ictal period were also compared between CPS and SPS. Random effects analyses were performed and results were thresholded at $p<0.05$ corrected for multiple comparisons using Statistical Parametric Mapping software. Results: Compared to baseline, ictal activity in both SPS and CPS was characterized by a widespread, bilateral increase in EEG power from delta to beta frequencies. In addition, CPS were characterized by a sleep-like decrease in beta/delta ratio in posterior midline regions, which was not found during SPS ictal activity. A direct comparison between CPS and SPS revealed significantly higher theta power in posterior midline scalp regions compared to baseline during CPS ictal activity. Conclusion: While comparison to baseline EEG reveals widespread changes in all EEG frequencies during both SPS and CPS ictal activity, a higher increase in theta frequency and a decrease in beta/delta ratio were selectively observed in posterior midline scalp areas during CPS. This result is in line with recent studies identifying low-frequency activity in posterior parieto-occipital regions as most predictive for LOC during both NREM sleep and REM sleep. These results also confirm previous iEEG findings reporting the presence of sleep-like activity in extra-temporal cortex during CPS.

Disclosures: **R.Y. Verhagen:** None. **G. Findlay:** None. **B. Jones:** None. **E. Juan:** None. **T. Bugnon:** None. **A. Mensen:** None. **H. Blumenfeld:** None. **G. Tononi:** None. **R. Maganti:** None. **M. Boly:** None.

Poster

205. Epilepsy: Human Studies - Seizure Analysis and Modelling

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 205.06/D17

Topic: B.11. Epilepsy

Support: NIH NINDS Award R01NS095369

Title: Network inference for dynamic modeling of epileptic seizures

Authors: ***E. SPENCER**[1], L.-E. MARTINET[2], E. N. ESKANDAR[3], U. EDEN[1], C. CHU[3], E. KOLACZYK[1], S. S. CASH[4], M. KRAMER[1]
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Abstract: Epilepsy is one of the most common neurological syndromes, affecting an estimated 3 million people in the United States. In one-third of these patients, seizures cannot be controlled despite maximal medical management. The complexity of the brain network dynamics that define the epileptogenic cortex and drive seizure initiation and spread makes understanding and treating epilepsy a unique challenge. Several approaches have been proposed to infer functional networks from neural time series, including methods based on statistical modeling of the voltage activity and their interactions (e.g., Granger causality). However, fitting such models remains computationally challenging as the long history dependent structure in brain activity requires the use of a large number of parameters to fully capture its dynamics. In the case of the large-scale networks studied in patients with epilepsy, this can result in very slow or intractable computations. We develop a new method based on the traditional multivariate Granger causality. Assuming a smooth structure of the parameters at each lag of the autoregressive model, we model the data with a lower dimensional cardinal spline basis using significantly less parameters. We show that this approach allows us to extract accurate brain dynamics and functional networks, using simulations as well as brain activity recorded during seizures from patients with pharmacoresistant epilepsy. Our results have significant potential clinical applications in better identifying and understanding functional networks during seizures, which may lead to improved surgical targets and seizure control strategies.

Disclosures: **E. Spencer:** None. **L. Martinet:** None. **E.N. Eskandar:** None. **U. Eden:** None. **C. Chu:** None. **E. Kolaczyk:** None. **S.S. Cash:** None. **M. Kramer:** None.

Poster

205. Epilepsy: Human Studies - Seizure Analysis and Modelling

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 205.07/D18

Topic: B.11. Epilepsy

Support: NIH NINDS Award R01NS095369

Title: Dynamic functional network analysis during human seizures

Authors: *L.-E. MARTINET[1], E. SPENCER[3], C. CHU[1], E. N. ESKANDAR[2], E. KOLACZYK[3], M. A. KRAMER[3], S. S. CASH[1]
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Abstract: Epilepsy, one of the most common neurological syndromes, is increasingly recognized as involving complex brain network dynamics, making understanding and treating this disease a unique challenge. To address this issue, we have created a data analysis pipeline to infer and track brain networks through time during spontaneous human seizures. Our method first infers dynamic functional networks based on several standard coupling statistics (correlation, coherence and Granger causality based measures). Then we apply a recently developed graph theory approach to the inferred functional networks to identify and track through time well-connected subsets of nodes known as communities. In order to validate our approach, we implement a set of simulations using coupled source dipoles spatially distributed through a cortical layer and generating electrical fields propagating across a standard 4-shell spherical head model (from cortex, to cerebrospinal fluid, skull and scalp). The implemented couplings between dipoles include simple neighbor-to-neighbor connections as well as more realistic connectivity derived from human brain diffusion tensor imaging data. We show that the network inference and community detection methods perform accurately when applied to simulated scalp and cortical signals. We also apply our method to both invasive and non-invasive human brain recordings (ECoG and EEG, respectively) obtained from patients with intractable epilepsy. This dynamic network analysis and statistical modeling of human seizure data could provide new approaches to improve patient care of medically refractory epilepsy, such as principled surgical target identification, surgical outcome prediction and alternative seizure control strategies.

Disclosures: L. Martinet: None. **E. Spencer:** None. **C. Chu:** None. **E.N. Eskandar:** None. **E. Kolaczyk:** None. **M.A. Kramer:** None. **S.S. Cash:** None.

Poster

205. Epilepsy: Human Studies - Seizure Analysis and Modelling

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 205.08/D19

Topic: B.11. Epilepsy

Support: NSF DMS Award #1451384

NIH NINDS Award R01NS072023

Title: A new method to assess cross frequency coupling with changes in low frequency amplitude: Application to human seizures

Authors: *J. NADALIN[1], L.-E. MARTINET[1], G. FIDDYMENT[1], E. N. ESKANDAR[2], C. CHU[2], S. S. CASH[3], M. KRAMER[1]
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Abstract: Cross-frequency coupling (CFC) has been proposed to play an important role in information processing and memory in both humans and animal models. It is also thought to be involved with pathological brain activity. Here, we examine instances of CFC from microelectrode array (10x10 grid, 0.4 mm spacing) recordings in four human patients with pharmacoresistant epilepsy. During a seizure, voltage fluctuations appear across a broad range of frequencies, from very slow (< 1Hz) to very fast (>100 Hz). How these rhythms coordinate is not well understood. To address this, we develop a new modeling framework to characterize the extent of cross-frequency coupling (CFC) observed at seizure onset. Through this modeling framework, we assess the standard relationships between high frequency amplitude and low frequency phase, as well as the relationship between high and low frequency amplitude. In this way, the method allows us to address an important confound in the characterization of CFC from noisy data in which the low frequency amplitude may vary. Through simulations, we show that the proposed modeling framework is more sensitive to increases in CFC strength than methods that do not account for changes in the low frequency amplitude, and detects changes in CFC where other methods may not. Our preliminary results show that, at seizure onset, the amplitude of fast (100-140 Hz) activity is modulated by the phase of a slow (4-7 Hz) oscillation. A deeper understanding of CFC at human seizure onset may provide new insight into the mechanisms involved in seizure initiation and propagation, and suggest improved therapeutic strategies to control seizures.

Disclosures: **J. Nadalin:** None. **L. Martinet:** None. **G. Fiddyment:** None. **E.N. Eskandar:** None. **C. Chu:** None. **S.S. Cash:** None. **M. Kramer:** None.

Poster

205. Epilepsy: Human Studies - Seizure Analysis and Modelling

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 205.09/D20

Topic: B.11. Epilepsy

Title: Cellular and synaptic pathology in intractable epilepsy: Observations from surgically resected seizure foci

Authors: *M. VARGHESE[1], L. COUTO[1], W. G. JANSSEN[1], T. VASILKOVA[1], Y. GROSSMAN[1], D. DUMITRIU[1], K. SARPONG[2], D. DEL VALLE[2], N. TSANKOVA[3], L. MARCUSE[4], F. PANOV[5], P. MCGOLDRICK[5], S. WOLF[6], S. GHATAN[6], D. MEYER[7], D. PINTO[2], P. R. HOF[1]
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Abstract: Intractable epilepsy, which does not respond to pharmacological treatment, occurs in nearly one third of patients with epilepsy. Imbalance of excitatory/inhibitory function in pyramidal neurons of the cortex plays a role in hyperactive synchrony causing seizures. However, cell type-specific neurochemical markers and morphology have not been quantified at synaptic levels in intractable epilepsy. The possible contribution of neuroinflammation and glial cell activation to pathology in the epileptogenic areas is also relatively unexplored.
We have unprecedented access to epileptogenic brain tissue surgically resected as treatment for intractable epilepsy. This tissue was prepared to enable high-resolution quantitative cellular and synaptic analyses in the human cerebral cortex, using methods previously available only for studies using animal models. We have comprehensively analyzed synaptic and cellular morphology and markers of function in layer III pyramidal neurons, as well as distribution of glia, in seizure-onset and seizure-spread zones of cortical tissue resected from patients with epilepsy. Additionally, single-cell 3' RNA-Seq using the Chromium 10x Genomics system provides gene expression profiling and characterization of thousands of individual cells from epileptic foci.
Through immunofluorescence approaches, our preliminary evidence indicates significant changes in inhibitory neurochemical markers, like subunits of the γ-aminobutyric acid receptor and transporter, in the seizure-onset zone. Using 3-dimensional reconstruction of neurons iontophoretically injected with Lucifer Yellow, and investigation of synaptic ultrastructure using electron microscopy, our analysis of dendritic spines revealed decreases in synaptic density and spine head diameters at glutamatergic synapses in the seizure onset zone. Our highly multiplexed immunofluorescence method reveals abnormal morphology of glial cells in seizure onset zones. The presence of columnar microglia and astroglial clustering around blood vessels possibly

indicates elevated neuroinflammation.
These comprehensive analyses enable direct assessment of altered cellular and synaptic elements within neural circuits in addition to detection of glial contributors to pathology in seizure onset zones in intractable epilepsy.

Disclosures: **M. Varghese:** None. **L. Couto:** None. **W.G. Janssen:** None. **T. Vasilkova:** None. **Y. Grossman:** None. **D. Dumitriu:** None. **K. Sarpong:** None. **D. del Valle:** None. **N. Tsankova:** None. **L. Marcuse:** None. **F. Panov:** None. **P. McGoldrick:** None. **S. Wolf:** None. **S. Ghatan:** None. **D. Meyer:** None. **D. Pinto:** None. **P.R. Hof:** None.

Poster

205. Epilepsy: Human Studies - Seizure Analysis and Modelling

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 205.10/D21

Topic: B.11. Epilepsy

Support: R03NS104669

Title: Proliferative glial pathology in drug resistant human epilepsy

Authors: J. TOME-GARCIA[1], E. CABALLERO[1], S. GHATAN[2], F. PANOV[2], L. MARCUSE[3], J. YOO[3], W. JANSSEN[4], S. AKBARIAN[4], E. ZASLAVSKY[3], *P. R. HOF[5], N. TSANKOVA[1]
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Abstract: Temporal lobe epilepsy (TLE) is one of the most common forms of epilepsy, often refractory to drug therapy. While current seizure medications target abnormal neuronal hyperexcitability, pathological epileptic tissue also shows reactive astroglial scar and subtle dysregulation of myelin. The functional and molecular contributions of each specific neural cell type to disease maintenance in epilepsy remains to be defined. In this study, we aimed to better characterize, both functionally and molecularly, the pathological changes in astrocytes and oligodendroglia associated with epilepsy, using primary, electrode-mapped epileptic and perilesional cortical tissue from patients with drug resistant TLE and age-matched postmortem normal temporal cortex as control. In vivo characterization by immunofluorescence revealed accumulation of proliferative Ki67+ glia, some of which were astroglial (GFAP+), while others - oligodendroglial (OLIG2+), in contrast to the largely quiescent glia in normal adult cortex, suggesting a reversion to an immature glial phenotype in the epileptic tissues. Next, we used fluorescently conjugated EGF ligand to sort EGFR+ glia from fresh TLE tissue, a technique previously used to prospectively isolate neural and glioblastoma stem cell populations. While

EGFR is not normally expressed in adult human cortex, epileptic tissue showed a discrete subpopulation of EGFR+ glia, some of which were also GFAP+. These cells displayed selective ability for neurosphere proliferation in vitro, consistent with an immature progenitor-like phenotype. To further characterize the molecular phenotype of the immature glial cells in the same patient's samples, we developed a fluorescence-activated nuclei sorting (FANS) strategy to isolate nuclei from neurons, oligodendroglial progenitors (OPCs), and astrocytes from frozen cortex. RT-qPCR confirmed enrichment of neuronal, OPC, and astrocytic markers in each FANS-isolated nuclei population, prior to deep nuclear transcriptome sequencing. Our results demonstrate an increased number of proliferative glia within epileptic tissue, and implicate an aberrant, immature phenotypic remodeling of epileptic astrocytes, associated with EGFR re-expression. Differential RNAseq transcriptome analysis in these glial subpopulations is defining the cell-type specific transcriptional networks dysregulated in TLE, and hopes to uncover the specific proliferative pathways associated with the observed immature EGFR+ glial phenotype. Further understanding of these glial-specific dysregulated pathways will allow design of better therapies for synapse restoration in this debilitating disease.

Disclosures: **J. Tome-garcia:** None. **E. Caballero:** None. **S. Ghatan:** None. **F. Panov:** None. **L. Marcuse:** None. **J. Yoo:** None. **W. Janssen:** None. **S. Akbarian:** None. **E. Zaslavsky:** None. **P.R. Hof:** None. **N. Tsankova:** None.

Poster

205. Epilepsy: Human Studies - Seizure Analysis and Modelling

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 205.11/D22

Topic: B.11. Epilepsy

Title: Task-synchronized vagus nerve stimulation (VNS) showed the improvement of cerebral blood flow responsiveness in the VNS responders

Authors: *S. SHIMADA[1], N. KUNII[1], T. KOIZUMI[1], K. KAWAI[2], N. SAITO[1]
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Abstract: <Introduction> The antiepileptic mechanism of vagus nerve stimulation (VNS) is still unknown. Although changes of local cerebral blood flow have been reported in the literature, the results have been inconsistent. In order to investigate the relationship between immediate effects on cerebral blood flow and antiepileptic effects of VNS, we measured blood flow changes of the frontal lobe by near-infrared spectroscopy (NIRS) and compared these immediate effects with the clinical outcome. <Methods> Immediate blood flow changes by VNS were recorded by NIRS in 21 patients who had been treated with VNS for more than 6 months in The University of Tokyo Hospital. We measured the blood flow changes in the frontal lobe without and with a verbal fluency task (VF task). Two different doses (therapeutic and half of the therapeutic

current) of stimulation were delivered in the rest condition (only VNS, without a VF task) and three different doses (therapeutic, half of the therapeutic and zero current) of stimulation were used in the VF task condition (task-synchronized VNS). We compared the differences of the magnitude and the speed (the magnitude of the slope) of the blood flow changes with the clinical outcome (responders/ non-responders). <Results> In the rest condition (only VNS), no significant differences of the blood flow changes were observed between the different doses of current and between the clinical outcome. In the task condition (task-synchronized VNS), the magnitude and the speed of the blood flow changes of the responder group significantly increased along with the VNS intensity. On the other hand, the blood flow changes of the non-responder group showed no significant intensity-dependent differences. <Discussion> Intensity-dependent blood flow changes in the frontal lobe were observed only in the task condition of the responder group. These results suggested that one of the antiepileptic effects of VNS is produced through the improvement of cerebral blood flow responsiveness.

Disclosures: S. Shimada: None. **N. Kunii:** None. **T. Koizumi:** None. **K. Kawai:** None. **N. Saito:** None.

Poster

205. Epilepsy: Human Studies - Seizure Analysis and Modelling

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 205.12/D23

Topic: B.11. Epilepsy

Title: Epilepsy seizures in children with rare diseases

Authors: *O. V. GLOBA, L. KUZENKOVA, T. PODKLETNOVA
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Abstract: Childhood epilepsies a heterogeneous group of disorders and syndromes with different severity, prognosis and treatment. The purpose of study was to recognise the possible reason of nonadequate answer on AED treatment and to find the ways for owercome it. **Methods: 33** patients with different forms of epilepsy aged from 3 months to 16 years not the candidate for surgical treatment have been studied. The long duration EEG, high resolution MRI, biochemical, lactate level, genetic investigation were performed to these children. **Results:** in 11 children the respiratory chain disorders confirmed by mtDNA sequence were found. Metabolic diseases were discovered in 8 patients: two glutaric aciduria type1, one propionic aciduria, one methylmalonic aciduria, one Gaucher type3, one glycogenosis type6, two ceroid lipofuscinosis. In four children mutation in genes SCN8A, GRIN2A, KCNMA1 and duplication 15q11.2q13.3 were revealed. In other cases with normal MRI the reason of pharmacoresistant seizures was not discover yet. In children with metabolic disorders and energy metabolism disorders we use the specific therapy(diet, Lcarnitine, vitamins, enzyme replacement therapy etc) in cases which it

possible, avoid valproic acid in treatment, as well we use the phenytoin in patient with potassium channel mutation. These treatment management leads to reduction in seizures frequency or even to seizures remission in some cases. **Conclusions**: the recognition and diagnostic of underlying the etiologies of intractable seizures improve the treatment management in many cases.

Disclosures: O.V. Globa: None. **L. Kuzenkova:** None. **T. Podkletnova:** None.

Poster

205. Epilepsy: Human Studies - Seizure Analysis and Modelling

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 205.13/D24

Topic: B.11. Epilepsy

Title: Long-term correlation structure is preserved in time-shifted intracranial EEG signals

Authors: *R. B. JOSHI[1], I. I. GONCHAROVA[3], R. B. DUCKROW[3], J. L. GERRARD[4], D. D. SPENCER[4], L. J. HIRSCH[3], D. W. GODWIN[2], H. P. ZAVERI[5]
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Abstract: Objective: In a recent study, we analyzed correlations in slow (<0.15 Hz) amplitude modulations of intracranial EEG (icEEG) band power time-series (i.e., the second spectrum), for evidence of relationship between distant brain regions and their correspondence with fMRI-defined resting state networks. Though we reported a lack of support for the fMRI-based default mode network, our results and other studies suggest that these envelope correlations may form the basis for distant spatial coupling in the brain [1]. As the slow modulations of interest in our study contain activity on the order of seconds to minutes, we speculated that some correlation structure may be preserved even with some time lag between signals. In this study, we used time-lag analysis to study the timescale of these second spectrum correlations.
Methods: We studied icEEG data collected from 13 medically refractory epilepsy patients who underwent monitoring at Yale-New Haven Hospital. For each patient, we selected hour-long background icEEG epochs before and after antiepileptic drug (AED) taper, that were at least 6 hours removed from seizure, when patients appeared to be resting quietly with eyes open. For each epoch, we selected 5000 random electrode contact pairs and estimated magnitude-squared coherence (MSC) below 0.15 Hz of band power time-series in the delta, theta, alpha, beta, and gamma bands. Using these same contact pairs, we then shifted one signal of the pair by random durations in 15 second increments, between 0 and 300 seconds (i.e. 5,000 trials each with a random lag between 0-15 seconds, 16-30 seconds, etc.). We then aggregated these data across all patients to determine how second spectrum MSC varies with duration of lag. In order to set a threshold for considering an MSC estimate significantly nonzero, we also calculated second spectrum MSC on 25,000 randomly selected contact pairs, where each pair contained contacts

from two randomly selected patients (i.e., signals which are known to be uncorrelated).
Results: The mean MSC decreases monotonically with increasing time lag until 105 seconds of lag, then plateaus between 106 and 300 seconds. Significantly nonzero ($p < 0.001$; as determined by our threshold) second spectrum MSC is preserved in all frequency bands until about 105 seconds of time lag between the two signals. This observation was consistent both before and after AED taper.
Conclusions: Second spectrum metrics capture correlated oscillatory activity in the brain at timescales on the order of seconds to minutes.
[1] RB Joshi et al, "Regional and network relationship in the intracranial EEG second spectrum." Clin Neurophysiol, 2016.

Disclosures: R.B. Joshi: None. **I.I. Goncharova:** None. **R.B. Duckrow:** None. **J.L. Gerrard:** None. **D.D. Spencer:** None. **L.J. Hirsch:** None. **D.W. Godwin:** None. **H.P. Zaveri:** None.

Poster

205. Epilepsy: Human Studies - Seizure Analysis and Modelling

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 205.14/D25

Topic: B.11. Epilepsy

Title: Characterizing single unit activity from putative excitatory neurons in limbic structures during spontaneous focal seizures in patients with medically refractory epilepsy

Authors: *B. ELAHIAN[1], N. LADO[1], K. A. MOXON[2], A. MISRA[3], A. SHARAN[4], I. FRIED[5], M. YEASIN[6], J. ENGEL, Jr.[7], M. SPERLING[4], R. STABA[8], S. A. WEISS[1]
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Abstract: Objective:
Neuronal spiking activity during limbic seizure initiation and spread is highly heterogeneous, suggesting complex interactions among different types of neurons. In animal models of mesial temporal lobe epilepsy (MTLE), during spontaneous low-voltage fast (LVF) onset seizures, the firing rate of inhibitory interneurons increase, while the firing rate of principle neurons decrease and then rebound. We asked if spontaneous focal seizures in patients also exhibit similar changes in putative excitatory and inhibitory firing during LVF activity.
Method:
Seizure onset zone (SOZ) and non-SOZ regions were classified on the basis of visual inspection of macroelectrode recordings by a board certified epileptologist. We used wavelet clustering and

temporal autocorrelations to characterize single unit activity in the local field potential (LFP) of microelectrode recordings from limbic structures before and during LVF activity during spontaneous human seizures. LVF onset was confirmed by inspecting wavelet spectrograms of the LFP at seizure onset and denoting prolonged increases in beta (12-20 Hz) and gamma (20-80 Hz) power. LVF offset was selected when ictal clonic bursts appeared. Putative excitatory and inhibitory single units were distinguished on the basis of waveform morphology such as half width at half spike maximum (HWHM), and trough/peak amplitudes, as well as the autocorrelation function.
Result:
Preliminary data suggests that the shape of action potential waveforms was not altered during the transition to LVF ictal activity. For 191 implanted microelectrodes, we found 33 channels with 41 units. Of these 41 units 39% were in the SOZ. In the SOZ, a reduction in the firing rate of the putative principal cells was seen at the time of LVF onset. A rebound in the firing rate was seen in 46.3% of the neurons before the end of LVF. Some units exhibited an increase in firing rate during LVF activity and may be putative inhibitory neurons.
Significance:
The differential changes in firing between principal and non-principal cells suggest focal limbic seizures beginning with LVF activity correspond with an abnormal increase in inhibitory activity that initially suppresses and then subsequently recruits principal cells during seizure propagation.

Disclosures: B. Elahian: None. **N. Lado:** None. **K.A. Moxon:** None. **A. Misra:** None. **A. Sharan:** None. **I. Fried:** None. **M. Yeasin:** None. **J. Engel:** None. **M. Sperling:** None. **R. Staba:** None. **S.A. Weiss:** None.

Poster

205. Epilepsy: Human Studies - Seizure Analysis and Modelling

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 205.15/D26

Topic: B.11. Epilepsy

Support: NIH Grant NS100235

Title: Development of a wearable, EEG-based seizure diary for people living with epilepsy

Authors: *M. J. LEHMKUHLE[1,3], M. ELWOOD[2], J. WHEELER[2], J. MORRISON[2], R. LINGSTUYL[2], M. FRANKEL[2], F. DUDEK[4], M. WATSON[5], L. FREY[5], A. SHRESTHA[5], C. DREES[5], M. BROWN[5], P. KORB[5], L. STROM[5], M. SPITZ[5]
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Abstract: There is currently no quantitative means to track seizures in a person already diagnosed with epilepsy. Seizure diaries are incomplete and prone to error, while long hospitals stays in the wired EEG long-term monitoring unit (LTM) are expensive and impractical. We suggest that a miniature EEG system could provide long-term quantitative EEG in the everyday environment and would be a welcome tool for improving the quality of life and therapeutic options for those living with epilepsy. Epitel has developed a discrete, waterproof, patch-like device, Epilog^{TM}. Epilog is a wearable human interface that allows unrestricted mobility. Epilog is a 1-channel (2 electrode) differentially amplified transmitter and data logger. Epilog is used *after* seizure onset and propagation has been determined with traditional wired EEG. Prior knowledge of seizure foci through traditional multi-channel wired EEG will determine the most effective location(s) on the scalp for placement of one or more Epilog. To determine the efficacy of Epilog, we first seek to answer the question as to how well a single-channel of EEG can be used by epileptologists to identify (count) seizures in people with epilepsy. In this study, adults electively entered the EEG LTM unit at the University of Colorado for standard-of-care evaluation using video-EEG monitoring techniques. Four Epilogs were placed between wired EEG electrodes during EEG application. Only EEG form those patients who experienced at least one seizure were used. Seizures were identified as part of standard-of-care evaluation of full-montage EEG. For analysis, 5 min epochs of EEG from single-channel wired and Epilog were extracted. These data are shuffled with “catch trials” that consist of 5 min epochs of non-seizure EEG. Data are blinded as to (1) patient ID or seizure type, (2) electrode location, (3) seizure vs. non-seizure epoch, and (4) single-channel from traditional wired vs. Epilog. The epileptologist then analyzes the EEG using a GUI to answer the question: “Is this a seizure?” Initial analyses (68% complete) indicate that epileptologists are able to distinguish seizures on a single-channel of EEG with 72.2% accuracy for all seizure types, regardless if the single channel was from a wired electrode or Epilog. We will further determine accuracy for specific seizure types. Lastly, we will re-analyze the data for the real-world scenario where the epileptologists have prior knowledge of (1) who their patient is, (2) what their diagnosis was, (3) what their typical EEG seizure looks like, and (4) where Epilog was placed on the scalp. This interface will likely improve epileptologist performance at identifying seizures in single-channel EEG.

Disclosures: **M.J. Lehmkuhle:** A. Employment/Salary (full or part-time):; Epitel, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Epitel, Inc. **M. Elwood:** A. Employment/Salary (full or part-time):; Epitel, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Epitel, Inc. **J. Wheeler:** A. Employment/Salary (full or part-time):; Epitel, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Epitel, Inc. **J. Morrison:** A. Employment/Salary (full or part-time):; Epitel, Inc. **R. Lingstuyl:** A. Employment/Salary (full or part-time):; Epitel, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Epitel, Inc. **M. Frankel:** A. Employment/Salary (full or part-time):; Epitel, Inc. **F. Dudek:** F. Consulting Fees (e.g., advisory boards); Epitel, Inc.. **M. Watson:** None. **L. Frey:** None. **A. Shrestha:** None. **C. Drees:** None. **M. Brown:** None. **P. Korb:** None. **L. Strom:** None. **M. Spitz:** None.

Poster

205. Epilepsy: Human Studies - Seizure Analysis and Modelling

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 205.16/D27

Topic: B.11. Epilepsy

Support: NIH Grant R01NS079533

VA Grant I01RX000668

Pablo J. Salame '88 Goldman Sachs endowed Assistant Professorship of Computational Neuroscience at Brown University

Title: The role of slow ictal wavefronts and fast spike-and-wave discharges during propagation and termination of focal seizures

Authors: T. PROIX[1], V. K. JIRSA[2], *W. TRUCCOLO[1]
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Abstract: Recent studies have revealed a diversity of spatiotemporal patterns by which focal epileptic seizures spread outside of the seizure onset zone (SOZ) and evolve through neuronal networks across both local and distal brain regions. While a slow ictal wavefront spreads from a SOZ location, which tends to change little across seizures in a same patient, the source of faster traveling spike-and-wave ictal discharges can either move with the propagating ictal wavefront or remain stationary at the SOZ. In addition, focal seizures can terminate either in a quasi-synchronous or asynchronous fashion across brain areas. To provide a unifying perspective on the observed diversity of spatiotemporal dynamics for seizure propagation and termination, we introduce here the Epileptor neural field model. We highlight the multiscale dynamical mechanisms that play an essential role in supporting the spatiotemporal pattern diversity. These mechanisms, together with variations in short and long-range connectivity strength, play a central role on seizure initiation, spread, maintenance and termination. We demonstrate how the Epileptor field model predicts the previously reported diversity in seizure spread dynamics. In addition, we confirm the predictions for synchronous or asynchronous (clustered) seizure termination in human seizures recorded via stereotactic EEG. Our findings provide new insights into seizure spatiotemporal dynamics and may contribute to the development of new therapies for focal epilepsy.

Disclosures: **T. Proix:** None. **V.K. Jirsa:** None. **W. Truccolo:** None.

Poster

205. Epilepsy: Human Studies - Seizure Analysis and Modelling

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 205.17/D28

Topic: B.11. Epilepsy

Support: the John D. and Catherine T. MacArthur Foundation

the Alfred P. Sloan Foundation

the Army Research Laboratory and the Army Research Office through contract numbers W911NF-10-2-0022 and W911NF-14-1-0679

the National Institute of Mental Health (2-R01-DC-009209-11),

the National Institute of Child Health and Human Development (1R01HD086888-01)

the Office of Naval Research, and the National Science Foundation (BCS-1441502, BCS-1430087 and PHY-1554488)

Title: Seizure-onset assessment in ECoG via dynamical stability analysis

Authors: *A. ASHOURVAN[1,8], S. PEQUITO[2], S. N. BALDASSANO[3,4], A. KHAMBHATI[5,10], J. M. VETTEL[9,11], B. LITT[6,12,4], G. J. PAPPAS[7], D. S. BASSETT[3,4]
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Abstract: Understanding brain dynamics in epilepsy is critical for establishing rigorous control objectives that enable new therapeutic methods to mitigate seizure occurrence. In multichannel electrocorticography (ECOG) recordings acquired in 21 subjects during a total of 88 seizures, we apply dynamical systems stability analysis to assess the balance *versus* imbalance of the dynamics across different timescales and brain regions. Specifically, we consider a sliding time window multivariate autoregressive linear approximation of the data captured by the ECOG channels, where eigendecomposition of the estimated matrix of coefficients describes the contribution of different regions to the spatiotemporal process (eigenvectors) associated with a particular timescale (eigenvalues). Interestingly, we observe a pattern of eigenvalue evolution and slowly changing (or approximately time-invariant) eigenvectors across both seizures and

subjects. The seizure-onset is commonly marked by an increase in high frequency spatial information to which a few regions contribute for a long period. By contrast, the seizure termination is characterized by a sudden, small time period change in dynamics to which many regions contribute. Furthermore, seizures that generalize across the cortex exhibit abnormalities localized to a few regions that lead the underlying process at high spatiotemporal frequency. Our methodology offers a careful characterization of the spatiotemporal behavior of the seizure, providing new insights into the interplay between cortical regions at different timescales. More generally, our approach informs the development of objectives that can be used to deploy new control strategies to prevent seizure evolution or hasten seizure termination.

Disclosures: **A. Ashourvan:** None. **S. Pequito:** None. **S.N. Baldassano:** None. **A. Khambhati:** None. **J.M. Vettel:** None. **B. Litt:** None. **G.J. Pappas:** None. **D.S. Bassett:** None.

Poster

205. Epilepsy: Human Studies - Seizure Analysis and Modelling

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 205.18/D29

Topic: B.11. Epilepsy

Support: ANR-13-PRTS-0011 - Project “Vibrations”

Title: Modeling of epileptic high frequency oscillations recorded by clinical macro-electrodes

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Abstract: Context and objective. Pathological high-frequency oscillations (HFOs, 200-600 Hz) observed in depth-EEG recordings are recognized to be potentially valuable markers of the epileptogenic zone (EZ) responsible for seizures. However, the relationship between the EZ, on the one hand, and the features of HFOs as observed on intracranial multi-contact electrodes, on the other hand, is not straightforward and there is still a lack of understanding on the critical information that is carried by HFOs. In this study we aim to identify the key (patho)physiological mechanisms and biophysical factors which impact the observability of HFOs and which determine their morphological and spectral features. **Methods.** We combined novel computational models of neuronal populations with virtual brain and virtual electrode models in order to accurately replicate HFOs as observed on clinical macro-electrodes used in presurgical evaluation of patients with pharmaco-resistant epilepsy. Both (patho)physiological mechanisms (synaptic transmission, depolarizing $GABA_A$ effect, hyperexcitability) and physical factors (geometry of extended cortical sources, size and position of electrodes) were taken into account in the modeling approach. Extensive simulations and signal-processing-based quantitative comparison of real and simulated HFOs were performed. **Results.** For the first time, our results

revealed that HFO pathological activity is being generated by feed-forward activation of cortical interneurons that produce fast depolarizing GABAergic post-synaptic potentials (PSPs) onto pyramidal cells. Out of phase patterns of depolarizing GABAergic PSPs explained the shape, entropy and spatiotemporal features of real human HFOs. In addition, new insights regarding the observability of HFOs along clinical depth-EEG electrodes were gained in terms of spatial extent and 3D geometry of neuronal sources comprised in recorded cortical areas (open- vs. closed field configurations). Our results also strongly suggest that the terminology "high-frequency oscillation" (HFO) might be misleading as the fast ripple component (200-600Hz) is more likely a "high-frequency activity" (HFA), the origin of which is independent from any oscillatory process.

Disclosures: F. Wendling: None. **M. Shamas:** None. **A. Nica:** None. **I. Merlet:** None. **P. Benquet:** None.

Poster

205. Epilepsy: Human Studies - Seizure Analysis and Modelling

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 205.19/D30

Topic: B.11. Epilepsy

Support: National Institutes of Health (NIH: R01-NS092882 and R01-NS063039)

Czech Republic Grant agency (P103/11/0933)

European Regional Development Fund - Project FNUSA - ICRC (CZ.1.05/ 1.1.00/02.0123)

Title: Gamma activity in epileptic and non-epileptic brain during a verbal memory task

Authors: *F. KHADJEVAND, M. T. KUCEWICZ, B. BERRY, J. CIMBALNIK, V. KREMEN, L. MILLER, B. H. BRINKMANN, J. VAN GOMPEL, M. STEAD, G. A. WORRELL
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Abstract: Rationale
High-frequency oscillations (HFOs: 30-600 Hz) recorded during intracranial EEG (iEEG) have been proposed as biomarkers of epileptic brain tissue. Prior studies report 'task-related' ripple frequency HFOs (100 - 250 Hz) can be distinguished from ripple HFOs associated with interictal epileptiform spikes. Yet, whether this dichotomy between physiological and pathological HFO extends to 'task-related' gamma HFOs (γHFO: 30 - 100 Hz) remains unclear. Here we studied γHFO recorded during a verbal memory task within seizure onset zone (SOZ) and all other brain regions (NSOZ), to build a better understanding of how γHFO within epileptic tissue differ from

non-epileptic brain.
Methods
We used iEEG recorded during encoding of words in 11 epilepsy patients to analyze γHFO within SOZ and NSOZ. Patients were implanted with subdural and depth electrodes for prolonged iEEG monitoring as part of evaluation for drug-resistant epilepsy. Lists of twelve words were presented on a laptop (each for 1600ms) for subsequent recall. The iEEG signals were sampled at 500 Hz, and γHFO were detected in each trial using previously validated detectors. Spectral and time domain properties of each γHFO detection were determined. Detections in low gamma (30-55 Hz) and high gamma (65-100 Hz) frequency ranges were included for further analysis. The properties of γHFO detections during the word presentation interval were compared within SOZ and NSOZ electrodes in each subject, across all subjects, and in different brain structures.
Results
We observed higher maximum and mean amplitude (in 8/11 patients for the low γHFO and 7/11 patients in the high γHFO ($p<0.05$)), and longer duration (in 7/11 patients for the low γHFO, and 8/11 patients in high GA, ($p<0.05$)) in SOZ compared to NSOZ. When considering all electrodes from all patients the γHFO detections in SOZ had higher maximum amplitude ($p<0.001$), mean amplitude ($p<0.001$) and longer duration ($p<0.001$) than those in NSOZ.
Conclusions
γHFO events recorded during word encoding have higher amplitude and longer duration within the SOZ compared to NSOZ. The results support that the neuronal assemblies underlying tasks induced γHFO within the SOZ are pathologically synchronous and cognitive task may be useful for mapping both normal and pathological brain regions.

Disclosures: F. Khadjevand: None. **M.T. Kucewicz:** None. **B. Berry:** None. **J. Cimbalnik:** None. **V. Kremen:** None. **L. Miller:** None. **B.H. Brinkmann:** None. **J. Van Gompel:** None. **M. Stead:** None. **G.A. Worrell:** None.

Poster

205. Epilepsy: Human Studies - Seizure Analysis and Modelling

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 205.20/D31

Topic: B.11. Epilepsy

Support: NIH Grant NINDS K23 NS094633-01A1

Title: Bimodal coupling of ripples and slower oscillations during sleep in the frontal and parietal lobe of patients with medically refractory epilepsy

Authors: *I. SONG[1], I. OROSZ[5], I. CHERVONEVA[2], Z. J. WALDMAN[1], I. FRIED[6], C. WU[3], A. SHARAN[3], N. SALAMON[5], R. GORNIAK[4], S. DEWAR[5], A. BRAGIN[7], J. ENGEL, Jr.[8], M.

SPERLING[1], R. J. STABA[7], S. A. WEISS[1]
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Abstract: In patients with epilepsy, high-frequency oscillations in the ripple band (80-150 Hz) occur during the transitional periods between the up and down state of slow waves. The preferred phase angles of this form of phase event amplitude coupling are bimodally distributed, and the ripples that occur during the up-down transition are generated more often in the seizure onset zone (SOZ). We investigated if ripple event amplitude was also bimodally coupled to two phases of faster sleep oscillations (delta [2-4 Hz], theta [4-10 Hz], and spindle [12-16 Hz]), and if the preferred phase angles of coupling could be utilized to identify the SOZ. Using an automated ripple detector, we identified all ripple events in 40-60 minute iEEG recordings from 23 patients with medically refractory mesial temporal lobe or neocortical epilepsy. The detector quantified epochs of sleep oscillations and computed instantaneous phase. We utilized a ripple phasor transform, ripple-triggered averaging, and circular statistics to investigate phase event-amplitude coupling. We found that at some individual recording sites, ripple event amplitude was coupled with sleep oscillatory phase and the preferred phase angles exhibited two distinct clusters ($p<0.05$). Other recording sites exhibited coupling with just one cluster of preferred phase angles ($p<0.05$). At recording sites within parietal and frontal lobe SOZs, bimodal coupling (i.e., two clusters) was more prevalent, as compared with sites in the surrounding NSOZ. The distribution of the pooled mean preferred phase angle, defined by combining the means from each cluster at each individual recording site, also exhibited two distinct clusters ($p<0.05$). Based on the range of preferred phase angles defined by these two clusters, we partitioned each ripple event at each recording site in to two groups: depth peak-trough and trough-peak. The mean ripple rates of the two groups in the SOZ and NSOZ were compared using a repeated measures zero-inflated negative binomial generalized estimated equation model. We found that in the frontal (spindle, $p=0.009$; theta, $p=0.006$, slow, $p=0.004$) and parietal lobe (delta, $p=0.002$, slow, $p=0.001$) the SOZ incidence rate for the ripples occurring during the trough-peak transition was significantly increased. Our findings support prior work demonstrating, in patients with frontal and parietal lobe focal epilepsy, that ripples that occur during the up-down transition slow waves are putatively pathological. In addition, we conclude that ripples that occur during the trough-peak of delta, theta, and spindle-band oscillations are also putatively pathological.

Disclosures: I. Song: None. **I. Orosz:** None. **I. Chervoneva:** None. **Z.J. Waldman:** None. **I. Fried:** None. **C. Wu:** None. **A. Sharan:** None. **N. Salamon:** None. **R. Gorniak:** None. **S. Dewar:** None. **A. Bragin:** None. **J. Engel:** None. **M. Sperling:** None. **R.J. Staba:** None. **S.A. Weiss:** None.

Poster

205. Epilepsy: Human Studies - Seizure Analysis and Modelling

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 205.21/D32

Topic: B.11. Epilepsy

Support: NIH grant NS094399

Doris Duke Charitable Foundation

Title: Removing electromyographic activity-related events improves the accuracy of intracranial high frequency oscillations as biomarker for epilepsy

Authors: *S. REN[1], S. GLISKE[2], W. C. STACEY[3]
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Abstract: Rationale
Though intracranial EEG is often assumed to be free of artifacts, accumulating evidence suggests that it is susceptible to non-cerebral electrical sources such as eye movement and electromyography (EMG) activity. While these artifacts are much less prominent than on scalp EEG, the intracranial appearance of EMG as low-amplitude, high-frequency, sporadic events makes it resemble high frequency oscillations (HFOs), a promising new biomarker for epilepsy. Thus, EMG activity may create false positive HFO detections that are very difficult to identify if only intracranial EEG is recorded. This work aims to evaluate the clinical significance of EMG-derived intracranial HFOs in the context of seizure onset zone localization and to develop strategies to remove those false HFOs automatically.
Method
20 patients with simultaneous scalp and intracranial EEG recordings lasting for multiple days are included in this study. Interictal HFOs were obtained by running a previously-validated automated detector on intracranial EEG, and a novel EMG detector was used to identify EMG activity on scalp EEG. Intracranial HFOs coincident with scalp EMG were labeled as 'false-EMG' HFOs, and verified by visual review. In order to identify false-EMG HFOs in the absence of scalp EEG, we trained a classifier on those labeled events and performed leave-one-out cross validation across multiple patients. The impact of EMG contamination was evaluated by computing the percentage of false-EMG HFOs, redacting them, and comparing the spatial distribution of interictal HFO rates before and after the removal.
Results
False-EMG classification on intracranial EEG had 80%-95% agreement with scalp EEG labels. All 20 patients had false-EMG HFOs, ranging from 1-40% of their total HFOs. For some patients, EMG contamination had led to poor localization of the seizure onset zone, and redaction of those false-EMG HFOs led to a different spatial distribution of detected interictal

HFOs that was more strongly associated with the clinically-defined seizure onset zone.
Conclusion
Our results suggest that EMG contamination of intracranial EEG is more ubiquitous than commonly expected and can distort the relationship between HFOs and epileptic network. This algorithm successfully removes false-EMG HFOs, which assures the remaining HFOs are more likely to be physiological and improve their accuracy as a biomarker for epilepsy.

Disclosures: S. Ren: None. **S. Gliske:** None. **W.C. Stacey:** None.

Poster

205. Epilepsy: Human Studies - Seizure Analysis and Modelling

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 205.22/D33

Topic: B.11. Epilepsy

Title: A GUI-based platform for human brain functional mapping in epilepsy patients

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Abstract: Direct electrical stimulation (DES) has been considered the “gold standard” for brain functional mapping both extraoperatively and intraoperatively for patients undergoing brain surgeries in close vicinity to eloquent areas. However, the lack of clinical research tools for data collection, visualization, and sharing has prevented the use of these data in understanding the reorganization of human brain functional networks in epilepsy patients. In this study, we developed a new platform to address above-mentioned issues for human brain functional mapping based on DES. A total of 53 patients’ mapping results (2004-2017) were obtained for this study. To localize the intracranial electrode locations, the co-registrations between pre-op MRI and post-op CT were performed using our toolbox. The electrodes’ coordinates were transformed into MNI space. The neurologists’ hand-written notes were entered into the program by research assistants, EEG/LTM technicians, and neurologists. Data entry was conducted in a GUI-based application developed in Matlab. All mapping results can be visualized in both patient-specific MRI space and MNI standardized space and would be updated in the database, where users could search for a certain function and see how it is distributed in the MNI brain in comparison to the patient’s brain. The application could also provide a clinical reference for stimulation currents which have been applied to previous patients and produced observable responses within various anatomical areas. This new platform could be a very useful clinical and

educational tool for anyone interested in human brain mapping. Furthermore, the adaptation of this GUI-based platform could be used to compile datasets across institutions under a single framework, which is not practical with current clinical practices.

Electrode +	MRI Coordinates	MNI Coordinates	Electrode -	MRI Coordinates	MNI Coordinates	Function	Comment	Time
UHG01	1.68, -30.97, 21.67	1.37, -35.63, 33.41	UHG02	2.30, -20.59, 23.70	2.20, -24.49, 35.48	No Response	7.5 mA	3/20/2017 9:40
UHG02	2.30, -20.59, 23.70	2.20, -24.49, 35.48	UHG03	3.86, -10.25, 24.66	3.00, -13.52, 36.22	No Response	9.5 mA	3/20/2017 9:40
UHG03	3.86, -10.25, 24.66	3.00, -13.52, 36.22	UHG04	4.43, 0.23, 25.69	3.79, -2.38, 37.04	SMA	3 mA	3/20/2017 9:41
UHG03	3.86, -10.25, 24.66	3.00, -13.52, 36.22	UHG04	4.43, 0.23, 25.69	3.79, -2.38, 37.04	Right Arm Twitching	3 mA	3/20/2017 9:41
UHG03	3.86, -10.25,24.66	3.00, -13.52, 36.22	UHG04	4.43, 0.23, 25.69	3.79, -2.38, 37.04	Right Leg Twitching	3 mA	3/20/2017 9:42
UHG04	4.43, 0.23, 25.69	3.79, -2.38, 37.04	UHG05	3.67, 9.58, 24.62	3.16, 7.37, 35.33	Bilateral Arm Response	2.5 mA	3/20/2017 9:42
UHG04	4.43, 0.23, 25.69	3.79, -2.38, 37.04	UHG05	3.67, 9.58, 24.62	3.16, 7.37, 35.33	Bilateral Leg Response	2.5 mA	3/20/2017 9:42
UHG05	3.67, 9.58, 24.62	3.16, 7.37, 35.33	UHG06	3.13, 20.42, 23.69	2.80, 18.7, 33.72	Right Hand Movement	8.5 mA	3/20/2017 9:42
UHG05	3.67, 9.58, 24.62	3.16, 7.37, 35.33	UHG06	3.13, 20.42, 23.69	2.80, 18.7, 33.72	Left Hand Movement	8.5 mA	3/20/2017 9:43
UHG05	3.67, 9.58, 24.62	3.16, 7.37, 35.33	UHG06	3.13, 20.42, 23.69	2.80, 18.7, 33.72	Bilateral Hand Movement	8.5 mA	3/20/2017 9:43
UHG06	3.13, 20.42, 23.69	2.80, 18.7, 33.72	UHG07	2.31, 29.87, 21.62	2.14, 28.46, 30.75	Bilateral Hand Movement	9.5 mA	3/20/2017 9:43
UHG07	2.31, 29.87, 21.62	2.14, 28.46, 30.75	UHG08	0.44, 39.58, 18.60	1.44, 38.40, 26.61	Bilateral Hand Movement	8.5 mA	3/20/2017 9:43
UHG09	1.41, -30.37, 31.97	1.56, -33.94, 46.11	UHG10	2.03, -19.98, 34.00	0.66, -22.79, 48.19	Right Arm Movement	3.5 mA	3/20/2017 9:44
UHG09	1.41, -30.37, 31.97	1.56, -33.94, 46.11	UHG10	2.03, -19.98, 34.00	0.66, -22.79, 48.19	Bilateral Leg Movement	3.5 mA	3/20/2017 9:44
UHG10	2.03, -19.98, 34.00	0.66, -22.79, 48.19	UHG11	2.59, -9.50, 35.03	1.46, -11.65, 49.00	Right Arm Movement	3.5 mA SMA	3/20/2017 9:45
UHG10	2.03, -19.98, 34.00	0.66, -22.79, 48.19	UHG11	2.59, -9.50, 35.03	1.46, -11.65, 49.00	Bilateral Leg Movement	3.5 mA SMA	3/20/2017 9:45
UHG10	2.03, -19.98, 34.00	0.66, -22.79, 48.19	UHG11	2.59, -9.50, 35.03	1.46, -11.65, 49.00	SMA	3.5 mA SMA	3/20/2017 9:45
UHG11	2.59, -9.50, 35.03	1.46, -11.65, 49.00	UHG12	2.10, 1.23, 35.10	1.13, -0.33, 48.65	Right Arm Extension	3.5 mA	3/20/2017 9:46

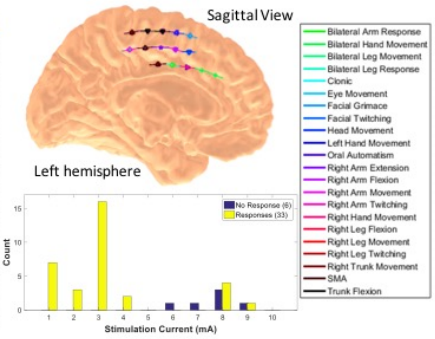

Fig. Patient-specific functional mapping report (in Excel) and figure.

Disclosures: **Y. Song:** None. **M.A. Gorenstein:** None. **K.C. Hartstein:** None. **P.U. Tse:** None. **D.W. Roberts:** None. **J. Hong:** None. **K.A. Bujarski:** None. **E.J. Kobylarz:** None. **V.M. Thadani:** None. **G.P. Thomas:** None. **B.C. Jobst:** None.

Poster

205. Epilepsy: Human Studies - Seizure Analysis and Modelling

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 205.23/D34

Topic: B.11. Epilepsy

Title: Role of ictal brain SPECT in refractory epilepsy in comparison with MRI and EEG - Experience from a tertiary center in southern India

Authors: *J. HEPHZIBAH, M. M. THOMAS, D. MATHEW, N. SHANTHLY
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Abstract: Brain Single Photon Emission Computed Tomography (SPECT) is useful in the preoperative planning for medically refractory epilepsy and to identify the lateralization and localization of an epileptogenic focus before surgery. Nuclear medicine functional neuroimaging techniques can actively improve decision-taking process in complex cases of epilepsy. Data of patients with refractory epilepsy between 2014-16 were analysed. All patients were on more than 2 antiepileptic drugs. Electro encephalogram (EEG) and Magnetic resonance imaging (MRI) was done for all and whenever necessary MRI was fused with SPECT images for anatomical localization to assist for exact surgical excision if warranted. Tc99m ECD was injected during or within 20 seconds of seizure activity onset. Interictal images was interpreted in conjunction with ictal images whenever possible. Fifty three patients between age group from 1 -21 years were

studied. These patients underwent ictal brain SPECT (IBS), MRI and EEG. The concordance of ictal brain SPECT was compared with MRI and EEG. Of these 53 patients 10 (18.8%) underwent surgical excision of the epileptogenic zone (EZ), 4 was concordant with MRI and SPECT with unifocal activity and one was SPECT negative but MRI positive, 2 were MRI negative, 3 had multifocal uptake in SPECT and gliosis in MRI; and EEG was normal in 3 and multifocal in 7. Of the 10 who underwent surgery the biopsy of 3 was reported as focal cortical dysplasia, 2 astrocytosis, 1 gliosis and 4 as mild oligodendroglial hypercellularity with ischemic changes in neurons respectively. Fifty one patients showed tracer uptake in IBS out of which 16 (31%) patients had multifocal uptake and 35 (69%) had unifocal uptake in the EZ. Of the 35 patient with unifocal uptake, EEG and MRI was negative in 6 and 18 patients respectively. MRI was concordant with unifocal site in IBS in 9 (26%) patients and EEG in two (6%) patients. Ictal brain SPECT is a useful imaging modality to localize epileptogenic zone and is complementary to MRI and EEG in refractory epilepsy. Depending exclusively on EEG and MRI will limit the diagnosis of a definitive epileptogenic focus.

Disclosures: J. Hephzibah: None. **M.M. Thomas:** None. **D. Mathew:** None. **N. Shanthly:** None.

Poster

205. Epilepsy: Human Studies - Seizure Analysis and Modelling

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 205.24/D35

Topic: B.11. Epilepsy

Support: MRC grant G0301067

Wellcome Trust grant 101092/Z/13/Z

Title: Automated classification and quantification of human epileptic spikes for the purpose of modelling simultaneously acquired intracranial EEG-fMRI

Authors: *N. SHARMA[1], C. PEDREIRA[2], M. CENTENO[1], U. J. CHAUDHARY[1], D. W. CARMICHAEL[3], T. YADEE[1], T. MURTA[1], M. LEITE[1], B. DIEHL[1], L. LEMIEUX[1]
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Abstract: Purpose: Haemodynamic correlates of interictal epileptiform discharges (IEDs) can provide useful information regarding the regions of the brain responsible for generating IEDs (the irritative zone). To better understand the region responsible for the generation of IEDs, it is important to classify IEDs consistently. We propose using automated IED classification and

quantification to increase the reliability and sensitivity of IED-related BOLD models.
Method: We analysed data from five patients (4 Male; 1 Female) with severe drug-resistant epilepsy that underwent simultaneous intracranial EEG-fMRI. For each patient two fMRI analyses were performed, one based on the visual classification of IEDs and one based on automated classification and quantification of IEDs. A modified version of an automated spike classification algorithm, Wave_clus (WC), was used to automatically classify IEDs based on their field distribution and waveforms. The width of the sharp wave of each IEDs was measured and used as a parametric effect in a general linear model to map BOLD changes over the entire brain. In summary the concordance level for each IED-related BOLD map was assessed using the following criteria: concordant if a BOLD cluster was present in the epileptogenic zone; discordant if there was no cluster present in the epileptogenic zone.
Results: Across all subjects the number of IED classes identified were 14 and 20 for the automated and expert EEG reviewer, respectively. The BOLD maps for the automated classification-based model were more concordant with the epileptogenic zone compared to the visually classified-based model.
Conclusion: The automated classification and quantification of IEDs is an efficient tool to assist mapping IED-related BOLD changes and can be used to assess brain networks associated with IEDs.

Disclosures: **N. Sharma:** None. **C. Pedreira:** None. **M. Centeno:** None. **U.J. Chaudhary:** None. **D.W. Carmichael:** None. **T. Yadee:** None. **T. Murta:** None. **M. Leite:** None. **B. Diehl:** None. **L. Lemieux:** None.

Poster

205. Epilepsy: Human Studies - Seizure Analysis and Modelling

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 205.25/D36

Topic: B.11. Epilepsy

Support: NS064571

UL1TR000135

Title: Systemic markers of inflammation and neuronal injury in patients with epilepsy

Authors: *S. KUNDA, R. LAFRANCE-COREY, F. KHADJEVAND, G. WORRELL, C. L. HOWE
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Abstract: Epilepsy is a chronic neurologic disorder characterized by recurrent seizures and variable cognitive and neurodevelopmental issues. In many individuals the underlying

pathogenesis is unknown, but burgeoning evidence indicates a link between neuroinflammation and seizure development. Therapeutically targeting inflammation in epilepsy is of particular interest for patients that do not respond to the current standard of care. Likewise, identifying changes in peripheral immune status may provide a unique biomarker for seizure prediction. Using high-resolution repeated measures temporal profiling of serum cytokine levels and flow cytometric analysis of the activation status of circulating neutrophils and monocytes, we established an immune profile for patients undergoing multi-day continuous video-EEG monitoring. We identified an apparent temporal correlation between clinical seizure events and increased levels of serum CCL2, as well as evidence of acute peri-ictal changes in the status of inflammatory monocytes ($CD14^{++}CD16^{+}$ and $CD14^{+}CD16^{++}$) in 4 patients. We also measured acute peri-ictal changes in a marker of neuronal injury in these patients. Ongoing studies will correlate patient immune status with neuronal injury markers and attempt to incorporate analysis of sub-clinical EEG changes with the immunophenotype.

Disclosures: S. Kunda: None. **R. LaFrance-Corey:** None. **F. Khadjevand:** None. **G. Worrell:** None. **C.L. Howe:** None.

Poster

205. Epilepsy: Human Studies - Seizure Analysis and Modelling

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 205.26/D37

Topic: B.11. Epilepsy

Support: Academy of Finland, grant #234772

JAE Foundation grant

Title: Mapping interictal MREG signal variance abnormality in intractable epilepsy

Authors: *J. KANANEN[1], T. TUOVINEN[1], H. ANSAKORPI[2], V. KORHONEN[1], V. RAATIKAINEN[1], N. HUOTARI[1], H. HELAKARI[1], A. RASILA[1], V. KIVINIEMI[1]
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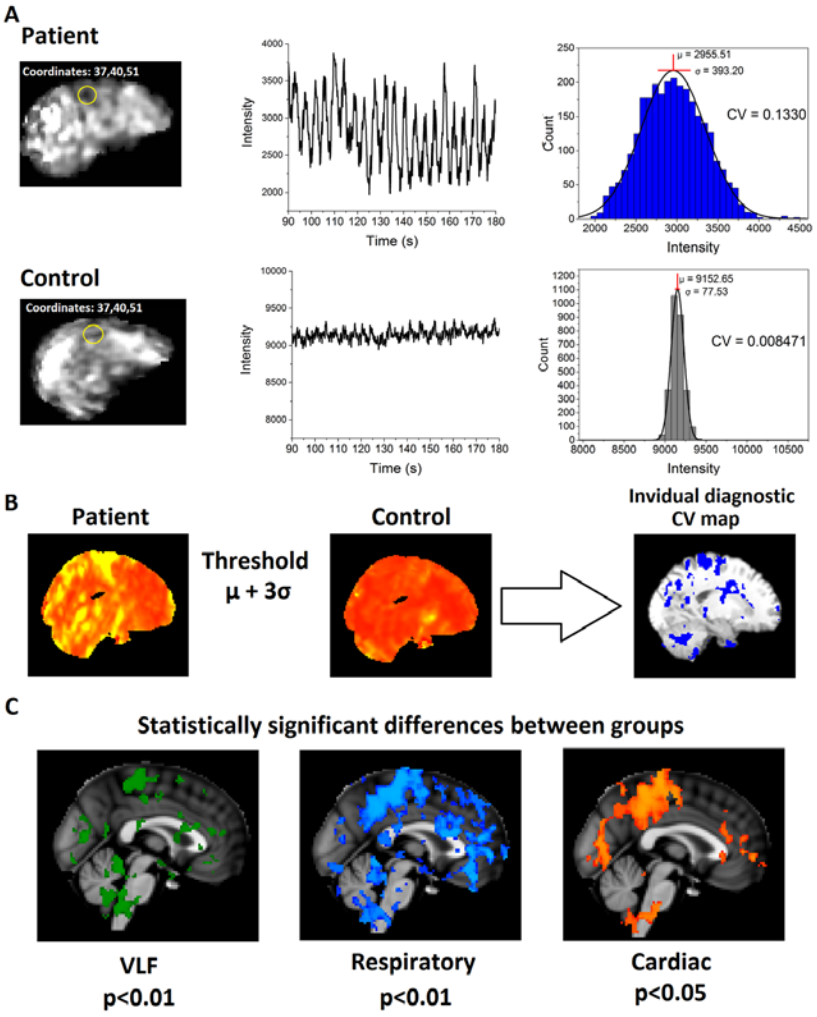
Abstract: Introduction: Magnetic resonance encephalography (MREG) enables precise detection of epileptic spike activity[1,2]. We estimated if MREG signal coefficient of signal variance (CV)[3] could detect abnormal interictal activity in intractable epilepsy (IE).
Methods: After informed consent 10 healthy and 10 IE subjects, were imaged using Siemens 3T Skyra MREG-sequence (TR=100ms, TE=36 ms, FA=25º, FOV= $(192\ mm)^3$, $(3\ mm)^3$ voxel) for 5-min. Standard FSL pre-processing[4] with FIX-ICA, was used[5]. The data was band-pass filtered to very low frequency (VLF = 0.009-0.1 Hz), respiratory (0.12-0.4 Hz) and cardiac (0.9-1.5 Hz) for physiological estimation.

Voxel-wise CV is calculated as, CV = σ/μ, where μ = signal mean and σ = standard deviation, Fig 1 A. Voxel wise control group (μ+3σ) CV value was used to threshold IE data, Fig 1 B. Data from two consecutive IE patient scans data were merged to show repeated supra-threshold changes. FSL randomise (TFCE, 10 000 permutations) was used to evaluate statistical group differences, Fig 1.C.

Results: Each IE patient showed repeatedly elevated CV above μ+3σ threshold, an example shown in Fig.1 B. The CV elevation predominated in periventricular grey and white matter, thalami and brain stem. Fig.1C. Respiratory band had most prominent changes, followed by VLF and cardiac bands, Fig 1 C. Neither physiological signals (heart & respiration rate) nor brain motion (relative and absolute) explained the differences.

Conclusions: The MREG signal variation is significantly increased in patients with intractable epilepsy compared to matched controls. Notably the CV change is repeated in two consecutive scans 3 standard deviations above control mean value. CV mapping shows potential for individual diagnostics in the absence of ictal activity. Increased respiratory and VLF band noise characteristics suggest abnormality in brain pulsations mechanisms in intractable epilepsy.



1. Jacobs et al. NeuroImage 2014, 2. Korhonen et al., BrainConnect 2014, 3. Jahanian et al., PLoS One 2014, 4. Jenkinson et al., NeuroImage 2012, 5. Griffanti et al., NeuroImage 2014

Disclosures: **J. Kananen:** None. **T. Tuovinen:** None. **H. Ansakorpi:** None. **V. Korhonen:** None. **V. Raatikainen:** None. **N. Huotari:** None. **H. Helakari:** None. **A. Rasila:** None. **V. Kiviniemi:** None.

Poster

205. Epilepsy: Human Studies - Seizure Analysis and Modelling

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 205.27/D38

Topic: B.11. Epilepsy

Title: Efficacy and tolerability of perampanel in refractory epilepsy

Authors: D. BARR[1], R. CASTILLO[2], *B. F. KIRMANI, ESQ[4,3]
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Abstract: Epilepsy is a seizure disorder that affects approximately 1.2 million Americans. 30% of these individuals remain medically intractable. Patients who have failed multiple classes of antiepileptic drugs (AEDs) and/or surgical procedures, newly FDA-approved drugs are of particular interest. Perampanel is an orally active, non-competitive AMPA-type glutamate receptor antagonist approved in >40 countries, including the US and in the EU, for adjunctive treatment of refractory seizures based on the efficacy and safety results of the 3 Phase III double-blind studies. Perampanel was shown to reduce seizure frequency in patients receiving 1-3 concomitant AEDs. The current subanalysis evaluates the efficacy and safety of Perampanel by baseline AEDs in subjects with uncontrolled seizures.Methods: A retrospective chart review was conducted on patients who were 12 years of age or older who were treated with perampanel at Scott and White Hospital/TexasA & M HSC College of Medicine, Temple, TX. Subject data were acquired from electronic medical records. Approval of this retrospective analysis was given by our hospital's Institutional Review Board. Patient demographics included age, gender, epilepsy type, and concomitant and failed anticonvulsants and seizure frequency. Outcome measures were efficacy and tolerability of perampanel. Results: We retrospectively analyzed 18 patients who met our inclusion criteria. There were 12 males (66%) and 6 females (33%). The age range for all patients was 14-75 years. 12 (66%) had partial epilepsy and 6 (33%) had generalized epilepsy. 3 (17%) of patients were on 0-1 AED before starting perampanel, 13(72.2%) were on 1-3 AEDs, and 2 (11.1%) were on 4 or more AEDS prior to starting perampanel. The starting dose of perampanel was 2-4 mg daily. The primary objective was to assess response based on patient reported seizure frequency and side effects. Response to perampanel was reduction of seizure frequency in 12 (66.6 %) of 18 patients, 3 (16.6%) patients

reported no change, and 3 (16.6%) patients reported increased seizure frequency. 8 patients (44.4%) were tapered off perampanel due to side effects. dose range before discontinuation of perampanel was 4mg-8mg daily. The major reason of discontinuation were aggressiveness or behavioral complaints seen in 5 patients (27.7 %). The other side-effects were sedation, dizziness and ineffectiveness respectively. The patients are followed in the epilepsy clinic from 3 months to a year. Conclusions: Perampanel has shown to be beneficial in patients with partial and generalized epilepsy as adjunctive therapy. However, the study is limited due to the small sample size and behavioral side-effects.

Disclosures: D. Barr: None. **R. Castillo:** None. **B.F. Kirmani:** None.

Poster

206. Astrocytes: Disease Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 206.01/D39

Topic: B.12. Glial Mechanisms

Support: NIH Grant R01 NS088260

Title: Exploring the effect of DBS-like high frequency electrical stimulation on human astrocytes through single cell RNA sequencing

Authors: *S.-Y. CHANG[1], J. JANG[6], C. CHOI[2], J. YI[7], I. KIM[3], K. BUTTERS[4], A. BHAGWATE[5], J. JEN[6]
[2]Dept. of Physical Med. and Rehabil., [3]Neurol., [4]Anatom. Pathology, [5]Bioinformatics Core, [1]Mayo Clin., Rochester, MN; [6]Med. Genome Facility, Mayo Clilnic, Rochester, MN; [7]Neurosci. Program, Pomona Col., Claremont, CA

Abstract: Deep brain stimulation (DBS) is a neurosurgical treatment for movement disorders and other neurologic diseases, whose therapeutic benefits have demonstrated potential of electrical stimulation to become an integral part of medicine. DBS is thought to modulate pathological neural activity; although astrocytes, the most numerous cell type in the brain, play a significant role in neurotransmission, chemical homeostasis and synaptic plasticity, the role of astrocytes in DBS mechanism has not been fully examined. In this study, to investigate astrocytic functions in DBS, we applied DBS-like high frequency electrical stimulation *in vitro* to human astrocytes and used single-cell RNA-Seq analysis. We observed that DBS-like high frequency stimulation negatively impacts astrocyte metabolism and promotes the release of matricellular proteins, including IGFBP3, GREM1, IGFBP5, THBS1, and PAPPA. Our results suggest that astrocytes are involved in long-term modulation of perineuronal environments, and that they may influence persistent cell-to-cell interaction and help maintain neuromodulation over time.

Disclosures: **S. Chang:** None. **J. Jang:** None. **C. Choi:** None. **J. Yi:** None. **I. Kim:** None. **K. Butters:** None. **A. Bhagwate:** None. **J. Jen:** None.

Poster

206. Astrocytes: Disease Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 206.02/D40

Topic: B.12. Glial Mechanisms

Support: DRDO

ICMR

Title: Role of connexin 43 in hypobaric hypoxia induced glutamte excitotoxicity in rat hippocampus

Authors: *A. DHEER[1], V. JAIN[1], M. PANT[2], N. KUSHWAH[1], R. KUMAR[1], D. PRASAD[1], P. SETH[2], S. SINGH[3]
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Abstract: Introduction: Ascend to high altitude encounters a decrease in atmospheric pressure resulting in low O_2 availability to the tissues. Such a condition is referred to “Hypobaric Hypoxia”. The Brain being most vulnerable to oxygen deprivation is reported to be one of the first organs to be affected. HH has severe effects on the central nervous sytem. Neuronal apoptosis, glutamate excitotoxicity, oxidative stress and cognitive decline have been associated with hypobaric hypoxia. The extent of damage is a direct effect of the degree and duration of hypoxic exposure. Owing to the significance of glial cells in monitoring various vital brain functions the present study was carried out to understand the role of glial cells in HH condition.
Material and methods: The study was carried out in-vivo using healthy male Sprague Dawley rats weighing 200-230gms. They were subjected to hypobaric hypoxia in an animal decompression chamber housed in the institute. During the exposure atmosphere pressure was maintained equivalent to 25000ft altitude whereas temperature and humidity were maintained at 25°C and 56% respectively.
Results: Our results have suggested that HH induced glutamate excitotoxicity is due to the reduced glial glutamate transporter (GLT-1/EAAT2) expressed abundantly in astrocytes on chronic exposures to HH. We also looked into the mechanism of glutamate increase and study suggests that it could be accounted for by upregulated Connexin43 which form hemichannels and gap junction in the cells.
Conclusion: These findings reflect that upon chronic exposure to hypoxia the astrocytes instead

of protecting the brain add to neurodegeneration thereby leading to cognitive decline. HH mediated neurodegeneration can be associated with glutamate excitotoxicity. The study highlights the role of astrocytes in HH. Therefore, further investigation needs to be done to understand the neuro-glial interactions under HH which can provide an insight to several other neurodegenerative disorders.

Disclosures: A. Dheer: None. **V. Jain:** None. **M. Pant:** None. **N. Kushwah:** None. **R. Kumar:** None. **D. Prasad:** None. **P. Seth:** None. **S. Singh:** None.

Poster

206. Astrocytes: Disease Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 206.03/D41

Topic: B.12. Glial Mechanisms

Support: NIMH

Novo Nordisk Foundation

Title: Astroglial differentiation block in childhood-onset schizophrenia may be relieved by suppression of REST and TGFB/SMAD4-dependent signaling

Authors: *Z. LIU[1], M. OSIPOVITCH[2], J. BATES[1], D. CHANDLER-MILITELLO[1], M. NEDERGAARD[1,2], M. WINDREM[1], A. BENRAISS[1], P. TESAR[3], S. GOLDMAN[1,2,4]
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Abstract: Astrocytic differentiation is developmentally impaired in a proportion of patients with childhood-onset schizophrenia. To define the basis for this apparent impediment to terminal glial differentiation, we generated glial progenitor cells (GPCs) from induced pluripotent stem cells (iPSCs) derived from both schizophrenia (SCZ) and control (CTL) patients, assessed their differential expression of signal effectors involved in glial differentiation, and used a combination of shRNAi and pharmacological knock-down strategies to establish the causal role of several differentially expressed transcriptional regulators in SCZ-associated glial differentiation defects. We found that TGFβ signaling was significantly upregulated in SCZ GPCs, and that this sustained GPCs at the progenitor stage. Similarly, the nuclear repressor REST was relatively upregulated in SCZ hGPCs, contributing to the inhibition of terminal glial differentiation. In accord with their disrupted differentiation, potassium channel-associated gene expression and potassium uptake were deficient in SCZ astrocytes, compared to that in CTL glia.

Knockdown of SMAD4, a downstream effector of TGFB signaling, then rescued normal astroglial differentiation by SCZ hGPCs, as did REST knockdown; each of these significantly promoted both potassium-associated gene expression and rescued astroglial potassium uptake. These data suggest that the astrocytic differentiation defects in childhood-onset SCZ and their attendant disruption in brain potassium homeostasis, each of which may contribute significantly to SCZ pathogenesis, may both be rescued by targeting TGFB/SMAD4 and REST-dependent transcription.

Disclosures: Z. Liu: None. **M. Osipovitch:** None. **J. Bates:** None. **D. Chandler-Militello:** None. **M. Nedergaard:** None. **M. Windrem:** None. **A. Benraiss:** None. **P. Tesar:** None. **S. Goldman:** None.

Poster

206. Astrocytes: Disease Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 206.04/D42

Topic: B.12. Glial Mechanisms

Support: NIH R01 NS052741

NMSS RG4958

Mayo Clinic Center for Regenerative Medicine

Title: Astrocyte heterogeneity across the brain and spinal cord occurs developmentally, in adulthood and in response to demyelination

Authors: *H. YOON[1,2], G. WALTERS[1], A. PAULSEN[1], I. A. SCARISBRICK[1,2,3]
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Abstract: Astrocytes have emerged as essential regulators of function and response to injury in the brain and spinal cord, yet very little is known about fundamental differences that may exist between those located in each region. Here we directly compare brain and spinal cord astrocytes in terms of their expression of key astroglial markers (glial fibrillary acidic protein (GFAP) and Aldehyde Dehydrogenase-1 Family Member L1 (ALDH1L1)) across these disparate poles of the neuraxis, tracking their expression developmentally and in the context of demyelination. In addition, we document changes in the astrocyte regulatory cytokine interleukin 6 (IL-6), and its signaling partner signal transducer and activator of transcription 3 (STAT3), *in vivo* and *in vitro*. Specifically, we quantified expression levels of each in the intact brain and spinal cord developmentally, in purified cortical or spinal cord astrocytes cultures, and in the context of a demyelinating injury in adult corpus callosum or spinal cord white matter. Results demonstrate

that GFAP protein and RNA levels were higher in both the developing and adult spinal cord relative to whole brain. Comparisons between GFAP and ALDH1L1 expression suggest that elevations in spinal cord GFAP during the early postnatal period reflect an accelerated appearance of astrocytes as defined by ALDH1L1, while GFAP/ALDH1L1 ratios suggest that elevations in the adult spinal cord likely reflect higher levels of expression by individual astrocytes. Notably, increases in spinal cord compared to whole brain GFAP were paralleled by higher levels of IL-6 and STAT3. Equivalent elevations in GFAP, GFAP/ALDH1L1 ratios, and in IL-6, were observed in primary astrocyte cultures derived from spinal cord compared to cortex. Also, significantly higher levels of astrocyte reactivity 2 weeks after lysolecithin-induced demyelination was observed in spinal cord white matter compared to corpus callosum. Altogether, these studies point to key differences in astrocyte abundance and the expression of GFAP and IL-6 across the brain and spinal cord that are positioned to influence regional specialization developmentally and responses occurring in the context of CNS white matter injury and disease.

Disclosures: H. Yoon: None. **G. Walters:** None. **A. Paulsen:** None. **I.A. Scarisbrick:** None.

Poster

206. Astrocytes: Disease Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 206.05/D43

Topic: B.12. Glial Mechanisms

Support: NIH/NINDS Grant NS079637 (DMW)

Title: Astrocytic end-foot degeneration as a key mediator of vascular cognitive impairment and dementia

Authors: *B. R. PRICE[1], T. L. SUDDUTH[3], E. M. WEEKMAN[1], D. M. WILCOCK[2]
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Abstract: Background:
Vascular cognitive impairment and dementia (VCID) is the second leading cause of dementia behind Alzheimer's disease (AD). In addition, VCID is a frequent co-morbidity with AD, complicating the diagnosis and treatment of AD for a significant proportion of AD patients. Despite its prevalence, VCID remains relatively understudied compared to AD, and little is known about the molecular mechanisms underlying the cognitive dysfunction resulting from cerebrovascular disease.
The astrocytic end-feet almost completely surround intraparenchymal blood vessels in the brain and express a variety of channels and markers indicative of their specialized functions in the

maintenance of ionic and osmotic homeostasis and gliovascular signaling. The channels enriched at the astrocytic end-feet are the aquaporin 4 water channel (AQP4), the inward rectifying potassium channel Kir4.1 and the calcium-dependent potassium channel BK. Our lab has previously shown decreased expression of these end-feet channels in a mouse model of VCID, and are now examining them in an AD/VCID co-morbidity mouse model.

Methods:

Both wildtype and APP/PS1 transgenic mice were placed on diet for a period of 22 weeks. Following euthanasia, we examined the tissue histologically for astrocytic end-foot makers AQP4, Kir4.1, BK and dystrophin-1 (Dp71). Further, we isolated both microglia and astrocytes from the brains of these animals to determine the cell specific effects of HHcy.

Results:

We found that astrocytic end-foot markers AQP4, Dp71, Kir4.1 and BK were all reduced significantly following HHcy induction. We have also found that neuroinflammatory mediators associated with a pro-inflammatory response are significantly increased by the HHcy, with a shift from an anti-inflammatory to a pro-inflammatory bias in the APP/PS1 mice when HHcy is induced. We are working to determine the cell-specific changes in our isolated cell preparations.

Conclusions:

HHcy results in the disruption of the astrocytic end-foot connection in association with an increased pro-inflammatory response. These observed changes could represent a common cellular mechanism of VCID and, therefore, may be a target for therapeutic development.

Disclosures: B.R. Price: None. **T.L. Sudduth:** None. **E.M. Weekman:** None. **D.M. Wilcock:** None.

Poster

206. Astrocytes: Disease Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 206.06/D44

Topic: B.12. Glial Mechanisms

Support: IISER Postdoctoral Fellowship

Wellcome-DBT Intermediate Fellowship

Title: Consequences of altered calcium signaling in astrocytes with implications on Alzheimer's disease pathology

Authors: *A. G. PILLAI[1], S. NADKARNI[2]

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Abstract: The astrocytes, the most abundant cells in the brain, regulate synaptic transmission and plasticity via glutamate and ATP receptor-mediated gliotransmitter release. However, it is not clear how calcium signaling in astrocytes, in both healthy and disease conditions, modulate gliotransmitter release. In this study, we examined the functional outcomes of modified astrocytic calcium signaling as observed in Alzheimer's disease (AD) models using a detailed computational modeling paradigm.

Intracellular elevations in astrocytic calcium levels have been observed in response to a wide range of ATP concentrations and durations. Independently, changes in cytosolic calcium have been shown to initiate release of gliotransmitters including ATP. But, there is no quantitative description of how purinergic signaling in astrocytes via IP3 receptor mediated calcium release, activates gliotransmitter release and mediate normal function. Building on some of the previous work, we developed a biophysically detailed model of intracellular calcium signaling and calcium-mediated vesicular release in astrocytes.

The model parameters were constrained to accurately reproduce the peak amplitude, rise time and decay of the calcium profile as well as dose-response curve for ATP measured using fluo-4 calcium dye. Although astrocytes predominantly express synaptotagmin 4 (Syt4) and not Syt1, (fast synchronous release sensor in neurons), it has also been shown that replacing Syt4 with Syt1 in astrocytes did not alter overall release. This indicates that the main bottleneck for astrocytic vesicular release might be the slow calcium dynamics rather than the kinetics of calcium-sensor itself. We have systematically tested this by comparing the profile of calcium-mediated release in astrocytes with three release machineries - Syt1 & 7, Syt4. We propose a hybrid sensor model that has only 4 calcium-binding sites but has fast and slow kinetics similar to Syt1 and Syt7 respectively.

Recent research established that alongside the synaptic changes, the Alzheimer's disease pathology is also associated with disrupted calcium signaling in astrocytes. Not only there is an increase in resting calcium levels (80%), but signaling through the metabotropic ATP receptor is also enhanced in animal models of Alzheimer's disease. We employ the quantitative framework for purinergic signaling described here to characterize the consequences of these disrupted astrocytic mechanisms as seen in AD.

Disclosures: **A.G. Pillai:** None. **S. Nadkarni:** None.

Poster

206. Astrocytes: Disease Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 206.07/D45

Topic: B.12. Glial Mechanisms

Support: NSERC Discovery Grant to NS

CRC to NS

CFI to NS

Title: Profiling cortical astroglial cells in response to stress

Authors: *S. SIMARD[1], G. COPPOLA[2], S. HAYLEY[1], N. SALMASO[1,2]
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Abstract: Recent studies have suggested that cortical astroglial cells may play an important role in both the etiology and treatment of depression. Many hypotheses as to potential astroglial contribution to a depressive phenotype can be proposed based on known functions such as glutamate recycling and synaptic plasticity. However, to date, the mechanisms by which astroglial cells contribute to a depressive phenotype (or protect against it) remain unknown. Using transgenic bacTRAP mice (AldH-L1-L10-GFP) that express green fluorescent protein (GFP) in astroglial cells, we employed a chronic variable stress (CVS) paradigm previously shown to induce depressive behaviours. As expected, CVS significantly increased anxiety and depressive-like behaviours and basal corticosterone levels. Using immunohistochemistry we found that in contrast to previous studies, the total number of astroglial cells marked by GFP in the cortex did not change in response to stress, however, the expression of astroglial intermediate filament proteins did (GFAP, Vimentin). In order to further profile astroglial changes, the astroglial transcriptome was profiled using translating ribosome affinity purification (TRAP) in conjunction with RNASeq.
We identified significant over-expression of translating mRNAs related to cell membranes, lysosomes, cholesterol biosynthesis, synaptic transmission and extracellular matrices. In particular, significant changes in extracellular matrices associated with cortical perineuronal nets (PNNs) were observed in response to stress. Interestingly, PNNs are disrupted in the post-mortem cortices of patients with a history of mood disorders and schizophrenia, diseases that include chronic stress as a risk factor. Furthermore, astroglia are responsible both for the creation and maintenance of PNNs. To validate our findings and elucidate the role of PNNs in recovery from chronic stress, we degraded PNNs in the prefrontal cortex of mice exposed to CVS and found a complete reversal of the depressive phenotype, with only subtle to no effects on anxiety behavior. Together these studies suggest a pivotal role for astroglia in both the effects of chronic stress on depressive behaviors. Further studies will be needed to assess the therapeutic potential of astroglial manipulations.

Disclosures: S. Simard: None. **G. Coppola:** None. **S. Hayley:** None. **N. Salmaso:** None.

Poster

206. Astrocytes: Disease Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 206.08/D46

Topic: B.12. Glial Mechanisms

Support: NICHD 5R00HD058044-05

Title: Cuprizone induced GFAP+ astrocyte activation is FGF8 dependent

Authors: *C. E. STEWART, W. C. CHUNG
Biol. Sci., Kent State Univ., Kent, OH

Abstract: Reduced fibroblast growth factor (FGF) 8 signaling delayed the maturation of anterior brain midline glial fibrillary acidic protein expressing (GFAP+) astrocytes. Indeed, in contrast to perinatal development, the anterior brain midline GFAP+ astrocyte population did not exhibit marked deficits in adulthood. Nonetheless, we cannot rule out the possibility that reduced FGF8 signaling may have disrupted adult GFAP+ astrocytic function or reactivity. Especially in light of *in vitro* studies reporting that FGF8 increased cortical astrocytic branching complexity to facilitate wound healing. Here, we asked whether FGF8 signaling deficits impair adult GFAP+ astrocyte activation. For this purpose, adult wildtype (WT) and *Fgf8* hypomorphic ($^{+/neo}$) mice were given a 0.2% cuprizone (CPZ) diet for two or three weeks. CPZ treatment increased GFAP expression in the cortex and corpus callosum. After two weeks, cortical GFAP expression increased in a non-genotype dependent fashion. However, after three weeks cortical GFAP expression was reduced in *Fgf8*$^{+/neo}$ mice when compared to WT mice. GFAP expression in the medial corpus callosum (i.e., genu) increased in a non-genotype dependent fashion, whereas it was reduced in lateral corpus callosum (i.e., cingulum) of *Fgf8*$^{+/neo}$ mice when compared to WT mice. We also asked whether FGF8 signaling deficits exacerbate CPZ-induced GFAP+ astrocyte branching as a measure for functional gliosis, Using Sholl analysis, we showed that after two weeks secondary branching increased in WT mice whereas tertiary branching increased in *Fgf8*$^{+/neo}$ mice. Together, our results showed that a developmental disruption in FGF8 signaling had long-term effects on the responsiveness of midline GFAP+ astrocytes under demyelinating conditions. Currently, we are using qPCR to study whether CPZ alters *Fgf8* and *Fgf receptor* mRNA expression to induce astrocyte activation.

Disclosures: C.E. Stewart: None. **W.C. Chung:** None.

Poster

206. Astrocytes: Disease Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 206.09/D47

Topic: B.12. Glial Mechanisms

Title: The amyloid precursor protein is crucial for robust calcium activity in astrocytes

Authors: *S. CRUX[1,2,3], E. MONTAGNA[1,2,3], J. HERBER[1,3,4], C. SGOBIO[1], A.-V. COLOMBO[1], S. TAHIROVIC[1], S. LICHTENTHALER[1,3,4], J. HERMS[1,2,3]
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Abstract: The amyloid precursor protein (APP) is a neuronal and astrocytic transmembrane glycoprotein centrally involved in the pathogenesis of Alzheimer's disease, as the accumulation of its cleavage product amyloid beta is known to be the causative agent of the disease. In order to assess the potential and risks of amyloid beta targeting therapeutic strategies, it is of importance to understand the physiological function of APP. It has been shown that APP plays a role in neuronal development as well as in structural and functional synaptic plasticity in adult mice. However, the functional role of APP in astrocytes, the predominant non-neuronal cell type in the brain, is less well understood. As accumulating evidence suggests the implication of astrocytes in homeostasis of synaptic function via calcium (Ca^{2+}) signalling, we aim to decode the nature of APP in cortical astrocyte functioning.
Injection of an adeno-associated virus encoding an astrocytic membrane targeted Ca^{2+} indicator (Lck-GCaMP6) in conjunction with chronic *in vivo* and *ex vivo* two-photon microscopy enabled us to observe a significant reduction of spontaneous Ca^{2+} transients in cortical astrocytes of mice lacking APP (APPKO). Furthermore, we biochemically studied calcium homeostasis-related proteins and mitochondria morphology in APPKO astrocytes.
Our data demonstrate the essential role of APP in regulating astrocytic Ca^{2+} signalling and the implication of mitochondria in altered Ca^{2+} transients giving a new perspective on APP and glial involvement in synaptic signalling.

Disclosures: S. Crux: None. **E. Montagna:** None. **J. Herber:** None. **C. Sgobio:** None. **A. Colombo:** None. **S. Tahirovic:** None. **S. Lichtenthaler:** None. **J. Herms:** None.

Poster

206. Astrocytes: Disease Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 206.10/D48

Topic: B.12. Glial Mechanisms

Title: The role of kir4.1 in the development of epilepsy

Authors: *J. BONI[1,2], A. RANDOLPH[2], M. OLSEN[1]
[1]Virginia Tech, Sch. of Neurosci., Blacksburg, VA; [2]Univ. of Alabama at Birmingham, Birmingham, AL

Abstract: Kir4.1, a glial specific, inwardly rectifying potassium channel contributes significantly to astrocyte membrane properties and extracellular K^+ homeostasis. Reduced protein expression and channel function is observed in nearly every CNS pathology and astrocyte specific rescue reduces neuronal hyperexcitability and dysfunction, leading to the notion that Kir4.1 may represent a novel therapeutic target. Using a pilocarpine model of status epilepticus and spontaneous recurrent seizures in adult male rats we observed a > 50% reduction in hippocampal Kir4.1 expression 24 hours post status epilepticus. Reduced Kir4.1 protein levels were maintained through the latent period, preceded the onset of spontaneous recurrent seizures and were maintained in epileptic animals. Work underway is aimed at addressing 1) identifying the spatio-temporal extent of Kir4.1 reduction during the latency period of epileptogenesis 2) determine if the sustained reduction in Kir4.1 expression is due to changes in DNA methylation 3) determining if rescuing Kir4.1 expression in astrocytes of the CA1 region of the hippocampus reduce neuronal excitability.

Disclosures: J. Boni: None. **A. Randolph:** None. **M. Olsen:** None.

Poster

206. Astrocytes: Disease Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 206.11/D49

Topic: B.12. Glial Mechanisms

Title: Differential roles in temozolomide-resistant glioblastoma cells

Authors: *S.-W. LAI
China Med. Univ., Taichung, Taiwan

Abstract: Abstract Glioblastoma multiforme (GBM) is the most common type of primary and malignant tumor occurring in the adult central nervous system. Temozolomide (TMZ) has been considered to be one of the most effective chemotherapeutic agents to prolong the survival of patients with glioblastoma. Many glioma cells expressing drug-resistance for TMZ that mediated by increasing *O-6-methylguanine-DNA methyltransferase* (MGMT) levels. The expression of connexin 43 was increased in resistant U251 sublines compared with original U251 cell. Epithelial-mesenchymal transition (EMT)-associated regulators, including vimentin, N-cadherin, β-catenin were observed lower expression in resistant U251 sublines. In addition, resistant U251 sublines cells were also expressed lower cell migration and monocyte adhesion ability compared to original U251 cell. Furthermore, the resistant U251 sublines cells also had lower levels of vascular cell adhesion molecule (VCAM)-1 after treatment with recombinant TNFα. These findings suggest differenctial characteristers in drug resistant GBM from original glioma cells.
Keywords: glioblastoma; Temozolomide; connexin 43; drug-resistant

Disclosures: S. Lai: None.

Poster

206. Astrocytes: Disease Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 206.12/D50

Topic: B.12. Glial Mechanisms

Support: JSPS KAKENHI Grant 16K19016

Title: Mechanism underlying hypoxia-independent upregulation of astrocytic HIF-1α after ischemic preconditioning

Authors: *Y. HIRAYAMA[1,2], H. P. N. LE[1], S. KOIZUMI[1]
[1]Dept. of Neuropharm., Univ. of Yamanashi, Yamanashi, Japan; [2]Dept. of Pharm., Univ. of Yamanashi Hosp., Yamanashi, Japan

Abstract: In clinical settings, it is commonly observed that a mild ischemic episode protects neurons against a subsequent much severe ischemic injury. This phenomenon is known as “ischemic tolerance”. Such short and mild ischemia, known as preconditioning (PC), itself does not cause brain damages, but instead, induces ischemic tolerance. We previously showed that PC-induced activation of astrocytes, and their subsequent expression of hypoxia inducible factor (HIF)-1α is responsible for induction of ischemic tolerance. HIF-1α was also induced in neurons by PC, but neuronal HIF-1α was not involved in ischemic tolerance. Here, we show the difference in mechanism of HIF-1α increase between neurons and astrocytes, and ask why astrocytic HIF-1α is more important for ischemic tolerance. Firstly, using a middle cerebral artery occlusion model of mice, we examined a temporal difference in PC-evoked increase in HIF-1α in neurons and astrocytes, and found that the former was quick and transient (from 1 to 3 days after PC) and the latter was slow-onset and long-lasting (from 3 days to at least 2 weeks after PC). We thought that such a temporal difference would explain an importance of astrocytic HIF-1α in induction of ischemic tolerance, and thus, we next investigated difference in mechanisms underlying the induction of HIF-1α increase in these cells. Although HIF-1α is constitutively expressed in neurons, the expression levels are very low under the normoxic condition because of its oxygen-dependent degradation by prolylhydroxylase2 (PHD2). Hypoxia/ischemia decreases oxygen, which results in inhibition of PHD2, thereby leading to accumulation of HIF-1α and production of various neuroprotective molecules. In fact, HIF-1α was increased in neurons upon hypoxia *in vitro*. However, interestingly, this was not the case in astrocytes, i.e., HIF-1α was not increased by hypoxia in astrocytes. We also found that expression of PHD2 was very low in astrocytes, which could explain why astrocytic HIF-1α expression is independent of hypoxia. Instead, astrocytes showed persistent increase in P2X7 receptor in response to PC, which was a main mechanism for upregulation of HIF-1α in

astrocytes. Such novel hypoxia-independent mechanism of HIF-1α increase would allow astrocytes to cause persistent HIF-1α increase and subsequent strong ischemic tolerance. We also discuss a possible mechanism of P2X7 receptor activation in this phenomenon.

Disclosures: Y. Hirayama: None. **H.P.N. Le:** None. **S. Koizumi:** None.

Poster

206. Astrocytes: Disease Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 206.13/D51

Topic: B.12. Glial Mechanisms

Support: NIH Grant R01MH106490

FRAXA Research Foundation

Title: Investigation of local protein synthesis at peri-synaptic astrocyte processes in Fragile X Syndrome (FXS)

Authors: *H. HIGASHIMORI, Y. YANG, Y. MEN
Neurosci., Tufts Univ., Boston, MA

Abstract: Local peri-synaptic astrocyte processes (PAPs) are emerging as crucial locations in astrocyte communication and modulation of synaptic signaling. The unique PAP structural arrangement, covering individual synapses, suggests that it could form a functional satellite microdomain that functions independently from the astrocyte cell body. Recently, we demonstrated the localization of eGFP-tagged ribosome subunit L10a in cortical and hippocampal astrocyte PAPs in EM images of BAC *aldh1l1*-TRAP mice. We discovered that ribosomes in hippocampal PAPs appeared a week earlier (P7) than those in cortical PAPs (P14), suggesting regionally specific functional PAP development during brain maturation. From confocal images, we also found the phosphorylated ribosome protein s6, which closely associated with active translation at PAPs in EAAT2-Tdt reporter mice. Moreover, we selectively isolated and detected abundant astrocytic mRNA, particularly GLT1, Kir4.1, in mouse cortical astrocyte PAPs through a novel isolation method, synaptoneurosome isolation followed by translational ribosome affinity purification (SNS-TRAP) preparation in BAC *aldh1l1*-TRAP mice. Furthermore, we performed time-lapse imaging using the GFP-encoding mRNA and fluorescence recovery after photo-bleaching (FRAP) technique to show that the GFP reporter protein can be locally synthesized at astrocyte processes in cortical slices. PAP protein synthesis was diminished upon treatment with the protein synthesis inhibitors anisomysin and cyclohexamide. In addition, we extended our investigation to Fragile X Syndrome (FXS), which is caused by loss of fragile X mental retardation protein (FMRP), one of the leading causes of

inherited mental retardation. FMRP has been well characterized as an important local translational repressor in neuronal dendrites; however, the role of FMRP in local protein synthesis in astrocyte PAPs remains essentially unknown. EM images of P28 Fmr1-KO PAPs showed a 20% decreased of eGFP-tagged ribosomes compared to WT. Additionally GFP reporter florescence and indication of protein synthesis in time lapse imaging appeared significantly earlier (by 3-5 min.) in Fmr1-KO PAPs compared to WT. Currently, we are selectively isolating PAP enriched transcriptomes, using the SNS-TRAP procedure, from astrocyte PAPs of Fmr1-KO BAC *aldh1l1*-TRAP mice followed by RNA-sequencing to characterize PAP-enriched astrocyte mRNA. We will also perform a GLT1 protein synthesis assay in SNS. In summary, this study suggest that there is local protein synthesis in astrocytes which could be altered in developmental disorders and contribute to proper synaptic development.

Disclosures: H. Higashimori: None. **Y. Yang:** None. **Y. Men:** None.

Poster

206. Astrocytes: Disease Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 206.14/D52

Topic: B.12. Glial Mechanisms

Support: NIH

PCOM DO/PhD Program

T. Dianne Langford at Temple University

Title: Role of microRNA and opiates in HIV-1 Tat protein neuropathogenesis

Authors: *K. CHEN[1,2], L. SARDO[1], S. MITA[1], Z. KLASE[1]
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Abstract: Nearly one-half of people infected with HIV-1 virus experience HIV-associated neurocognitive disorder (HAND) despite combination of anti-retroviral therapy (cART). Mechanisms underlying HAND progression remain unclear. HIV-1 Tat viral protein and opiate abuse have both been independently implicated in exacerbation of brain inflammation. Tat protein can inhibit Dicer endoribonuclease cleavage necessary for microRNA (miRNA) maturation. We recently found that Tat binds and inhibits miRNAs to downregulate Wnt/β-catenin signaling, a pathway shown to be protective against HIV-1 brain inflammation. The direct mechanism behind Tat-miRNA and β-catenin downregulation is unknown. Our objective is to determine the role of miRNAs altered by HIV-1 Tat protein and opiates in worsening

HAND outcome. To address this hypothesis, we cultured U-87MG astrocyte cell line and primary fetal astrocytes (PFA), transfected with Tat plasmid, and subsequently treated with morphine. Luciferase assay with reporter was used to quantify expression levels of β-catenin. We then analyzed the profiles changes of 380 miRNAs by RT-qPCR on Tat and morphine treated cells. In PFA, β-catenin signaling showed stronger suppression in Tat and morphine combined treatments compared to astrocytes with only Tat treatment in a dose-specific manner. Similarly, U-87MG cells with combined Tat and morphine conditions showed greater β-catenin suppression at selective doses of morphine compared to Tat condition alone. In U-87MG cells, 90 miRNAs were uniquely dysregulated by a 3-fold change in combined Tat and morphine treatment. We observed that β-catenin signaling was suppressed in Tat and morphine treated astrocytes. Moreover, aberrant miRNAs were more frequent in combined treatments compared to individual treatments. Our finding suggests worsening neuropathology in joined Tat and opiate interactions. Further analysis of large miRNA aberrations and Tat specific interactions can provide mechanistic insight on dysregulation in β-catenin signaling and offer potential HIV CNS therapy to attenuate Tat- and miRNA-mediated dysregulation.

Disclosures: K. Chen: None. **L. Sardo:** None. **S. Mita:** None. **Z. Klase:** None.

Poster

206. Astrocytes: Disease Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 206.15/D53

Topic: B.12. Glial Mechanisms

Title: Adrenergic modulation of Cerebellar Glial activity during Nociception

Authors: S. KIM[1], S.-E. ROH[1], S. KIM[3], *S. KIM[2]
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Abstract: The alteration of the cerebellar metabolic level in pain state has been observed in previous human brain imaging studies. However, it is unknown whether and how the cerebellar Bergmann glia (BG) is involved in pain processing. To address this question, we monitored the calcium activity of BG in intact cerebellar cortex lobule IV/V by using *in vivo* two-photon calcium imaging in anesthetized mice. Various noxious electrical stimuli were delivered to the mouse hind-paw during calcium imaging with pharmacological manipulation. Capsaicin was also injected to the hind paw to identify BG calcium responses under an acute spontaneous pain condition. We found that strong calcium activation in BG network was evoked by noxious electrical stimuli. This calcium activation was blocked by an infusion of alpha1-adrenergic receptor (α1-AR) antagonist into the cerebellar cortex, but not by glutamatergic or purinergic receptor antagonists. The capsaicin injection also induces strong BG calcium responses, which

were blocked by a cerebellar infusion of the α1-AR antagonist. Moreover, the capsaicin-induced pain behavior (i.e. licking duration) was robustly reduced by an α1-AR antagonist infusion. Taken together, we suggest that noradrenergic signaling mediates the activation of the glial network during noxious information processing in the cerebellum.

Disclosures: S. Kim: None. **S. Roh:** None. **S. Kim:** None. **S. Kim:** None.

Poster

206. Astrocytes: Disease Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 206.16/D54

Topic: B.12. Glial Mechanisms

Support: GARP

Title: Serum response factor regulates astrogliosis in a cell autonomous manner

Authors: *M. JAIN[1], P. Y. LU[2], S. KORADA[1], D. GUTMANN[3], N. RAMANAN[1]
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Abstract: In response to injuries, infections or in neurodegenerative disorders, astrocytes get activated to become reactive. This phenomenon is called astrogliosis and is marked by a spectrum of changes which encompasses structural, functional and genetic changes in astrocytes. Until now, the molecular mechanisms regulating astrogliosis remain poorly understood. Recently, a study from our lab showed that conditional ablation of the stimulus-dependent transcription factor, serum response factor (SRF) in neural precursor cells during early development leads to a significant loss in astrocyte and oligodendrocyte numbers both *in vivo* and *in vitro*. This suggests a critical role for SRF in glial specification. SRF has been shown to regulate the expression of a variety of genes involved in cell growth and differentiation, neuronal development, synaptic plasticity and learning and memory. To further study the role of SRF in astrocyte development, SRF was deleted in astrocytes using a GFAP-Cre transgenic mouse line. In the resultant $Srf^{f/f;GFAP\text{-}Cre+/-}$ (SRF-GFAP-cKO) conditional mutant mice, there was a 50% reduction in the number of astrocytes at birth. However, by 3-4 weeks of age, the astrocytes in SRF-GFAP-cKO appeared hypertrophic and resembled gliosis astrocytes with enhanced expression of GFAP and other gliosis markers. The astrogliosis in the SRF-GFAP-cKO mice persisted throughout adulthood and was also accompanied by activation of microglia. To further study whether the gliosis observed in SRF-GFAP-cKO mice is due to developmental effects from embryonic deletion of SRF, we generated a tamoxifen-inducible conditional mutant mouse, $Srf^{f/f;GFAP\text{-}CreERT+/-}$ (SRF-GFAP-ERT-cKO). Administration of tamoxifen (Tam) to 6-8 week old SRF-GFAP-ERT-cKO mice resulted in gliosis astrocytes at 2 months post-injection while

vehicle injected mice exhibited normal astrocytes. The astrogliosis in Tam-injected SRF-GFAP-ERT-cKO mutant mice also persisted throughout adulthood. Together our observations suggest that SRF is critical for maintenance of astrocytes in their normal state and that SRF loss in astrocytes results in astrogliosis in a cell-autonomous manner.

Disclosures: M. Jain: None. **P.Y. Lu:** None. **S. Korada:** None. **D. Gutmann:** None. **N. Ramanan:** None.

Poster

206. Astrocytes: Disease Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 206.17/D55

Topic: B.12. Glial Mechanisms

Support: NIH Grant NS087783

AMRF gift

LLHF Grant 2014-A-033-FEL

Title: Astrocyte heterogeneity after stroke: Identifying new targets for neural repair

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Abstract: Astrocytes play many important functions in the healthy and injured brain, including interacting with the immune system, influencing synapse formation and elimination, modulating circuit excitability, and inducing blood vessel formation and maturation. All of these functions are likely involved in post-stroke tissue repair, making astrocytes an excellent target to enhance repair and recovery after stroke. However, little is known about exactly how astrocytes respond to ischemic injury, or how those responses change depending on the distance from the injury or the location of the stroke. To that end, we have mapped the morphologic, phenotypic, and transcriptomic changes astrocytes undergo after stroke, using both cortical and white matter stroke models. We are using this dataset to identify novel targets to promote neural repair and recovery after stroke.
To assess the morphologic changes astrocytes undergo after stroke, we developed lentiviral vectors to induce expression of new reporters called spaghetti monsters specifically in astrocytes. Sparse delivery of these viruses has made it possible to quantify the detailed morphology of individual astrocytes at different distances from the infarct border in both white matter and cortical stroke. Astrocyte morphology changes in stereotyped ways with increasing reactivity,

with cells closest to the infarct core showing fewer, shorter, and thicker processes. We have combined this analysis with a phenotypic analysis, assessing how expression of key proteins changes by distance from the infarct. Together, these two approaches were used to define reactive astrocyte zones in both white matter and cortical stroke models.
These morphologic and phenotypic analyses were then used to inform a transcriptomic analysis. By using a GFAP-Cre/Ribotag mouse, in which a ribosomal subunit is tagged under Cre control, it is possible to isolate astrocytic ribosomes and their associated mRNA. By combining this system with laser capture microdissection, we isolated mRNA from distinct astrocytic zones in both white matter and cortical stroke tissue. We have analyzed these samples by RNAseq, creating a comprehensive picture of how both white matter and cortical astrocytes change by proximity to ischemic injury. We are now using this dataset to identify novel targets for neural repair, including targets that may be involved in astrocytic modulation of angiogenesis.
Supported by Dr. Miriam and Sheldon G. Adelson Medical Research Foundation.

Disclosures: **A.J. Gleichman:** None. **R. Kawaguchi:** None. **M.V. Sofroniew:** None. **G. Coppola:** None. **S. Carmichael:** None.

Poster

206. Astrocytes: Disease Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 206.18/D56

Topic: B.12. Glial Mechanisms

Support: JSPS KAKENHI 26120514

JSPS KAKENHI 16H01541

JSPS KAKENHI 17H05285

MIC SCOPE 141203025

Naito Foundation

Yazaki Memorial Foundation for Science and Technology

Title: Analysis of astrocyte morphology during hypoxia adaptation using higher-order image features extracted by deep convolutional neural network

Authors: S. TANAKA, T. NISHINO, M. NITTA, T. SUGASHI, K. MASAMOTO, *Y. MIYAWAKI
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Abstract: Astrocytes adaptively change their shape under pathological conditions, supposedly playing functional roles in microvasculature remodeling to cope with environmental changes in the brain. However, it is unclear what morphological characteristics are specifically influenced and how they dynamically change after the onset of the pathological conditions. In this study, we propose a method using a deep convolutional neural network (DCNN), a computational model to represent objects by integrating image features hierarchically, to extract higher-order image features that represent morphological changes of astrocytes during hypoxia adaption. A two-photon microscopy was used to measure fluorescently labeled images of the same astrocytes in the somatosensory cortex of one anesthetized mouse at multiple days (D0, D7, D14, D21) after hypoxia induction. Five images were obtained with different depth to cover each astrocyte volume and were converted into a single image by the maximum intensity projection (MIP). One hundred MIP images were selected from each day for the following analyses. To extract image features from the astrocytes data set, we used a DCNN pre-trained with a large number (~10^6) of natural images, and performed classification analysis to predict the hypoxia adaptation condition (pre- (D0) or post-adaptions (D7/D14/D21)) using image features extracted from given astrocyte images. To compare prediction performance, classification analyses were also performed using other lower-order image features. Results showed that prediction accuracy gradually increased as days after hypoxia induction. When hypoxia adaptation progressed, the number of image features necessary for the prediction decreased and less than 10^1 of higher-order image features were enough to achieve high accuracy, suggesting that a small number of higher-order image features is crucial to represent morphological changes of astrocytes after hypoxia adaptation. Further analyses revealed that the predictive image features partially overlapped between different stages of hypoxia adaptation. These results suggest that DCNN-extracted image features are effective to capture dynamical changes of astrocyte morphology during hypoxia adaptation.

Disclosures: S. Tanaka: None. **T. Nishino:** None. **M. Nitta:** None. **T. Sugashi:** None. **K. Masamoto:** None. **Y. Miyawaki:** None.

Poster

206. Astrocytes: Disease Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 206.19/D57

Topic: B.12. Glial Mechanisms

Support: NIH-NINDS NS084030

NIH-NINDS F32NS096858

Paralyzed Veterans America Grant #3080

Dr. Miriam and Sheldon G. Adelson Medical Foundation

Wings for Life

Title: Transcriptional regulators of astrocyte reactivity

Authors: *J. E. BURDA[1], R. KAWAGUCHI[2,3], G. COPPOLA[2,3,4], M. V. SOFRONIEW[1]
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Abstract: Astrocytes respond to diverse central nervous system (CNS) insults with functional changes that can range broadly from modulating inflammation to impacting on neural tissue remodeling and synaptic plasticity. Genetic regulation of these responses is poorly understood. Here, using large scale genomic meta-analyses of mouse and human-derived data, we identified transcriptional regulators of astrocyte reactivity in multiple diverse CNS disorders. Over 20 transcriptional regulators were common across all nine disorders investigated. These regulators included both previously known molecules such as STAT3 and select SMADs, and newly identified molecules, whose critical roles are being validated by conditional gene deletion in mouse models of CNS injury and disease. Numerous additional transcriptional regulators were found to be selective to subsets of disorders and some to only a single disorder. Notably, there was significant disorder selective bias of downstream molecules targeted by these regulators. Our findings strongly support a model whereby astrocyte reactivity is highly diverse and disorder dependent rather than a stereotypic response constant across disorders. We provide a framework for understanding and potentially modulating the genetic control of astrocyte reactivity in different contexts. Supported by NIH-NINDS NS084030 and F32NS096858, Paralyzed Veterans America, the Dr. Miriam and Sheldon G. Adelson Medical Foundation, and Wings for Life.

Disclosures: J.E. Burda: None. **R. Kawaguchi:** None. **G. Coppola:** None. **M.V. Sofroniew:** None.

Poster

206. Astrocytes: Disease Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 206.20/D58

Topic: B.12. Glial Mechanisms

Support: KHIDI Grant HI17C0309

Title: Suppression of pro-inflammatory cytokines released from activated glia by Cinnamomi Cortex and its major phytochemical Coumarin alleviates oxaliplatin induced cold allodynia in rats

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Abstract: Activation of spinal glial cells, such as astrocytes and microglia, and increase of pro-inflammatory cytokines levels in the spinal cord play a crucial role in the pathogenesis of neuropathic pain. A single injection of oxaliplatin (6 mg/kg, i.p.), a widely used anti-cancer drug against metastatic colorectal cancer, can induce acute peripheral neuropathy. *Cinnamomi Cortex* has been used in East Asia to treat various pain symptoms. Anti-nociceptive effect of Coumarin, a major phytochemical of *Cinnamomi Cortex*, on different kind of pain was reported. This study investigated whether and how *Cinnamomi Cortex* and Coumarin alleviate oxaliplatin-induced cold and mechanical allodynia in Sprague Dawley rats. The behavioral signs of cold and mechanical allodynia were evaluated by a tail immersion test in cold water (4 ℃) and a von Frey hair test, respectively. Significant pain behaviors were observed three days after an oxaliplatin injection. *Cinnamomi Cortex* (200 mg/kg) and Coumarin (10 mg/kg) were orally administrated for five consecutive days after oxaliplatin injection. Behavioral studies reveal that *Cinnamomi Cortex* and Coumarin have potent relieving effects against oxaliplatin-induced cold allodynia by increasing the tail withdrawal latency to cold stimuli, whereas only *Cinnamomi Cortex* partially suppressed oxaliplatin-induced mechanical allodynia. Immunohistochemistry studies showed that *Cinnamomi Cortex* and Coumarin suppress activation of spinal astrocytes and microglia. Increased pro-inflammatory cytokines, interleukin-1β and tumor necrosis factor, after oxaliplatin injection were decreased by orally treated *Cinnamomi Cortex* in oxaliplatin rat model. Up-regulated tumor necrosis factor after oxaliplatin treatment (0.1 mM) on primary cultured astrocytes was down-regulated by Coumarin. In summary, *Cinnamomi Cortex* and its phytochemical Coumarin have potent anti-allodynic effect on oxaliplatin-induced neuropathic pain via attenuating activation of spinal glia and release of pro-inflammatory cytokines. This study suggests that *Cinnamomi Cortex* could be an alternative therapeutic agent on oxaliplatin-induced cold allodynia, and Coumarin may play a major role in this efficacy of *Cinnamomi Cortex*.
This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (HI17C0309)

Disclosures: **J. Lee:** None. **H. Chae:** None. **W. Kim:** None. **H. Bae:** None. **S. Kim:** None.

Poster

206. Astrocytes: Disease Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 206.21/D59

Topic: B.12. Glial Mechanisms

Title: DISC1 in astrocytes regulates glycolytic pathways and lactate production: Implications for psychiatric disorders

Authors: *Y. JOUROUKHIN[1], V. MISHENEVA[1], Y. KAGEYAMA[2], S. A. ANDRABI[5], C. Y. YANG[1], V. L. DAWSON[6], T. M. DAWSON[7], H. SESAKI[3], M. PLETNIKOV[4]
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Abstract: Astrocyte pathology resulting from expression of genetic risk factors is believed to contribute to psychiatric disorders. The underlying mechanisms whereby genetic variants could affect astrocyte functions remain poorly understood. We evaluated the role of Disrupted-In-Schizophrenia-1 in the astrocyte metabolism and energy supply to neurons. Similar to neurons, DISC1 is localized to mitochondria in astrocytes. Using *in vitro* and *in vivo* models, we demonstrate that both knockdown of endogenous DISC1 and over-expression of a dominant-negative variant of DISC1 (C-terminus truncated DISC1) led to abnormal oxidative phosphorylation and glycolysis in astrocytes, resulting in decreased lactate production and secretion. Expression of mutant DISC1 in astrocytes was linked to increased anxiety behavior in elevated plus maze, increased immobility in forced swim test and deficient hippocampus-dependent in trace fear conditioning test. All these behavioral changes were rescued with lactate treatment. Our results suggest that DISC1 could be involved in regulation of energy metabolism in astrocytes to support neuronal functioning and behaviors. Abnormal expression of DISC1 astrocytes may at least in part be responsible for aspects of abnormal behavioral phenotype associated with major psychiatric disorders.

Disclosures: Y. Jouroukhin: None. **V. Misheneva:** None. **Y. Kageyama:** None. **S.A. Andrabi:** None. **C.Y. Yang:** None. **V.L. Dawson:** None. **T.M. Dawson:** None. **H. Sesaki:** None. **M. Pletnikov:** None.

Poster

206. Astrocytes: Disease Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 206.22/D60

Topic: B.12. Glial Mechanisms

Support: Illinois Department of Health

CADRD

Title: Chronic systemic LPS administration induces aberrant Kir6.2 expression in reactive astrocytes

Authors: *C. M. GRIFFITH[1], A. A. SHARP[1], G. M. ROSE[1,2], P. R. PATRYLO[1,2]
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Abstract: K_{ATP} channels are inwardly rectifying potassium channels composed of 4 pore-forming subunits (Kir6.1 or Kir6.2) and 4 sulphonylurea regulatory subunits (SUR1, SUR2A, or SUR2B). These channels couple cellular excitability and metabolism by sensing ATP/ADP levels (i.e., decreased ATP causes K_{ATP} channels to open) and have been implicated in several neurodegenerative conditions including ischemia, Parkinson's disease, epilepsy, and Alzheimer's diseases (AD). While the Kir6.2 subunit was believed to be primarily neuronal in origin, we have shown that Kir6.2 is aberrantly expressed in hippocampal reactive astrocytes in a mouse model of AD, human post-mortem AD tissue (Griffith et al., 2016), and in pilocarpine-induced epileptic mice (a model of temporal lobe epilepsy (TLE); Patrylo et al., SFN abstract 688.01, 2016). While AD and TLE share several commonalities, one factor likely to contribute to the reactive astrogliosis seen in both conditions is chronic neuroinflammation. Consequently, we hypothesized that neuroinflammation could lead to reactive astrogliosis and the aberrant expression of Kir6.2 in astrocytes. To test this idea, 2-3 month old male C57/C129 mice were injected with lipopolysaccharide (LPS; 5 mg/kg, I.P.) or saline for 1 day (saline n = 4, LPS n = 5) or 3 days (saline n = 4, LPS n = 5) to model acute or chronic inflammation, respectively. One day following the final LPS injection mice were sacrificed, their brains fixed in 4% paraformaldehyde and cryoprotected in 30% sucrose. Coronal sections were cut at 30 μm, stored in cryoprotectant and then batch processed: blocked for 1 hour in 5% rabbit serum in PBS, incubated with primary antibodies overnight (Anti-GFAP 1:1000, Sigma-Aldrich, St. Louis, Mo.; Anti-Kir6.2 1:200, Alomone Labs, Jerusalem, Israel) and then incubated with appropriate secondary antibodies. Four evenly spaced sections (from bregma: -1.34 to -2.70 mm) from each animal were quantified using Volocity software (PerkinElmer) to assess GFAP and Kir6.2 immunoreactivity (IR) and their co-localization. These experiments revealed that 3 days, but not 1 day, of LPS-treatment caused a significant increase in Kir6.2 and GFAP co-localization in "reactive astrocytes" in hippocampal region CA1. These data suggest that chronic, but not acute, neuroinflammation can contribute to the aberrant expression of Kir6.2 in reactive astrocytes, which could subsequently contribute to the altered network dynamics seen in AD and TLE and thus may provide a novel therapeutic target for these neurodegenerative diseases.

Disclosures: C.M. Griffith: None. **A.A. Sharp:** None. **G.M. Rose:** None. **P.R. Patrylo:** None.

Poster

206. Astrocytes: Disease Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 206.23/D61

Topic: B.12. Glial Mechanisms

Support: NIH Grant R01DA041455 (KJR)

Title: The effect of cocaine self-administration on morphometric properties of astrocytes and synaptic colocalization within the reward circuitry

Authors: *A. TESTEN[1], M. SEPULVEDA[2], C. H. HILL[2], K. J. REISSNER[2]
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Abstract: While much is known about the effects of cocaine use on cellular function of neurons and synapses within the brain's reward circuitry, relatively little is known about the effects of cocaine on astrocytes. However, given the significant role that astrocytes play in modulating neuronal and synaptic function, this lack of knowledge regarding the contributions of astroglial adaptations to the neuropathology of drug abuse represents an important investigative need. We recently developed a method by which high-resolution confocal imaging of individual astrocytes can be applied to the investigation of structural plasticity of astrocytes following drug use. We found that astrocytes within the nucleus accumbens (NAc) exhibit decreased volume, surface area, and synaptic colocalization following cocaine self-administration and extinction, compared to NAc astrocytes from saline-administering animals (Scofield et al, 2016). It is well established that the NAc is a principal nucleus governing motivated behaviors, and accordingly the effects of cocaine self-administration on NAc astrocytes has raised numerous hypotheses regarding how impaired astroglial function and synaptic communication contribute to drug seeking behavior and maladaptive synaptic function. However, it is still unclear whether these cocaine-dependent changes in astrocytes are ubiquitous throughout the brain's reward circuitry, or represent specific adaptations within the NAc. In the current study we have extended this analysis to include measurements of morphometric properties and synaptic colocalization of astrocyte peripheral processes in the prelimbic region of the medial prefrontal cortex (PL) and basolateral nucleus of the amygdala (BLA), both known to also contribute significantly to the motivation-reward circuitry. To probe for this, rat brains were microinjected with AAV5 Lck-GFP virus expressed under control of the GFAP promoter into the BLA, PL and NAc, and rats were trained in cocaine versus saline self-administration and extinction. Following immunohistochemistry and confocal imaging, individual astrocytes were deconvolved and reconstructed in 3D space using Bitplane Imaris software. Volume, surface area, and colocalization with neuronal synaptic markers were recorded. Developing insights into the influence of cocaine abuse on the structure and physiology of astrocytes within the brain reward circuitry will inform both regional heterogeneity of astrocytes, as well as cellular mechanisms of drug reward and dependence.

Disclosures: **A. Testen:** None. **M. Sepulveda:** None. **C.H. Hill:** None. **K.J. Reissner:** None.

Poster

206. Astrocytes: Disease Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 206.24/D62

Topic: B.12. Glial Mechanisms

Support: 5R01MH083728-04

Title: Genetic risk factors in neuron-astrocyte interactions in mental disorders

Authors: *A. V. SHEVELKIN[1,2], Y. JOUROUKHIN[2], L. NUCIFORA[2], C. TERRILLION[2], O. MYCHKO[2], C. YANG[2], A. SAWA[2], F. NUCIFORA[2], M. PLETNIKOV[2]
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Abstract: Deficits in astrocyte energy supply could lead to abnormal neuronal functioning and behavioral abnormalities consistent with aspects of major psychiatric disorders. Patients with schizophrenia and bipolar disorder demonstrate signs of mitochondria dysfunction and metabolic alterations. The mechanisms of these metabolic changes in psychiatric disorders remain obscure. Recently, several genetic risk factors have been implicated in mitochondria energy metabolism in astrocytes. We evaluated the role of functional interplay between two such genetic risk factors, Disrupted-In-Schizophrenia-1 (DISC1) and Neuronal PAS domain protein 3 (NPAS3), that are involved in mitochondria respiration and glutamate metabolism in astrocytes. Our pilot observations indicated that selective perturbation of DISC1-NPAS3 interaction in astrocytes affected mitochondria respiration and glutamate metabolism, leading to neuronal dysfunction and deficits in learning and memory in mice. These studies help advance our understanding of how genetic risks factors converge on key metabolic pathways in astrocytes to regulate energy homeostasis and glutamate metabolism, which underlie neuronal activity and cognitive function.

Disclosures: A.V. Shevelkin: None. **Y. Jouroukhin:** None. **L. Nucifora:** None. **C. Terrillion:** None. **O. Mychko:** None. **C. Yang:** None. **A. Sawa:** None. **F. Nucifora:** None. **M. Pletnikov:** None.

Poster

206. Astrocytes: Disease Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 206.25/D63

Topic: B.12. Glial Mechanisms

Support: Sanofi Genzyme

Title: The extracellular glutamate-to-glutamine ratio modulates glycolysis in primary murine astrocytes

Authors: *P. KABIRAJ, M. CAULFIELD, C. MCCARTHY, R. JOHNSON, C. F. LUCCHINETTI, C. HOWE
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Abstract: Astrocytes are critical for meeting neuronal energy requirements and maintaining CNS energy homeostasis. Astrocytes are primarily glycolytic cells that can survive at length without oxidative phosphorylation. Neurons depend on production of glutamine by astrocytes as a substrate for glutamate synthesis. Astrocytes take up glutamate released from neurons and convert it to glutamine, thus completing a biosynthetic cycle, providing neurons an energy rich molecule, and protecting neurons from toxic levels of extracellular glutamate. Extracellular glutamate is thought to upregulate glycolysis and lactate production by astrocytes. However, under abnormal physiological conditions it is unknown how astrocytes respond bio-energetically to aberrations in the glutamine-glutamate shuttle. A better understanding of this mechanism could be relevant to diseases characterized by elevated glutamine to glutamate including depression, schizophrenia, and hepatic encephalopathy. The purpose of our study was to determine whether changes in the extracellular glutamine-to-glutamate ratio regulate astrocytic glycolysis and oxidative phosphorylation. A Seahorse XF platform was used to interrogate primary mature murine cortical astrocytes and mixed astrocyte/microglial cultures. After 1 hour exposure to 5 mM glutamine under non-CO_2 conditions, we observed a decrease in glycolysis, but an increase in the glycolytic reserve in both primary and mixed astrocytes in response to glycolytic stress. Mitochondrial stress however did not increase oxidative phosphorylation-mediated ATP production in response to increasing (0.5 mM -25 mM) glutamine concentrations. Our findings suggest the involvement of other anabolic pathways such as the pentose phosphate pathway, pyrimidine biosynthesis, or amino acid synthesis in the glycolytic switch. We next analyzed the concentration of TCA cycle metabolites by mass spectrometry following incorporation of a glucose tracer molecule ($U^{13}C_6$-glucose). One hour exposure to 25 mM glutamine increased levels of ^{13}C-labeled glutamate and aspartate and decreased lactate levels when compared to the absence of glutamine. These findings suggest that primary murine astrocytes rapidly upregulate anabolic pathways after exposure to increased levels of glutamine and produce the molecules needed for de novo pyrimidine synthesis. It is possible that the inhibition or modulation of anabolic pathways will alter astrocytic glutamine-glutamate utilization and stimulate CNS metabolic and oxidative stress pathways that may contribute to many traumatic, neurodegenerative, and psychological diseases of the CNS.

Disclosures: P. Kabiraj: None. **M. Caulfield:** None. **C. McCarthy:** None. **R. Johnson:** None. **C.F. Lucchinetti:** None. **C. Howe:** None.

Poster

206. Astrocytes: Disease Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 206.26/E1

Topic: B.12. Glial Mechanisms

Support: NIH Grant R01 NS085207

Target ALS

MDA

ALSA

Title: Effects of the C9orf72 repeat expansion on human iPSC-derived astrocytes in Amyotrophic Lateral Sclerosis

Authors: *J. T. PHAM[1], L. R. HAYES[1], J. DAIGLE[1], J. C. GRIMA[1,2], S. J. MILLER[1], X. TANG[1], W. ZHOU[1], L. XUE[1], S. VIDENSKY[1], S. MACKEY-ALFONSO[4], T. GENDRON[5], J. D. ROTHSTEIN[1,2,3]
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Abstract: Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disease resulting from progressive, irrevocable loss of upper and lower motor neurons as well as associated interneurons. While ALS research has primarily focused on neurons, our understanding of ALS pathogenesis has grown to encompass dysfunction in multiple cell types and cellular mechanisms. Glial cells, especially astroglia, can modulate disease progression by promoting more excitotoxic and/or neuroinflammatory cellular environments. Although studies have demonstrated aberrant RNA metabolism, protein homeostasis, and neurotransmitter metabolism in ALS astroglia, precise mechanisms by which astroglia become neurotoxic remain to be elucidated. Furthermore, most of the prior work on ALS astroglia utilized SOD1 ALS models, which only account for a small percentage of ALS cases. We decided to investigate the astroglial contribution to ALS resulting from a GGGGCC hexanucleotide repeat expansion (HRE) in the *chromosome 9 open reading frame 72* (*C9orf72*) gene. The *C9orf72* HRE is the most common genetic cause of familial and sporadic ALS as well as frontotemporal dementia. Using astroglia differentiated from patient fibroblast-derived induced pluripotent stem cells (iPSA), we found that astroglial development was unaffected by the HRE as shown by robust expression of astroglial markers. Glutamate handling also appeared normal in *C9orf72* ALS (c9ALS) iPSA as demonstrated by mRNA expression of excitatory amino acid transporter 2 (EAAT2), the principal glutamate transporter in the CNS found predominantly in astroglia, and

functional glutamate transport from the extracellular space. We measured *C9orf72* transcripts by qRT-PCR, detected HRE-containing RNA foci by RNA fluorescent in situ hybridization, and quantified levels of poly-glutamine-proline dipeptide repeats (a product of non-canonical translation of the HRE) by immunoassay in c9ALS iPSA. All of these c9ALS-related pathologies were less severe in astroglia than in neurons. Nuclear morphology, pore composition, and nucleocytoplasmic transport were also assessed in c9ALS iPSA. We then longitudinally analyzed co-cultures of human iPSC-derived astroglia and motor neurons for neuronal morphology and survival to evaluate alterations in glia-neuron interactions in the presence of the *C9orf72* HRE. Preliminary data indicate a decrease in viability of control human motor neurons cultured with c9ALS astroglia. Together these data suggest that the *C9orf72* HRE may alter astroglial physiology, glia-neuron interactions, and ultimately c9ALS pathophysiology.

Disclosures: J.T. Pham: None. **L.R. Hayes:** None. **J. Daigle:** None. **J.C. Grima:** None. **S.J. Miller:** None. **X. Tang:** None. **W. Zhou:** None. **L. Xue:** None. **S. Vidensky:** None. **S. Mackey-Alfonso:** None. **T. Gendron:** None. **J.D. Rothstein:** None.

Poster

206. Astrocytes: Disease Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 206.27/E2

Topic: B.12. Glial Mechanisms

Support: NIH Grant 1R01NS097195-01

NIH Grant R03 NS094071-01

Title: Antimicrobial peptides derived from human and bovine cathelicidins inhibit zika virus replication through interferon signaling

Authors: *M. HE[1,2], H. ZHANG[3], Y. LI[1], G. WANG[1], J. ZHAO[1], Y. HUANG[1], J. ZHENG[1]
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Abstract: Objective: Zika virus (ZIKV) is a neurotrophic flavivirus that is capable of infecting humans, leading to brain abnormalities during fetal development. Although there is a significant effort in identifying viral suppression strategies for ZIKV, currently no vaccines or specific therapies are available to treat ZIKV infection. Antimicrobial peptides, which are ancient and potent host defense molecules in nearly all forms of life, have been found to be effective against several types of viruses, such as HIV-1 and influenza A viruses. However, they have never been tested in ZIKV infection. We hypothesize that antimicrobial peptide treatment may become an effective viral suppression strategy against ZIKV infection. **Methods:** ZIKV infection was

propagated in Vero cells and tested in primary human fetal astrocytes that we previously identified as a susceptible brain cell type for ZIKV. Nine antimicrobial peptides derived from human and bovine cathelicidins and their corresponding control peptide were screened for their ability to suppress ZIKV infection. Viral infection levels were determined by quantification of intracellular and extracellular ZIKV RNA using real time RT-PCR, as well as by counting plaque-forming units in viral plaque-forming assays. **Results:** The initial screening of the antimicrobial peptides was performed in Vero cells at the multiplicity of infection of 0.2. Two peptides, D106L and D10, were found to have strong antiviral activities against ZIKV and little toxicity at effective doses. We further tested D106L and D10 in human fetal astrocytes, which are a natural host of ZIKV during viral transmission, and found that D106L and D10 effectively suppressed ZIKV infection in astrocytes. The viral suppression is consistent and not dependent on whether peptides were added before, during, or after ZIKV infection. Interestingly, pretreatment with D106L and D10 significantly reduced viral attachment and entry in astrocytes. Furthermore, treatment with the antimicrobial peptides was associated with significant upregulation of type I interferons. Inhibition of type I interferon signaling through a small molecule fludarabine reversed the suppression of ZIKV infection by D106L and D10, suggesting that D106L and D10 inhibited ZIKV replication through interferon signaling. **Conclusion:** Antimicrobial peptides protect cells from ZIKV infection through type I interferon signaling. Strategies that target antimicrobial peptides might be useful in halting ZIKV infection.

Disclosures: **M. He:** None. **H. Zhang:** None. **Y. Li:** None. **G. Wang:** None. **J. Zhao:** None. **Y. Huang:** None. **J. Zheng:** None.

Poster

207. Alzheimer's Disease: -Omics Approaches

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 207.01/E3

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

Support: NIH Grant P30AG053760

NIH Grant T32NS007222

Title: Ezrin upregulation is a potential early biomarker of tau-mediated neurodegeneration

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Abstract: Proteomics approaches are used to identify changes in the proteome that could help us understand the pathogenesis of pathological hallmarks and/or cellular stress responses associated with their accumulation. The identification of these potential biomarkers could lead to the development of diagnostic tools and/or therapeutic strategies that avert the epidemic of neurodegenerative diseases. However, due to the heterogeneity of postmortem tissue and overexpression of human proteins in animal models, it is important to define the protein samples based on brain region specificity and timing of neurodegeneration associated with specific proteome changes. Here, we described the identification of Ezrin as a protein that is upregulated in a brain region specific manner. First, we identified Ezrin upregulated in a tauopathy mouse model (JNPL3) that expresses human tau bearing a P301L mutation. JNPL3 mice developed motor impairment, which severity correlates with increase accumulation of pathological tau. Interestingly, Ezrin upregulation was identified before motor impairment is detected in JNPL3 mice. Ezrin upregulation was validated in temporal cortex of Alzheimer's disease patients but not in cerebellum, indicating that changes in Ezrin level takes place in selective regions affected by neurodegeneration. Additionally, Ezrin upregulation was also found in the temporal cortex of mild cognitive impairment cases, suggesting that Ezrin is an early biomarker of neurodegeneration. Moreover, knockdown of Ezrin orthologue (*erm-1*) in a *C. elegans* tauopathy model increases tau phosphorylation and motor impairment phenotype. Taken together, the results indicate that Ezrin is an early indicator of neurodegeneration that may serve as modulator of tau pathology.

Disclosures: I.E. Vega: None. **A. Umstead:** None. **C. Wygant:** None. **J.S. Beck:** None. **S.E. Counts:** None. **J.M. Van Raamsdonk:** None.

Poster

207. Alzheimer's Disease: -Omics Approaches

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 207.02/E4

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

Support: NIH grant 5R01AG047589

Title: An anatomical correlate of the mouse default mode network

Authors: *J. D. WHITESELL[1], A. LISKA[2], N. GRADDIS[1], P. BOHN[1], S. MIHALAS[1], A. GOZZI[2], J. A. HARRIS[1]
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Abstract: The default mode network (DMN) is a group of brain regions that display correlated activity during "alert rest" and deactivation during goal-directed tasks. The DMN has been

defined in humans and nonhuman primates on the basis of resting state functional MRI (fMRI), and a rodent correlate has recently been described using fMRI in anesthetized rats and mice. Several neurodegenerative disorders affect the DMN, including Alzheimer's disease (AD) where alterations in network activity occur across stages of the disease, and DMN regions show early and extensive deposition of amyloid-beta plaques. The structural correlates that support this functional network activity are not known; a better understanding may provide insight and tools for probing the selective vulnerability of the DMN in AD. We hypothesized that brain regions comprising the DMN are preferentially linked by one class of cells, while a separate cell class links these regions to non-DMN brain areas. We first examined the structural connectivity underlying the functionally-defined rodent DMN by performing graph theoretical analysis on a large dataset of stereotaxic viral tracing experiments (the Allen Mouse Brain Connectivity Atlas) to identify a group of anatomically connected regions that closely resembles the putative mouse DMN. We compared these regions with a DMN consensus map based on fMRI data registered to the Allen Mouse Common Coordinate Framework to identify which anatomical brain regions make up the functionally-defined DMN. We found that DMN regions send more cortical projections to other DMN regions than to regions outside the DMN. We then tested our hypothesis that there are specific classes of long-range projection neurons that preferentially target DMN regions using paired stereotaxic injections of retrograde CAV2-Cre virus and anterograde rAAV expressing Cre-dependent fluorescent protein (eGFP). For a given DMN source, retrograde Cre expression was produced by CAV2-Cre injections into both DMN and non-DMN targets, and the resulting Cre-dependent rAAV-eGFP projections were compared (in-DMN target-defined projections compared to outside-DMN target-defined projections). One DMN region, the retrosplenial cortex, possesses at least two classes of target-defined cell types, one that projects preferentially to DMN regions and another that projects to regions outside the DMN, while other DMN regions seem to have only one projection pattern. This collection of target-defined projection patterns will provide a detailed map of the specific anatomical circuit architecture underlying the functional rodent DMN.

Disclosures: J.D. Whitesell: None. **A. Liska:** None. **N. Graddis:** None. **P. Bohn:** None. **S. Mihalas:** None. **A. Gozzi:** None. **J.A. Harris:** None.

Poster

207. Alzheimer's Disease: -Omics Approaches

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 207.03/E5

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

Support: NIH Grant R01AG047928

NIH Grant R01AG053987

NIH Grant R01GM114260

Title: Neuronal expression of Alzheimer’s disease associated U1-70K fragment causes splicing dysfunction, impaired synaptic plasticity, and cognitive deficits in mice

Authors: *P.-C. CHEN[1], T. I. SHAW[2], B. TEUBNER[3], M. LIU[1], B. BAI[1], Y. LI[2], A. MANCIERI[1], Z. WU[1], I. T. BAYAZITOV[3], D. EDDINS[3], H. WANG[1], L. R. EARLS[3], S. S. ZAKHARENKO[3], R. J. SMEYNE[5], J. PENG[1,4]
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Abstract: Alzheimer's disease (AD) displays insoluble protein aggregates and progressive cognitive decline, but the causative mechanisms are still not fully understood. In addition to well-known β-amyloid and tau aggregation, recent proteomics profiling has identified, in sporadic and familial cases, an early, AD-specific pathology of U1 small nuclear ribonucleoprotein complex, including U1-70K and its N-terminal fragment (N40K). Here we characterize a transgenic mouse model by neuronal expression of N40K, which renders a dominant negative effect to downregulate full length U1-70K. The animals recaptures previously observed AD phenotypes, including N40K insolubility, U1-70K downregulation and cytoplasmic mislocalization, splicing deficiency, neuronal loss, as well as impairment of long-term potentiation and cognitive function. Deep transcriptomic analysis reveals concurrent aberrant splicing of synaptic components in the mice and human AD brain. Thus U1 snRNP dysfunction and splicing alteration may contribute to AD pathogenesis, representing a novel pathway for potential therapeutic intervention.

Disclosures: P. Chen: None. **T.I. Shaw:** None. **B. Teubner:** None. **M. Liu:** None. **B. Bai:** None. **Y. Li:** None. **A. Mancieri:** None. **Z. Wu:** None. **I.T. Bayazitov:** None. **D. Eddins:** None. **H. Wang:** None. **L.R. Earls:** None. **S.S. Zakharenko:** None. **R.J. Smeyne:** None. **J. Peng:** None.

Poster

207. Alzheimer's Disease: -Omics Approaches

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 207.04/E6

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

Support: AG042178

AG47812

Garrison Family Foundation

Title: MicroRNA-455-3p as a potential peripheral biomarker for Alzheimer's disease

Authors: *S. KUMAR, M. VIJAYAN, P. REDDY
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Abstract: The purpose of our study was to identify microRNAs (miRNAs) as early detectable peripheral biomarkers in Alzheimer's disease (AD). To achieve our objective, we assessed miRNAs in serum samples from AD patients and MCI subjects relative to healthy controls. We used Affymetrix microarray analysis and validated differentially expressed miRNAs using qRT-PCR. We further validated miRNA data using AD postmortem brains, APP transgenic mice and AD cell lines. We identified a gradual upregulation of four miRNAs: miR-455-3p, miR-4668-5p, miR-3613-3p, and miR-4674. A fifth miRNA, mir-6722, was down-regulated in persons with AD and MCI compared to controls. Validation analysis by qRT-PCR showed significant upregulation of only miR-455-3p (P=0.007) and miR-4668-5p (P=0.016) in AD patients compared to healthy controls. Further, qRT-PCR analysis of the AD postmortem brains with different Braak stages also showed upregulation of miR-455-3p (P=0.016). However, ROC curve analysis revealed a significant area under curve (AUC) value only for miR-455-3p in the serum (AUROC=0.79; P=0.015) and brains (AUROC=0.86; P=0.016) of AD patients. Expression analysis of APP transgenic mice also revealed high level of mmu-miR-455-3p (P=0.004) in the cerebral cortex (AD-affected) region of brain and low in the non-affected area i.e. cerebellum. Further, human and mouse neuroblastoma cells treated with the amyloid-$\beta_{(1-42)}$ peptide also showed a similarly higher expression of miR-455-3p. Functional analysis of differentially expressed miRNAs via the miR-path indicated that miR-455-3p was associated in the regulation of several biological pathways. Genes associated with these pathways were found to have a crucial role in AD pathogenesis. An increase in miR-455-3p expression found in AD patients and Aβ pathologies unveiled its biomarker characteristics and a precise role in AD pathogenesis.

Disclosures: S. Kumar: None. **M. Vijayan:** None. **P. Reddy:** None.

Poster

207. Alzheimer's Disease: -Omics Approaches

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 207.05/E7

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

Support: RO1 AG043375

PO1 AG107617

PO1 AG014449

Title: Quantitative analysis of endosomal-lysosomal markers within the septohippocampal circuit of Ts65Dn mice following maternal choline supplementation (MCS)

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Abstract: Down syndrome (DS) is the most frequent genetic cause of intellectual disability. Individuals with DS display impairments in hippocampal-dependent learning and memory, degeneration of basal forebrain cholinergic neurons (BFCNs), and by middle age many develop the neuropathological hallmarks of Alzheimer's disease (AD): amyloid-β plaques, neurofibrillary tangles, and abnormalities in early endosomes. We have previously hypothesized that BFCN degeneration within the septohippocampal circuit is due to deficient neurotrophic support, a result of dysregulated retrograde and endosomal transport. To study endosomal defects in BFCNs and examine the effect of a proposed maternal choline supplementation (MCS) treatment paradigm on this vulnerable neuronal population, we have employed the use of the Ts65Dn mouse model of DS/AD. We previously reported overexpression of positive effectors of endocytic uptake, transfer, and fusion in the Ts65Dn mouse. Single-population microarray and qPCR analyses indicate that MCS lowers the overexpression of several genes involved in endosomal-lysosomal pathways in the hippocampus and entorhinal cortex in young and aged Ts65Dn mice relative to normal disomic (2N) littermates. Additionally, we observed an improvement in neuronal size, shape, and density within the hippocampus of Ts65Dn mice following MCS. In the present study, we are performing morphometric cellular quantification of the effects of MCS within the septohippocampal circuit of aged Ts65Dn mice. Brains are being immunostained with neuronal and synaptic markers, as well as markers for endosomes, lysosomes, and autophagosomes. Unbiased neuronal counts and density measurements will be conducted on BFCNs and CA1 pyramidal neurons as well as measurements of size and shape that may point towards improvements in septohippocampal structure and function in MCS treated offspring. Unbiased regional surveys of endocytic and lysosomal vesicle distribution and localization within BFCNs and CA1 pyramidal neurons will provide novel data as to whether perinatal MCS attenuates DS endosomal pathology in Ts56Dn offspring, and improves the efficiency of retrograde transport between the hippocampus and basal forebrain. The translational implications of this project suggest that if MCS is able to increase neurotrophic signaling and enhance neurotransmission within septohippocampal neurons in Ts65Dn offspring, neurodegeneration may be partially rescued in patients with DS and AD with early choline treatment and/or delivery of choline mimetics.

Disclosures: M.K. Gautier: None. **M.J. Alldred:** None. **H.M. Chao:** None. **A. Saltzman:** None. **E.J. Mufson:** None. **S.D. Ginsberg:** None.

Poster

207. Alzheimer's Disease: -Omics Approaches

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 207.06/E8

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

Support: RO1 AG043375

PO1 AG107617

PO1 AG014449

Title: Single population RNA sequencing (RNA-seq) analysis of basal forebrain cholinergic neurons (BFCNs) within the medial septal nucleus in a mouse model of Down syndrome (DS) and Alzheimer's disease (AD) identifies unique transcriptional mosaics following maternal choline supplementation (MCS)

Authors: *H. M. CHAO[1,2], M. J. ALLDRED[1,2], A. SALTZMAN[1], A. HEGUY[3], S. D. GINSBERG[1,2,4,5]
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Abstract: Down syndrome (DS) is the most frequent genetic cause of intellectual disability (ID). Individuals with DS have ID and decreased cognitive function seen by impairments in hippocampal learning and memory and communication skills. Individuals with DS also develop Alzheimer's disease (AD) neuropathological hallmarks early in mid-life, including senile plaques, neurofibrillary tangles, and early endosomal abnormalities. The Ts65Dn mouse model mimics both cognitive and morphological deficits of DS and AD, including degeneration of basal forebrain cholinergic neurons (BFCNs). An inexpensive, nontoxic treatment, maternal choline supplementation (MCS), allows offspring to have increased choline available through their dams during critical brain development timepoints throughout the perinatal period. MCS in Ts65Dn offspring improves behavioral phenotypes associated with DS, and protects BFCNs from neurodegeneration. High-throughput functional genomics including RNA-seq enables genes and noncoding RNAs (ncRNAs) to be assessed quantitatively, which is relevant towards understanding the molecular pathogenesis of AD and DS. We report on the feasibility of utilizing single population RNA-seq to identify genes and signaling pathways that are MCS-responsive within individual neuronal subtypes in the septohippocampal pathway. We utilize laser capture microdissection (LCM) to isolate individual vulnerable populations of neurons to understand the mechanisms underlying neurodegeneration and link these expression level changes to established pathological hallmarks and cognitive decline for therapeutic development in human DS and AD.

Preliminary analysis consists of isolating via LCM ~500 BFCNs from the medial septal nucleus from adult offspring of choline normal and choline supplemented dams by immunohistochemically labeling unfixed frozen tissue for choline acetyltransferase (ChAT). RNA from these ChAT-positive isolated BFCNs was subjected to RNA-seq library preparation to determine the viability of isolating RNA from individual cell types for downstream transcriptional analysis. Preliminary results suggest that 500 BFCNs is sufficient for cDNA library preparation for RNA-seq. We further tested the viability of targeted cDNA library preparation for these small RNA input sample sizes. In sum, single-population RNA-seq of LCM-captured BFCNs will be performed in the Ts65Dn model of DS and AD relative to disomic littermates in conjunction with a noninvasive, nontoxic treatment, MCS, to understand the molecular and cellular underpinnings of selective vulnerability in an attempt to preserve the septohippocampal circuit in DS and AD.

Disclosures: H.M. Chao: None. **M.J. Alldred:** None. **A. Saltzman:** None. **A. Heguy:** None. **S.D. Ginsberg:** None.

Poster

207. Alzheimer's Disease: -Omics Approaches

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 207.07/E9

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

Support: RO1 AG043375

PO1 AG107617

PO1 AG014449

Title: Single-population RNA-sequencing (RNA-seq) analysis of septohippocampal neurons in trisomic mice identify differential expression profile mosaics following perinatal, prenatal, and postnatal maternal choline supplementation (MCS)

Authors: *M. J. ALLDRED[1,2], H. M. CHAO[1,2], T. LHAKHANG[3], Y. ZHANG[3], A. HEGUY[3], S. D. GINSBERG[1,2,4,5]
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Abstract: People with Down syndrome (DS) have intellectual disability and develop basal forebrain cholinergic neuron (BFCN) and hippocampal CA1 pyramidal neuron degeneration along with synaptic loss, neurofibrillary tangles, and amyloid plaques similar to that seen in Alzheimer’s disease (AD) by the third decade of life. Therefore, AD and DS exhibit similar selective vulnerability of neurons within the septohippocampal circuit. Unfortunately, there is a

lack of knowledge underlying the mechanism(s) driving this selective vulnerability, impeding drug discovery and therapeutic intervention. In this study, we have utilized the trisomic mouse model Ts[Rb(12.17^{16})]2Cje (Ts2) which presents phenotypic and pathological features similar to the well-established Ts65Dn mouse model. Ts2 mice recapitulate key aspects of DS and AD pathophysiology including cognitive dysfunction, namely memory and attention deficits, and septohippocampal degeneration, enabling mechanistic assessments to be translated to humans. A potential therapeutic strategy is maternal choline supplementation (MCS). We previously demonstrated that perinatal MCS (during pregnancy and lactation) attenuates cognitive dysfunction and attentional deficits in Ts65Dn offspring. We propose to identify the molecular and cellular underpinnings of these beneficial changes within individual cell types in the septohippocampal circuit compared to normal disomic (2N) littermates. BFCNs and CA1 pyramidal neurons will be accessed via laser capture microdissection (LCM) in concert with single-population RNA sequencing (RNA-seq) with custom-designed pathway-specific pipelines. MCS treatment was tested at 3 distinct developmental timeframes: perinatal, prenatal (gestation to birth), and postnatal (birth to weaning) to determine developmentally critical junctures for effective MCS treatment, which may have beneficial gene expression changes critical for normal cognition and BFCN development in DS offspring. Initial results show our ability to detect and quantitate many individual genes and signaling pathways of interest, including the known triplicated genes Dyrk1a and App. Preliminary comparison of MCS treatment by genotype yields promising results, as Dyrk1a is MCS responsive, whereas App does not appear to be affected. Importantly, we will determine whether supplementation during the entire perinatal period is required for beneficial effects on the septohippocampal memory circuit in vivo, or whether prenatal or early postnatal MCS is necessary or sufficient for structure-function stability, allowing for the generation of rational therapeutics.

Disclosures: **M.J. Alldred:** None. **H.M. Chao:** None. **T. Lhakhang:** None. **Y. Zhang:** None. **A. Heguy:** None. **S.D. Ginsberg:** None.

Poster

207. Alzheimer's Disease: -Omics Approaches

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 207.08/E10

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

Support: PO1 AG014449

RO1 AG043375

PO1 AG107617

R01 NS21072

R01 AG025970

P30 AG010161

P30 AG053769

Title: Downregulation of select neurotrophin and neurotrophin receptor genes within CA1 pyramidal neurons and hippocampus: Correlation with cognitive performance and neuropathology in mild cognitive impairment (MCI) and Alzheimer's disease (AD)

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[1]Ctr. for Dementia Res., [2]Psychiatry, [3]Neurosci. & Physiol., [4]NYU Neurosci. Inst., [5]Skirball Inst. of Biomolecular Med., Nathan S Kline Institute/NYU Langone Med. Ctr., Orangeburg, NY; [6]Banner Alzheimer's Inst., Phoenix, AZ; [7]Inst. of Functional Genomics, Montpellier, France; [8]Univ. de Montpellier, Montpellier, France; [9]Transl Sci. and Mol Med, Family Med., [10]Hauenstein Neurosciences Ctr., Michigan State Univ., Grand Rapids, MI; [11]Neurobio. and Neurol., Barrow Neurolog. Inst., Phoenix, AZ

Abstract: Hippocampal CA1 pyramidal neurons, a major component of the medial temporal lobe memory circuit, are selectively vulnerable during the progression of Alzheimer's disease (AD). The cellular mechanism(s) underlying degeneration of these neurons and the relationship to cognitive performance remains largely undefined. Here, we profiled neurotrophin and neurotrophin receptor gene expression within microdissected CA1 neurons along with regional hippocampal dissections from subjects who died with a clinical diagnosis of no cognitive impairment (NCI), mild cognitive impairment (MCI), or AD from the Rush Religious Orders Study (RROS) using laser capture microdissection (LCM), custom-designed microarray analysis, and qPCR of CA1 subregional dissections. Expression profiling data was correlated with cognitive performance and AD neuropathology criteria. We found a significant downregulation of several neurotrophin genes (e.g., Gdnf, Ngfb, and Ntf4) in CA1 pyramidal neurons in MCI compared to NCI and AD subjects. In addition, the neurotrophin receptor transcripts TrkB and TrkC were decreased in MCI and AD compared to NCI. Regional hippocampal dissections also revealed select neurotrophic gene dysfunction, including downregulation of Cntf, Ngfb, TrkA, TrkB, and TrkC in MCI and AD, providing evidence for vulnerability within the hippocampus proper during the progression of dementia. Downregulation of several neurotrophins of the NGF family and cognate neurotrophin receptor (TrkA, TrkB, and TrkC) genes correlated with antemortem cognitive measures including Mini-Mental State Exam (MMSE), composite global cognitive score (GCS), and performance on Episodic, Semantic, and Working Memory, Perceptual Speed, and Visuospatial tests. Significant correlations were found between select neurotrophic expression downregulation and neuritic plaques (NPs) and neurofibrillary tangles (NFTs), but not diffuse plaques (DPs). These results suggest that decreases in select neurotrophins/neurotrophin receptors are associated with an increase in NPs and NFTs likely indicating that this decrement contributes to hippocampal cellular dysfunction, particularly within vulnerable CA1 pyramidal neurons. In sum, these data suggest that dysfunction of

neurotrophin signaling and their cognate receptors occur in vulnerable hippocampal cell types associated with cognitive impairment and AD neuropathology during the onset of AD.

Disclosures: S.D. Ginsberg: None. **M.H. Malek-Ahmadi:** None. **M.J. Alldred:** None. **Y. Chen:** None. **F.D. Jeanneteau:** None. **T.M. Kranz:** None. **M.V. Chao:** None. **S.E. Counts:** None. **E.J. Mufson:** None.

Poster

207. Alzheimer's Disease: -Omics Approaches

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 207.09/E11

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

Support: P01AG014449

R01AG043375

P01AG107617

P30AG053760

R01AG044372

R01NS082730

R21AG053581

Title: Dysregulation of synaptic and neurotransmitter receptor gene expression is associated with tau oligomerization in nucleus basalis neurons during the progression of Alzheimer's disease

Authors: *C. T. TIERNAN[1], J. S. BECK[1], S. D. GINSBERG[3], N. M. KANAAN[1,4], E. J. MUFSON[5], S. E. COUNTS[1,2,4,6]
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Abstract: Tau is the predominant protein found in neurofibrillary tangles (NFTs), which contribute to neuronal dysfunction and cognitive decline in Alzheimer’s disease (AD) and other tauopathies. The exact role of tau in neurodegenerative diseases is not fully understood. However, accumulating evidence suggests that one of the toxic tau moieties may be soluble, oligomeric tau species. In this regard, tau oligomers appear prior to NFT formation within vulnerable forebrain projection neurons in AD and correlate more strongly with neuronal loss

than NFTs. Whether tau oligomerization is associated with potentially pathogenic alterations at the molecular and cellular level remains unknown. To address this question, we compared gene expression profiles of magnocellular nucleus basalis (NB) neurons singly immunostained for $p75^{NTR}$, an established cholinergic cell marker, or dual-labeled for $p75^{NTR}$ and tau oligomeric complex 1 (TOC1), a marker of tau oligomers. Laser capture microdissection and custom-designed microarray analysis were performed on $p75^{NTR}$ +/- TOC1 NB neurons using tissue obtained postmortem from Rush Religious Order Study participants who died with an antemortem clinical diagnosis of no cognitive impairment (NCI), mild cognitive impairment (MCI; a putative prodromal AD stage) or mild/moderate AD (n = 8/group). Preliminary analysis focused on TOC1-associated gene expression changes in the NCI group. We found a significant, ~25-40% downregulation of presynaptic (Syp and Vamp1) and postsynaptic (Dlg4 and Synpo) markers in $p75^{NTR}$/TOC1 co-labeled NB neurons compared to $p75^{NTR}$ singly-labeled NB neurons ($p < 0.05$). In contrast, kainate (Grik2 and Grik4) and AMPA (Gria2) glutamate receptor subunits were upregulated by ~30-35%, whereas NMDA (Grin2A, Grin2B, and Grin2C) receptor subunits were downregulated by ~30% ($p<0.05$) in dual-labeled neurons. We also observed dysregulation of several transcripts encoding G protein-coupled receptors for ascending subcortical afferents (e.g., downregulation of Drd1 dopamine receptor, Htr2C serotonin receptor, and Galr1 and Galr2 galanin receptors; upregulation of Adra1b noradrenergic receptor) in dual-labeled neurons compared to $p75^{NTR}$ singly-labeled NB neurons in NCI subjects. These initial observations at the single population level within a well-characterized clinical pathological postmortem cohort suggest that tau oligomerization plays a potentially mechanistic role in synaptic and neurochemical dysregulation in cholinergic NB cortical projection neurons in non-cognitively impaired elders.

Disclosures: C.T. Tiernan: None. **J.S. Beck:** None. **S.D. Ginsberg:** None. **N.M. Kanaan:** None. **E.J. Mufson:** None. **S.E. Counts:** None.

Poster

207. Alzheimer's Disease: -Omics Approaches

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 207.10/E12

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

Support: NIH Grant ES020715

Title: Sex specific metabolic and epigenetic changes in primary fibroblasts from patients with Alzheimer’s disease

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Abstract: Alzheimer's disease (AD) is the most common form of dementia in the elderly and sixth leading cause of death. Nearly 5.4 million Americans are affected by AD with numbers expected to triple by the year 2050. Complex changes that occur in AD patients and the lack of understanding early disease mechanisms have hindered the development of efficacious therapeutic interventions. Systems biology approaches that have recently become available offer an outstanding opportunity to monitor changes involved in AD development in multiple functionally connected pathways using readily available biofluids or primary cells such as fibroblasts. Moreover, since fibroblasts can be differentiated into neurons, cells that are directly affected in AD, the demonstration that human fibroblasts recapitulate metabolic alterations detected in CSF, plasma, and postmortem brain tissue from AD patients could validate the use of these cells for studying the disease mechanisms and the development of individualized treatment regimens.
We applied non-targeted and targeted metabolomics, stable isotope tracers and next generation sequencing to establish to what extent metabolic and epigenetic changes in fibroblasts from late onset AD patients recapitulate alterations established previously in CSF, plasma and postmortem brain tissue from individuals with mild cognitive impairment and AD. Our data revealed sex- and disease-specific signatures validating the use of human fibroblasts to study AD mechanisms.

Disclosures: J.M. Wilkins: None. **S. Trushin:** None. **T. Dutta:** None. **S. Baheti:** None. **D. Sakrikar:** None. **X. Persson:** None. **I. Lanza:** None. **E. Trushina:** None.

Poster

207. Alzheimer's Disease: -Omics Approaches

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 207.11/F1

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

Support: NIH Grant AG053987

NIH Grant AG047928

Title: Differential enrichment and elution proteome (DEEP) analysis of amyloid precursor protein interactome in Alzheimer's brain

Authors: *J. M. SIFFORD, B. BAI, Y. LI, J. PENG
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Abstract: Amyloid Precursor Protein (APP) is a transmembrane protein expressed in the brain and its genetic mutations are linked to Alzheimer's disease (AD). APP-derived amyloid-β

peptide highly accumulates in AD brain and is postulated to trigger pathogenic cascade. The physiological function and dysregulation of APP processing, however, are not fully illustrated. Here we report a comprehensive analysis of APP interactome directly in AD brain using an antibody-based differential enrichment and elution profiling (DEEP) strategy. The DEEP strategy utilized the 10-plex isobaric labeling method to compare the input of whole brain lysate with antibody-enriched eluates under different stringency, including regularly washed eluates and even unwashed eluates in which weak binding proteins survive. We quantified 7,804 proteins and extracted 323 putative APP interactors. The APP interactome was further ranked into multiple tiers according to differential enrichment at different elution conditions, reflecting variable binding affinity of individual proteins. In addition, we found that proteins associated antibody resins were more significantly affected by co-immunoprecipitation conditions than the usage of different antibodies. The enrichment of APP antigen itself can be used to evaluate antibody quality. The study revealed a large number of novel components involved in Notch and Wnt pathways, endocytosis and vesicle transport, the ubiquitin-proteasome system, cellular morphogenesis, and synaptic activities. Integration with AD genetic risk factors recapitulates possible involvement of inflammation in pathogenesis. Thus, the DEEP strategy improves the sensitivity and specificity of affinity purification by high throughput mass spectrometry; and the tiered APP interactome in human diseased brain provides a valuable resource for subsequent functional and pathological investigation.

Disclosures: **J.M. Sifford:** None. **B. Bai:** None. **Y. Li:** None. **J. Peng:** None.

Poster

207. Alzheimer's Disease: -Omics Approaches

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 207.12/F2

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

Support: Alzheimer’s association Grant AARF-16-443213

NIH Grant AG037481

NIH Grant AG037919

NIH Grant K01AG044490

NIH Grant ES024233

DOD Grant W81XWH-13-1-0384

Title: Integrated system approach reveals the dynamic changes of brain transcriptome associated with aging and amyloid pathology

Authors: *K. NAM, N. F. FITZ, C. M. WOLFE, F. LETRONNE, I. LEFTEROV, R. KOLDAMOVA
Envrn. and Occup. Heath, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Alzheimer's disease (AD) is a complex disease with a significantly increased risk for carriers of E4 allele. Aging is the strongest risk factor for AD while the lifestyle has a modulatory effect on disease progression. However, APOE isoform specific effect and its association with age-dependent changes in the brain transcriptome still remain poorly understood. To get further insight in the specific effect of APOE isoform in response to aging, we performed RNA-seq using brain samples and isolated microglia from WT and APP/PS1 mice expressing human APOE3 and APOE4 (WT/E3, WT/E4, APP/E3, APP/E4). The transcriptional profiles of young (6 month) and older mice (13 month) were further processed to identify gene co-expression networks that correlate to aging, APOE isoform and amyloid phenotype. Our data show that genes related to immune response were significantly up-regulated in older APP/E3 and APP/E4 transgenic mice but the effect was stronger in APOE4 expressing mice. Surprisingly, the immune response was a down-regulated category in older WT/E3 and WT/E4 mice versus their younger counterparts. In contrast, genes involved in synaptic transmission were down-regulated with aging in both APP transgenic and WT mice regardless of APOE isoform. The conclusions from this study are: a) aging is the strongest factor that affects brain transcriptome; b) APOE isoform-specific effect on brain transcriptome correlates to amyloid phenotype and is less pronounced in WT mice; c) the microglia transcriptome is affected by amyloid pathology, aging and APOE isoform.

Disclosures: K. Nam: None. **N.F. Fitz:** None. **C.M. Wolfe:** None. **F. Letronne:** None. **I. Lefterov:** None. **R. Koldamova:** None.

Poster

207. Alzheimer's Disease: -Omics Approaches

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 207.13/F3

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

Title: Dyregulation of AZGP1, AEBP1 and antisense RNAs in middle temporal gyrus of Alzheimer's Disease patients

Authors: *I. S. PIRAS[1], J. KRATE[2], E. DELVAUX[3], J. NOLZ[3], D. BROKAW[3], M. D. DE BOTH[1], D. F. MASTROENI[3], T. G. BEACH[4], P. D. COLEMAN[3], M. J. HUENTELMAN[1]
[1]Translational Genomics Res. Inst., Phoenix, AZ; [2]Univ. of Arizona Col. of Med., Tucson, AZ; [3]Arizona State Univ., Tempe, AZ; [4]Banner Sun Hlth. Res. Inst., Sun City, AZ

Abstract: We sequenced the whole transcriptome of the middle temporal gyrus (MTG - Area 21) of a sample of post-mortem brains from AD patients (*n* = 8) and Non-Demented (ND) controls (*n* = 8).
The samples were obtained from the Banner Sun Health Research Institute Brain and Body Donation Program (Sun City, AZ). They were age- and sex-matched and all with *APOE* 3/3 genotype. The RNA was extracted and sequenced using the Hiseq2000 (Illumina), whereas differential expression analysis and Fold Change (FC) were estimated by the DESeq2 method. The results were validated in a larger cohort and in a public dataset (*GSE5281*), both characterized by microarray and from the same brain region. Non-protein coding genes were validated in a public dataset from temporal cortex brain region (*syn6090802*). Finally, we investigated about the presence of genetic associations of Single Nucleotide Polymorphisms (SNPs) located in the candidate genes using International Genomics of Alzheimer's Project (IGAP) data.
We detected a total of 119 differentially expressed genes (False Discovery Rate Adj $p < 0.05$), including protein coding (*n* = 103; 86.6%), long non coding RNAs (*n* = 8; 6.7%), antisense RNAs (*n* = 6; 5.0%) and processed RNAs (*n* = 2; 1.7%). A total of 73 genes (61.3%) were overexpressed, whereas 46 (38.7%) were underexpressed in AD. We selected 18 candidate genes filtering for adj-*p* value and FC, validating 6 genes (4 protein coding and 2 antisense) in the expression profiling and RNA sequencing datasets: *HSD11B2*, *AZGP1*, *AEBP1*, *MYOT*, *JHDM1D-AS1*, and *RP4-773N10.4*. All genes with the exception of *JHDM1D-AS1*, were upregulated in AD. Moreover, *AEBP1* showed a significant positive correlation with Braak Staging in AD (*p* = 2.8E-05). Finally, in the IGAP cohort we detected 6 nominal significant SNPs located in *AZGP1*, and 1 nominal SNP in *AEBP1*. No significant correlations were found between antisense RNAs (asRNAs) and close genes.
Our results support the association of *AZGP1* (Alpha-2-Glycoprotein 1, Zinc-Binding) with AD. Recently, the expression of the protein was detected for downregulated in the serum AD patients, and in a different study overexpressed in the Cerebral Spinal Fluid. *AEBP1* was recently associated in the hippocampus of AD patients, and correlated with the degree of β-amyloid pathology. An haplotype in the functionally *HSD11B2* related gene *HSD11B1* was found associated with AD, whereas *MYOT* encode for a cytoskeletal protein. Finally, we reported for the first time in the MTG the dysregulation of the two asRNA genes *JHDM1D-AS1*, and *RP4-773N10.4*. Further studies are needed to establish the role of the proteins and asRNAs encoded from the associated genes.

Disclosures: I.S. Piras: None. **J. Krate:** None. **E. Delvaux:** None. **J. Nolz:** None. **D. Brokaw:** None. **M.D. De Both:** None. **D.F. Mastroeni:** None. **T.G. Beach:** None. **P.D. Coleman:** None. **M.J. Huentelman:** None.

Poster

207. Alzheimer's Disease: -Omics Approaches

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 207.14/F4

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

Support: BrightFocus

Stop Cancer

Title: Single nucleus RNA-sequencing of human AD brain

Authors: M. OTERO-GARCIA[1], Y. XUE[1], T. SHAKOURI[1], G. COPPOLA[2], *I. COBOS[1]
[1]Pathology & Lab. Med. - Neuropathology, [2]Departments of Psychiatry and Neurol., UCLA, Los Angeles, CA

Abstract: A salient feature of neurodegenerative diseases including Alzheimer disease (AD) is selective regional and cellular vulnerability to pathological changes and neurodegeneration. However, the precise identity of the cells that are affected and the molecular basis of neurodegeneration are largely unknown. Current single-cell and single-nucleus RNA-sequencing methods allow for unbiased cell identification and measuring differences in gene expression profiles between thousands of individual cells with unprecedented accuracy. To define the precise neuronal cell types that are affected and the mechanisms of selective vulnerability in AD, we conducted single-nucleus RNA-seq of postmortem human brain in combination with neuroanatomical studies. Associative (precuneus) and primary (primary visual cortex) cortices, which are affected at early and advanced stages of the disease, respectively, were studied to provide cell-to-cell comparisons between “early” and “late” stages within the same subject. Drop-seq technology was used to profile purified neuronal ($NeuN^+$) nuclei isolated by fluorescence-activated sorting. mRNA in situ hybridization (ISH) using markers for distinct subtypes of projection neurons (subcerebral, cortico-thalamic, and intracortical) and GABAergic interneurons was performed to define cell-specific neuronal loss in neocortex of AD. Double immunohistochemistry for tau and ISH for neuronal subtype specific markers was used to determine cell type-specific changes in tau pathology. Our results provide new insights into the contributions of distinct neuronal cell types to AD and the molecular basis of selective cell vulnerability.

Disclosures: M. Otero-Garcia: None. **Y. Xue:** None. **T. Shakouri:** None. **G. Coppola:** None. **I. Cobos:** None.

Poster

207. Alzheimer's Disease: -Omics Approaches

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 207.15/F5

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

Support: U01AG046152

U01AG046170

U01AG046139

U01AG046161

5R01AG046174

R01AG046171

Title: Systems biology resource for Alzheimer’s disease target prioritization: The AMP-AD Knowledge Portal

Authors: *K. DAILY[1], ***K. DAILY**[1], *K. DAILY[1], B. LOGSDON[1], M. PETERS[1], R. AL-OURAN[2], Y.-W. WAN[2], J. M. SHULMAN[2], Z. LIU[2], L. OMBERG[1], L. MANGRAVITE[1]
[1]Sage Bionetworks, Seattle, WA; [2]Baylor Col. of Med., Houston, TX

Abstract: Alzheimer’s disease is a progressive neurodegenerative disorder with tremendous unmet clinical need and disappointing drug development. Discovery efforts are acutely needed to identify and prioritize new therapeutic targets. The Accelerating Medicines Partnership Alzheimer’s Disease (AMP-AD) target discovery program is a multi-disciplinary consortium designed to advance AD target prioritization. AMP-AD teams are developing computational models to prioritize candidate AD targets from large-scale molecular data, including genomic, epigenomic, transcriptomic, and proteomic profiles from more than 2,000 human brain autopsies. Top ranked targets are being validated in experimental model systems. All AMP-AD molecular data and computational models are made available to the research community through the AMP-AD Knowledge Portal (www.synapse.org/ampad). We present a web application designed to aggregate evidence from AMP-AD research teams in support of cross-consortium target prioritization efforts and dissemination of project data to the wider research community. The goals of this application are to 1) host a dynamic ranked list of the most promising targets for potential AD therapeutic development based on integrative analyses of AMP-AD data; 2) provide a web-based tool for gene-based queries, making AMP-AD human datasets available to the AD and neuroscience research communities; and 3) permit rapid assessment of genes of interest to evaluate their AD-relevant clinical, pathologic, and multi-scale molecular profiles.

Aggregated evidence includes differential expression profiles, genetic evidence, gene and protein expression across brain collections, computational AD models, target tissue specificity, and assessments of druggability (based in part on input from pharmaceutical industry partners). Our tool leverages descriptive statistics and dynamic data visualization to engage users without specialized bioinformatics expertise. Initially focused on 80 candidate AD targets nominated by the AMP-AD consortium, future refinements of our tool will be scaled to represent all known genes and incorporate analyses of complementary molecular profiles from AD cellular and animal models, further enhancing target prioritization and facilitating selection of optimal experimental systems for functional investigation.

Disclosures: B. Logsdon: None. **M. Peters:** None. **R. Al-Ouran:** None. **Y. Wan:** None. **J.M. Shulman:** None. **Z. Liu:** None. **L. Omberg:** None. **L. Mangravite:** None.

Poster

207. Alzheimer's Disease: -Omics Approaches

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 207.16/F6

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

Support: Study data were provided by the Rush Alzheimer’s Disease Center, Rush University Medical Center, Chicago.

Data collection was supported through funding by NIA grants P30AG10161, R01AG15819, R01AG17917, R01AG30146, R01AG36836, U01AG32984, U01AG46152, the Illinois Department of Public Health, and the Translational Genomics Research Institute

The Mayo Clinic Alzheimers Disease Genetic Studies, led by Dr. Nilufer Taner and Dr. Steven G. Younkin, Mayo Clinic, Jacksonville, FL using samples from the Mayo Clinic Study of Aging, the Mayo Clinic Alzheimers Disease Research Center, and the Mayo

Data collection was supported through funding by NIA grants P50 AG016574, R01 AG032990, U01 AG046139, R01 AG018023, U01 AG006576, U01 AG006786, R01 AG025711, R01 AG017216, R01 AG003949

NINDS grant R01 NS080820, CurePSP Foundation, and support from Mayo Foundation.

Study data includes samples collected through the Sun Health Research Institute Brain and Body Donation Program of Sun City, Arizona

The Brain and Body Donation Program is supported by the National Institute of Neurological Disorders and Stroke (U24 NS072026 National Brain and Tissue Resource for Parkinsons Disease and Related Disorders)

Title: Understanding the molecular etiology of Alzheimers disease based on transcriptomic changes across seven brain regions

Authors: *T. M. PERUMAL[1,2], O. AMP-AD RNASEQ WORKING GROUP[3], L. MANGRAVITE[2]
[1]Systems Biol. Group, [2]Sage Bionetworks, Seattle, WA; [3]AMP-AD Consortium, Seattle, WA

Abstract: Many studies are interested in the evaluation of genes that contribute to progression of Alzheimer's disease (AD). To identify genes altered by or contributing to AD progression, we performed a meta-analysis across all RNA sequencing data generated from brain tissues within the Accelerating Medicines Partnership in Alzheimer's Disease (AMP-AD) consortium (www.synapse.org/ampad). Data were generated from postmortem human brain tissues collected across 7 distinct regions of brain. In total 1153 samples - 411 control and 742 AD cases - were collected across five distinct sources (the ROS and MAP cohorts, the Mt. Sinai Brain Bank and the Mayo Brain Bank and Banner Health Brain Bank) from seven brain regions: dorsolateral prefrontal cortex (DLPFC), inferior frontal gyrus (IFG), superior temporal gyrus (STG), parahippocampal gyrus (PHG), frontal pole (FP), cerebellum (CBE) and temporal cortex (TCX). This selection contained twice as many samples from female donors as male donors. Data was reprocessed using a common RNAseq processing pipeline. Adjusting for clinical and technical variations, gene-level differential expression was calculated separately for each brain region with a weighted mixed-effect linear regression using CQN-VOOM normalization. Meta-analysis was performed using Dersimonian-Laird method across brain regions. Gene expression differences between AD and control suggests DLPFC, PHG and TCX were most affected brain regions. At an FDR of 5% and fold change of 1.2, 318 (DLPFC), 77 (FP), 22 (IFG), 322 (STG), 1637 (PHG), 1835 (CER) and 4696 (TCX) genes were differentially expressed between AD and control. Further analysis suggested gender specific enrichment of differential expression between AD and control. Meta-analysis across the three affected regions showed 148 differentially expressed genes enriched for loss of neurons and synaptic transmission, and increased inflammation response and neurotransmitter transport. Genes differentially expressed in the TCX region were also enriched for AD GWAS loci. Our analysis identified high-confidence sets of genes that were differentially expressed between AD and control across 3 out of 7 brain regions. Future analytical efforts will seek to advance our understanding of AD etiology and to identify disease mechanisms that are robustly conserved.

Disclosures: T.M. Perumal: None. **O. AMP-AD RNAseq working group:** None. **L. Mangravite:** None.

Poster

207. Alzheimer's Disease: -Omics Approaches

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 207.17/F7

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

Support: AG046152

AG046139

AG046161

AG046170

Title: Cross study analysis highlights endothelial and microglial transcriptomic components of Alzheimer's disease risk

Authors: *B. LOGSDON, T. M. PERUMAL, S. K. SIEBERTS, L. OMBERG, L. M. MANGRAVITE
Sage Bionetworks, Seattle, WA

Abstract: Alzheimer’s disease is a troubling illness with no known successful disease modifying drugs available. Characterization of the molecular components of AD biology will be key to the development of new treatments for AD. Here we present a systems biology approach for the study of AD transcriptomic biology, by performing an integrative network analysis of all publicly available gene expression data from patients with Alzheimer’s Disease including the ROSMAP study, the MSSM study, the Mayo RNAseq study, the MCADGS study, and the HBTRC study. To identify disease modules that are robustly observed across data sets and methodologies, we learn an ensemble AD gene coexpression network by applying seventeen different coexpression network inference methods to each expression data from each study. These networks are aggregated into a single consensus network across network types and data sets. From that rank consensus network we produce an ensemble set of modules aggregated across nine module identification algorithms. We then annotate the ensemble gene modules in terms of their known disease functionality. We identify multiple conserved modules across data sets, brain regions, and disease states - generally associated with cell type specificity - and characterize drivers of those modules and their relation to disease risk. The gene expression modules across studies enriched for known AD GWAS loci (as identified from the IGAP study) and associated with changes in expression between AD cases and controls across studies are consistently modules highly enriched for microglial and endothelial cell type signatures. By performing an ensemble, cross study coexpression analysis we identify high confidence AD

specific gene expression modules. We further prioritize the importance of the endothelial and microglial components of disease risk, both in terms of genetics and gene expression.

Disclosures: B. Logsdon: None. **T.M. Perumal:** None. **S.K. Sieberts:** None. **L. Omberg:** None. **L.M. Mangravite:** None.

Poster

207. Alzheimer's Disease: -Omics Approaches

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 207.18/F8

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

Support: NIH Grant P30AG019610

ADHS Grant ADHS14-052688

Title: Characterization of astrocytic circular RNAs in late-onset Alzheimer's disease

Authors: *S. SEKAR[1], L. CUYUGAN[1], J. ADKINS[1], P. GEIGER[1], D. F. MASTROENI[2], P. D. COLEMAN[3], W. LIANG[1]
[1]Liang lab, Translational Genomics Res. Inst., Phoenix, AZ; [2]Biodesign Neurodegenerative Res. Inst., Arizona State Univ., Tempe, AZ; [3]ASU-Banner Neurodegenerative Res. Ctr., Tempe, AZ

Abstract: Background: Circular RNAs (circRNAs) are a novel class of endogenous, non-coding RNAs that form covalently closed continuous loops and are pervasively expressed in the eukaryotic transcriptome. Although circRNAs have been found to possess potential microRNA regulatory roles and are enriched in the mammalian brain, they have not been widely characterized in the context of diseases. Given the previous evidence of astrocyte-specific contributions to Alzheimer’s disease (AD), here we aim to characterize astrocytic circRNAs in the context of AD.
Methods: We laser capture microdissected astrocytes from the posterior cingulate (PC; N=10 AD, 10 controls), hippocampus (HIPP; N=6 AD, 6 controls) and substantia nigra (SN; N=6 AD, 6 controls) of late-onset AD (LOAD) subjects and no disease (ND) healthy elderly controls. RNA sequencing (RNAseq) libraries were prepared using total RNA extracted from these cells and paired-end sequenced. Raw fastqs were analyzed using six different circRNA prediction algorithms, find_circ, CIRI, DCC, Mapsplice, KNIFE and CIRCexplorer and parsed using custom bash, python and R scripts.
Results: We generated an average of 192,081,648 reads for the PC samples, 54,121,880 reads for the HIPP samples and 62,854,856 reads for the SN samples. In total, 2,375 and 2,380 circRNAs were predicted across all tools in the AD and ND astrocyte samples respectively (union across all tools). All six tools predicted 62 and 73 circRNAs in AD and ND PC samples respectively, 35

and 15 circRNAs in AD and ND HIPP samples respectively, and 15 and 20 circRNAs in AD and ND SN samples respectively. A circRNA derived from the *CDR1* (cerebellar degeneration-related protein 1) gene, a widely reported circRNA, was detected across all three brain regions. We also detected circRNAs generated from key genes previously implicated in AD and other neurological diseases, such as *IGF2R* (insulin like growth factor 2 receptor), *FAIM2* (Fas apoptotic inhibitory molecule 2) and *BPTF* (bromodomain PHD finger transcription factor). Conclusions: In this study, we evaluated the abundance of astrocytic circRNAs in LOAD samples and healthy controls in 3 different brain regions, and demonstrate the feasibility of performing circRNA detection in RNAseq data using bioinformatics algorithms. Though the relevance of circRNAs in the context of AD is not well understood, we observe that certain key genes previously implicated in AD and other neurodegenerative diseases, such as *CDR1*, *RTN4*, *GSN*, and *BPTF*, appear to give rise to circRNAs, suggesting that they may have a role in AD processes. Further functional studies are required to elucidate the role of circRNAs in AD other neurodevelopmental diseases.

Disclosures: S. Sekar: None. **L. Cuyugan:** None. **J. Adkins:** None. **P. Geiger:** None. **D.F. Mastroeni:** None. **P.D. Coleman:** None. **W. Liang:** None.

Poster

208. Synaptic Deficits in Alzheimer's Disease and Neurodegeneration I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 208.01/F9

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

Support: Wenzhou medical University Scientific Research Grant KYQD160601

Title: Autophagic degradation of stromal interaction molecule 2 by ER stress leads to inhibition of SOCE and dendritic spine degeneration

Authors: *J. ZHOU[1], S. WU[2]
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Abstract: Objective: Endoplasmic reticulum (ER) stress has been highlighted in the protein aggregation in Alzheimer’s (AD), Parkinson’s (PD) diseases; axon degeneration is an early manifestation in many neurodegenerative disorders. In this study, we aimed to explore the mechanism how ER stress induces dendrite degeneration. Methods: The rat primary cortical neurons were pretreated with ER stressors, tunicamycin or brefeldin A. The protein levels of store-operated calcium entry (STIM1/2), LC3, p62 expression were detected with western blot. SOCE was analyzed with ratiometric calcium measurement and cytoplasmic Ca2+ levels were determined using the probe Fluo-4 AM by use of flow cytometry. Transfection of siRNA targeting ATG7 was conducted to assess autophagic contribution to the reducing effect of

tunicamycin or brefeldin A on STIM2. For assessment of dendrite morphology, the primary cultures were transfected with TD-tomato at DIV7 and treated with tunicamycin or brefeldin A for 10 hrs at DIV14. At DIV15 or DIV17, cultures were fixed. A Z-stack of optical section was captured using a confocal microscope. Results: Tunicamycin or brefeldin A inhibited SOCE when endoplasmic reticulum luminal calcium was depleted by thapsigargin and the treatments reduced cytosolic calcium as well. Tunicamycin or brefeldin A reduced STIM2; at the same treatment, p62 protein levels were decreased and LC3II/protein levels increased. The reducing effect of tunicamycin or brefeldin A on STIM2 was restored by knocking down ATG7. Tunicamycin or brefeldin A, at a 10-h treatment, largely reduced dendritic arborization when observed on the first or third day after application. Conclusions: Subjected to ER stressor, SOCE was inhibited which was possibly associated with autophagic degration of STIM2. ER stressors compromised dendrite architecture, which was possibly linked to STIM2 degradation by autophagy. Our data highlight the unique mechanism of ER stress leading to neurodegeneration by disrupting dendrite architecture through autophagic degradation of STIM 2 protein.

Disclosures: **J. Zhou:** A. Employment/Salary (full or part-time):; Wenzhou Medical University. **S. Wu:** None.

Poster

208. Synaptic Deficits in Alzheimer's Disease and Neurodegeneration I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 208.02/F10

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

Support: NIH RO1 AG030205

Title: Defects in vacuolar ATP-ase affect lysosome-autophagosome regulation and synaptic vesicles in early stages of Alzheimer's disease

Authors: *S. H. MUSTALY[1], M. GARSTKA[1], N. KAPECKI[1], K. D. BEAMAN[2], A. GILMAN-SACHS[2], G. STUTZMANN[1]
[2]Microbiology and Immunol., [1]Rosalind Franklin Univ., North Chicago, IL

Abstract: Vacuolar H+ ATPase (V-ATPase) is a conserved proton pump that sustains the acidic environment necessary for intracellular organelle function, such as lysosomes and synaptic vesicles. Within lysosomes, the V-ATPase maintains an acidic pH needed for the catabolic autophagosome-lysosome pathway to degrade cellular proteins. Synaptic vesicles require an acidic environment for neurotransmitter uptake and synthesis. Disruptions in V-ATPase subunit composition can thus lead to a build-up of abnormal proteins, such as β-amyloid and tau species, and deficient synaptic vesicle stores, which would contribute to synaptic depression. Our hypothesis is that altered composition of V-ATPase influences lysosomal and synaptic vesicle

functionality thereby contributing to pathogenic protein aggregation and disrupted synaptic transmission in AD.
This study reveals defects in V1B2 V-ATPase subunit expression in 3-month old AD mice models (3xTg) compared to non-transgenic (NTg) controls. Using immunohistochemistry, confocal microscopy, and electrophysiological approaches, we show significantly decreased V1B2 and synaptophysin density in the hippocampus and cortex of 3xTg-AD mice relative to NTg controls. Also, mature autophagosomes (LC3B) density was increased in 3xTg-AD mice, consistent with impaired lysosomal degradation functions. Dual-labeling showed decreased V1B2 colocalization with pre-synaptic vesicles and with lysosomes in 3xTg-AD mice. These findings suggest that the decreased V1B2 expression in these organelles would alter their pH and impair protein clearance (supported by Aβ and tau aggregates) and synaptic transmission (as demonstrated by defective paired pulse facilitation). As these changes occur prior to abnormal protein aggregation, this suggests an upstream pathogenic mechanism; a candidate mechanism concurrent with the V-ATPase defects is ryanodine receptor (RyR)-mediated Ca^{2+} dyshomeostasis. We thus treated mice for 30 days (10mg/kg) with Ryanodex, a RyR modulator that normalizes Ca^{2+} levels, which restored V1B2, LC3B, and synaptic vesicle expression in AD mice to NTg levels. This indicates that altered Ca^{2+} signaling influences synaptic transmission and accumulation of aberrant proteins in part through altering functionality of critical organelles.

Disclosures: S.H. Mustaly: None. **M. Garstka:** None. **N. Kapecki:** None. **K.D. Beaman:** None. **A. Gilman-Sachs:** None. **G. Stutzmann:** None.

Poster

208. Synaptic Deficits in Alzheimer's Disease and Neurodegeneration I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 208.03/F11

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

Support: Ruth K Broad Biomedical Research Foundation

Title: Selective activation of the thalamic reticular nucleus reduces sleep fragmentation and improves slow wave sleep in Alzheimer’s disease mice

Authors: *R. JAGIRDAR[1], F. M. SEIBT[2], M. BEIERLEIN[2], J. CHIN[1]
[1]Memory and Brain Res. Center, Dept. of Neurosci., Baylor Col. of Med., Houston, TX; [2]Dept. of Neurobio. and Anat., McGovern Med. Sch. at UTHealth, Houston, TX

Abstract: Alzheimer’s disease (AD) is associated with memory impairment, cognitive dysfunction and sleep fragmentation. The incidence of unprovoked seizures is also higher in AD patients than in reference populations. These seemingly disparate symptoms of AD all have in common the fact that they are regulated by activity in the corticothalamic network. Transgenic

mice that express human amyloid precursor protein (APP) carrying mutations linked to AD also exhibit these symptoms. We recently identified robust alterations in activity in the corticothalamic network in APP mice, suggesting that dysfunction in this network may be a common denominator underlying many aspects of AD pathophysiology. We found that much of the dysfunction in the corticothalamic network of APP mice appears to be downstream of reduced activity in the thalamic reticular nucleus (TRN), a major inhibitory thalamic control nucleus. Such reduction was associated with sleep fragmentation, deficits in spatial memory, and seizures. We therefore hypothesized that restoration of activity in TRN might be a therapeutic strategy to improve cognition and behavior as well as reduce seizure incidence in APP mice. We achieved selective activation of TRN using DREADDs. Stereotaxic infusion of AAV-hSyn-DIO-hM3Dq-mCherry into the TRN of mice that express CRE specifically in GABAergic neurons was sufficient to induce DREADD expression throughout the TRN. Activation of DREADDs using CNO was confirmed both in vivo by post-fixing and staining brain sections with a marker of activity (FosB/ΔFosB) as well as by slice physiology using thalamocortical slices from animals that had received AAV. We also infused AAV-hSyn-DIO-hM3Dq-mCherry into the TRN of APP mice that had been crossed with GAD2-Cre mice to restrict DREADD expression to GABAergic neurons. Mice were also implanted with transmitters for EEG/EMG telemetry. We found that activation of DREADD-expressing TRN neurons in APP mice reduced sleep fragmentation and ameliorated the reductions in slow wave sleep exhibited by APP mice relative to control littermates. Together, these results demonstrate that TRN-specific expression of DREADDs enables selective activation of TRN to modify behaviour, and that the TRN may be a master regulator of function in several cognitive and behavioural domains in AD.

Disclosures: **R. Jagirdar:** None. **F.M. Seibt:** None. **M. Beierlein:** None. **J. Chin:** None.

Poster

208. Synaptic Deficits in Alzheimer's Disease and Neurodegeneration I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 208.04/F12

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

Title: SIRT3 agonist in an *In vitro* model of Alzheimer's disease

Authors: *T. LYND[1], M. Y. GOVINDARAJULU[2], G. BRIGGS[3], M. DHANASEKARAN[5], V. D. SUPPIRAMANIAM[4]
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Abstract: Honokiol is a SIRT3 agonist possessing mitochondrial NAD-dependent deacetylase activity, known to exhibit antioxidant and neuroprotective effects in several experimental

models. Amyloid β peptide (Aβ) is one of the pathological hallmarks of Alzheimer's disease, characterized by the accumulation of the extracellular, senile plaques in the brain leading to cognitive impairment and neuronal loss. The present study evaluates the neuroprotective qualities of Honokiol on Aβ-induced oxidative stress and neuronal dysfunction. Cultured rat hippocampal H19-7 neuronal cell line was pretreated with 5 & 10 μM of Honokiol for 4 hrs followed by 10 μM of Aβ (1-42) for 24 hrs. H19-7 cells treated with Aβ exhibited increased lipid peroxide levels and decreased enzymatic antioxidants including superoxide dismutase, catalase and non-enzymatic antioxidants such as glutathione compared to the control group. Aβ treatment also decreased the mitochondrial activity, decreased the expression of BDNF, and increased tau hyper phosphorylation. Post synaptic proteins expression, essential for synaptic maturity and plasticity, was decreased by Aβ treatment. Honokiol treatment attenuated the accumulation of lipid peroxide levels, up-regulated the antioxidant activities, improved mitochondrial biogenesis and functions, decreased β-secretase activity and improved the expression of BDNF and postsynaptic proteins in Aβ treated H19-7 cells. These findings highlight the neuroprotective effect of Honokiol in preventing Aβ-induced oxidative damage and neuronal dysfunction *in vitro*.

Disclosures: T. Lynd: None. **M.Y. Govindarajulu:** None. **G. Briggs:** None. **M. Dhanasekaran:** None. **V.D. Suppiramaniam:** None.

Poster

208. Synaptic Deficits in Alzheimer's Disease and Neurodegeneration I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 208.05/G1

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

Title: Developmental cannabinoid exposure causes cognitive deficits in offspring

Authors: *P. D. PINKY, J. E. BLOEMER, R. HESLIN, S. SETTI, A. ALHOWAIL, M. GOVINDARAJULU, M. REED, V. SUPPIRAMANIAM
Drug Discovery and Develop., Harrison Sch. of Pharmacy, Auburn Univ., Auburn, AL

Abstract: Cannabinoids are one of the most commonly used illicit substances among pregnant women. Prenatal cannabinoid exposure may be associated with persistent deficits in the cognitive functions of offspring. We investigated the impact of prenatal cannabinoid on the offspring in hippocampal dependent learning and memory through behavioral and electrophysiological testing. An osmotic pump filled with either N-Methyl-Pyrulol(NMP) or the cannabinoid receptor full agonist WIN55,212-2(2.5mg/kg body weight/day) was inserted subcutaneously in the pregnant rats at the Gestational Day -3 (GD-3), and was left there until delivery of the pups. Contextual Fear Conditioning (CFC) and Morris Water Maze (MWM) were performed to observe hippocampal dependent spatial memory deficit in adolescent rats (PND45-

PND55). Since glutamate, the major excitatory neurotransmitter, plays a vital role in memory and learning, we also measured the amount of glutamate release in Schaffer-Collateral Pathway (CA1, CA3) and Dentate Gyrus (DG) of hippocampus through Multi Electrode Array (MEA) in the anaesthetized animals. Further, the downstream signaling of glutamate through AMPA and NMDA receptor was also investigated. We found that there is significant change in the learning process during the behavioral tests between the two groups. In the electrophysiology experiment, LTP in the Developmentally Cannabinoid exposed (DCAN) animals were reduced by 50% compared the control animals. Also, prenatal cannabinoid exposure reduced glutamate release in both CA3 and CA1. These results indicate that cannabinoid exposure during the gestational period may lead to significant functional and neurochemical alterations through changes in glutamatergic synaptic transmission and result in learning and memory deficit.

Disclosures: P.D. Pinky: None. **J.E. Bloemer:** None. **R. Heslin:** None. **S. Setti:** None. **A. Alhowail:** None. **M. Govindarajulu:** None. **M. Reed:** None. **V. Suppiramaniam:** None.

Poster

208. Synaptic Deficits in Alzheimer's Disease and Neurodegeneration I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 208.06/G2

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

Title: Mice lacking adiponectin display synaptic plasticity deficits and central insulin resistance

Authors: *J. BLOEMER[1], D. BHATTACHARYA[1], A. H. ALHOWAIL[1], P. DAS PINKY[1], M. GOVINDARAJULU[1], R. JUDD[2], V. D. SUPPIRAMANIAM[1]
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Abstract: Adiponectin is an insulin-sensitizing hormone produced by adipocytes, which has recently been under investigation for potential neuroprotective effects. Insulin resistance in the brain is one factor that can lead to hippocampal dysfunction and cognitive impairment in disorders such as Alzheimer’s disease (AD). In fact, a recent study showed that the adiponectin receptor agonist, osmotin, decreased pathogenic amyloid beta and phosphorylated tau, which are major hallmarks of AD. Therefore, the goal of this research is to determine the role for adiponectin and adiponectin receptors in cognitive function and synaptic plasticity. There is a high density of adiponectin receptors in the hippocampus, but function of these receptors related to synaptic plasticity is unknown. We hypothesize that mice lacking adiponectin display age-related cognitive deficits related to changes in central insulin sensitivity. We first determined behavioral and synaptic deficits produced by male adiponectin knockout mice compared to controls. Deficits were observed in the novel object recognition test. Supporting the behavioral data, synaptic plasticity was also impaired in these rodents. In addition, these animals show changes in glutamate receptors and markers of increased central insulin resistance. We also plan

to use the adiponectin receptor agonist, AdipoRon, in a mouse model of AD. This research may provide evidence for drug development and clinical trials involving adiponectin-signaling pathways in AD. Because adiponectin receptor signaling pathways have also been investigated for therapeutic effects for other brain disorders, such as stroke, greater understand could provide basis for testing in other models of central nervous system disease.

Disclosures: J. Bloemer: None. **D. Bhattacharya:** None. **A.H. Alhowail:** None. **P. Das Pinky:** None. **M. Govindarajulu:** None. **R. Judd:** None. **V.D. Suppiramaniam:** None.

Poster

208. Synaptic Deficits in Alzheimer's Disease and Neurodegeneration I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 208.07/G3

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

Support: NIH grant R15 AG048643-01A1

Title: Novel PPAR-gamma agonist improve pathology and memory deficits in a 3xTg-Ad mouse model of Alzheimer’s disease

Authors: *M. Y. GOVINDARAJULU
Dept. of Drug Discovery and Develop., Auburn Univ., Auburn, AL

Abstract: Epidemiological and research evidence suggest a possible shared pathophysiology between type 2 diabetes mellitus (T2DM) and Alzheimer's disease (AD) and thus establishing the disease as a form of ‘type 3 diabetes’.Thiazolidinediones (TZDs) are insulin sensitizing peroxisomal proliferator activating receptor gamma (PPARγ) agonists and have been recognized as promising agents for memory deficits in patients with AD. Although currently available PPARγ agonists show promise for improving memory deficits in AD, poor blood brain barrier permeability results in inadequate bio-availability in the brain requiring high dosing with chronic time frames that are associated with increased incidences of adverse cardiovascular events. Therefore we have developed novel selective PPARγ modulators with high blood brain barrier permeability and less incidence of adverse unwanted deleterious effects.
We hypothesize that our lead compound(Compound 9) a PPARγ modulator, improves cognitive deficits and pathologies associated from Alzheimer's disease better than current TZDs (pioglitazone) in a triple transgenic 3x Tg-AD mouse model. Triple transgenic 3xTg-AD and C57BL/6J mice were utilized. Two month aged mice representing mild to moderate AD were treated with either Compound 9 or Pioglitazone until six months of age. Six month age group represents advanced stage of AD and the mice were treated for 4 weeks. Behavioral analysis was done using novel-object recognition, Y-maze and contextual fear conditioning tests. Long-term potentiation (LTP) theta-burst protocol was utilized to measure hippocampal field potentials in

Schaffer collateral pathway in the hippocampus.
Our initial data indicate that Compound 9 decreases Beta amyloid levels and reduced Beta secretase activity better than when compared to Pioglitazone in an in vitro model. Y maze, novel-object recognition and contextual fear conditioning showed improvement in cognitive deficits. In addition these mice restored memory deficits in transgenic mice similar to control group in electrophysiological studies.
We plan to conduct further biochemical and electrophysiological evaluation studies to will determine and validate the nature of synaptic deficits and pharmacokinetic studies to test the brain bioavailability of compound 9 compared to pioglitazone.

Disclosures: M.Y. Govindarajulu: None.

Poster

208. Synaptic Deficits in Alzheimer's Disease and Neurodegeneration I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 208.08/G4

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

Title: Cerebellar neurotoxic effects of nicotine on prenatal exposed rodent models

Authors: *G. H. BRIGGS[1], M. Y. GOVINDARAJULU[2], M. DHANASEKARAN[3], D. BATTACHARYA[4]
[1]Neurophysiol., Harrison Sch. of Pharm., Nashville, TN; [2]Neurophysiol., Harrison Sch. of Pharm., Auburn, AL; [3]Harrison Sch. of Pharmacy, Auburn Univ., Auburn, AL; [4]Auburn Univ., Auburn, AL

Abstract: Specific Aim: Evaluate the neurotoxic effects of nicotine exposure in a rodent model of fetal alcohol spectrum disorder
Background: Cerebellum receives information from the sensory systems and plays an important role in motor control and learning. Cerebellum controls the behavior, posture, balance, coordination, and speech. Alcohol is one of the most commonly abused and socially accepted psychoactive substances. Interestingly, nicotine is also consumed regularly during alcohol consumption. Alcohol consumption during pregnancy has shown to induce behavioral, biochemical and neurochemical changes to the fetus resulting in cognitive and motor impairment.
Experimental Design: We used a Fetal Alcohol Spectrum Disorder rodent model and exposed it to nicotine using subcutaneous-mini osmotic pump. We assessed the neurotoxic effects in the cerebellum. We studied the effects of nicotine and alcohol on various markers associated with oxidative stress, mitochondrial functions and apoptosis.
Results: Nicotine enhanced the oxidative stress by significantly increasing the generation of reactive oxygen species and inducing lipid peroxidation in cerebellum. However, it had no

significant effects on the mitochondrial functions. Furthermore, nicotine enhanced the activity of monoamine oxidase. In addition, pre-synaptic and postsynaptic protein expressions involved in synaptic plasticity were altered.
Conclusion: Prenatal nicotine exposure significantly potentiates the neurotoxic effects of alcohol in the cerebellum.

Disclosures: G.H. Briggs: None. **M.Y. Govindarajulu:** None. **M. Dhanasekaran:** None. **D. Battacharya:** None.

Poster

208. Synaptic Deficits in Alzheimer's Disease and Neurodegeneration I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 208.09/G5

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

Support: Maratona da Saúde

Santa Casa da Misericórdia

FCT (PTDC/NEU-NMC/4154/2014)

Centro2020 (CENTRO-01-0145-FEDER-000008:BrainHealth 2020)

Title: Adenosine A2A receptor over-activation is necessary and sufficient for the emergence of memory and synaptic plasticity deficits in animal models of early Alzheimer's disease

Authors: *R. A. CUNHA[1], P. AGOSTINHO[2]
[1]CNC -Center For Neurosci. and Cell Biol., Coimbra, Portugal; [2]CNC-Center for Neurosci. and Cell Biol., Coimbra, Portugal

Abstract: Regular consumption of caffeine prevents age-related memory dysfunction and inversely correlates with the incidence of Alzheimer's disease (AD) and animal models confirmed this prophylactic benefit of caffeine (J Alzheimers Dis 20:S95). In keeping with caffeine acting as an antagonist of adenosine receptors, caffeine neuroprotection is mimicked by blockade or inactivation of adenosine A_{2A} receptors ($A_{2A}R$) (J Neurochem 139:1019). In APP/PS1 or in 3xTg mouse models of AD, the genetic or pharmacological blockade of $A_{2A}R$ reverts memory deficits at their onset. Surprisingly, there were no alteration of the density or function of AMPA or NMDA receptors, and $A_{2A}R$ blockade was sufficient to recover the hampered synaptic plasticity in hippocampal excitatory synapses of AD mice. Furthermore, pharmacological or optogenetic over-activation of $A_{2A}R$ in naive mice was sufficient to trigger memory deficits. We next enquired if this involved neuronal or astrocytic $A_{2A}R$. We report that β-amyloid peptides ($A\beta_{1-42}$)-induced depression of hippocampal long-term potentiation was

abrogated in neuronal (CAM-KII-driven)-$A_{2A}R$ knockout mice and was unchanged in astrocytic (GFAP-driven)-$A_{2A}R$ knockout mice, thus implicating neuronal $A_{2A}R$. We next tested if $A_{2A}R$ over-activation resulted from increased $A_{2A}R$ density and/or from increased formation of adenosine activating $A_{2A}R$, which is known to be ATP-derived adenosine formed by CD73, an ecto-5'-nucleotidase (J Neurosci 33:11390). As occurs in AD patients (Brain Pathol 18:211), we report an up-regulation of $A_{2A}R$ in hippocampal synapses, namely in glutamatergic synapses, of different early AD mouse models. We also found an increased ATP release and an increased density and activity of CD73 in hippocampal synaptosomes of icv $A\beta_{1-42}$-treated mice with memory deficits, and the blockade of CD73 phenocopied $A_{2A}R$ blockade in the control of synaptic plasticity and memory deficits of these early AD-like mice. This shows that aberrant $A_{2A}R$ over-function is paramount to disrupt synaptic plasticity and hamper memory in animal models of early AD. The triggers of $A_{2A}R$ over-function are unknown but may represent a compensatory mechanism to attempt maintaining synaptic function, in a manner similar to the control of synaptogenesis by $A_{2A}R$.

Disclosures: R.A. Cunha: None. **P. Agostinho:** None.

Poster

208. Synaptic Deficits in Alzheimer's Disease and Neurodegeneration I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 208.10/G6

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

Support: NIA R21AG053067

Title: Early hippocampal denervation of the TgF344-AD rat

Authors: *A. GOODMAN[1], C. E. STRANG[2], L. SMITH[3], L. MCMAHON[3]
[1]Cell, Developmental, and Integrative Biol., Univ. of Alabama At Birmingham, Irondale, AL; [2]Psychology, [3]Cell, Developmental, and Integrative Biol., Univ. of Alabama At Birmingham, Birmingham, AL

Abstract: Prodromal Alzheimer's disease (AD) is characterized by degeneration of subcortical nuclei and is highly correlated with regional tauopathy. Degeneration of cholinergic neurons in the basal forebrain and noradrenergic neurons in the locus coeruleus (LC) leads to a loss of acetylcholine and norepinephrine in key brain regions involved in learning and memory, such as hippocampus. Recent data from humans with AD suggest that the LC is first to degenerate, however this is not recapitulated in transgenic AD mouse models, which also do not show appreciable cholinergic degeneration. The TgF344-AD rat model harboring two human transgenes causing familial AD (FAD), APPSwe and PSEN1DeltaE9, driven by a mouse prion promoter is becoming recognized as the most comprehensive and clinically relevant rodent

model of AD to-date (Cohen et al., 2013). We chose this model to investigate whether cholinergic and noradrenergic fibers degenerate and how this relates to AD pathology and synaptic deficits. Here, we report that the TgF344-AD rat displays loss of tyrosine hydroxylase (TH) positive axons in hippocampus as early as 12 months. We also find significant reductions in cholinergic innervation as evidence by decreased density of fibers positive for the p75 neurotrophin receptor and choline acetyltransferase. The remaining noradrenergic and cholinergic fibers in the TgF344-AD rat show noticeable changes in morphology, with shorter lengths and a knobby appearance. Furthermore, the degeneration of these loci predictably appears by 12 months of age and steadily worsen up to 24 months. This data presents a unique opportunity to draw comparative time-points to early stages of human AD pathogenesis. Our laboratory has previously shown deficits in synaptic plasticity in this model as early as 6 months old at medial-perforant pathway synapses onto dentate granule cells prior to changes at CA3-CA1 synapses. Importantly, reductions in noradrenergic and cholinergic fibers follow this same pattern of regional degeneration, starting in the DG and followed by the CA1 region. This emerging pattern mirrors human studies and provides evidence to support that pathology in TgF344-AD rats better recapitulates the complex characteristics of human AD than any previous rodent model. We posit that the TGF344-AD rat model is a more physiologically relevant platform to study synaptic deficits and their relationship with subcortical nuclei degeneration in the early phases of AD.

Disclosures: **A. Goodman:** None. **C.E. Strang:** None. **L. Smith:** None. **L. Mcmahon:** None.

Poster

208. Synaptic Deficits in Alzheimer's Disease and Neurodegeneration I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 208.11/G7

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

Support: NIA R21AG053067

NIH F31AG054087

Title: Early synapse vulnerability targets dentate gyrus in the novel TgF344-Alzheimer's disease rat model

Authors: *L. A. SMITH, L. L. MCMAHON
Cell, Developmental, and Integrative Biol., Univ. of Alabama, Birmingham (UAB), Birmingham, AL

Abstract: The earliest and most insidious stages of Alzheimer’s disease (AD) are characterized by altered brain function at the level of the synapse, where pathology begins in the entorhinal

cortex (EC) and spreads via functionally connected synapses to the hippocampus. As soluble toxic species of amyloid-beta oligomers and hyper-phosphorylated tau rise, EC-to- hippocampal synaptic weakening results and occurs decades prior to clinical presentation of cognitive symptoms. Therefore, there is great need for disease modifying therapies that can slow or halt disease progression before debilitating symptoms arise. The newly developed TgF344-AD rat model is recognized as the most comprehensive and clinically relevant rodent model of AD to-date. Key features include an early rise in soluble amyloid-beta oligomers, soluble hyper-phosphorylated tau, and gliosis at 6 months of age and occur prior to plaques, tangles, cellular loss, and behavioral impairment on hippocampus-dependent learning tasks, which begin between 12-15 months. Whether synaptic alterations occur in hippocampus prior to learning and memory deficits or overt lesion pathology is not known. Furthermore, it is unknown if hippocampal subfields are differentially affected by progressing AD pathology, or if gender differences exist during presymptomatic pathogenesis in TgF344-AD rats. Here, we investigated the time-course of synaptic changes in basal transmission, presynaptic release probability (PPR), and long-term potentiation (LTP) using extracellular dendritic fEPSP recording and spine density by Golgi stain in two hippocampal sub-regions in both male and acutely-ovariectomized female TgF344-AD rats and wildtype littermates. Longitudinal studies reveal that the TgF344-AD rat model has hippocampal synaptic alterations that precede documented appearance of plaques and tangles. Basal synaptic transmission is impaired in TgF344-AD rats at MPP-DGC prior to CA3-CA1 synapses. Interestingly, impaired basal synaptic transmission at CA3-CA1 begins earlier in TgF344-AD males than females. PPR and dendritic spine density is unchanged at MPP-DCG and CA3-CA1 synapses in TgF344 AD rats at 9 months, suggesting a postsynaptic mechanism for altered basal synaptic strength at this time-point. Finally, LTP magnitude is unaltered at CA3-CA1 synapses, yet is pathologically enhanced at MPP-DCG synapses in TgF344-AD rats at 6 months of age. Together these data confirm presymtomatic synaptic function is altered prior to the onset of reported behavioral deficits and bolsters the use of TgF344-AD rat model for investigations into disease-modifying therapies.

Disclosures: L.A. Smith: None. **L.L. Mcmahon:** None.

Poster

208. Synaptic Deficits in Alzheimer's Disease and Neurodegeneration I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 208.12/G8

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

Support: R01 NS42818

Title: Amyloid precursor protein family regulates synaptic function and neuronal excitability in the adult mouse hippocampus

Authors: *S. LEE[1], A. HO[1], H. WATANABE[1], J. KANG[1], V. Y. BOLSHAKOV[2], J. SHEN[1]
[1]Neurol., Brigham & Women's Hospital, Harvard Med. Sch., Boston, MA; [2]Psychiatry, McLean Hospital, Harvard Med. Sch., Belmont, MA

Abstract: Mutations in the amyloid precursor protein (APP) are linked to familial forms of Alzheimer's disease (AD). Despite the importance of APP in AD pathogenesis, its normal physiological role in the adult brain remains unclear due to the presence of APP functional homologues, APP-like protein 1 (APLP1) and APP-like protein 2 (APLP2), and the lack of appropriate conditional knockout (cKO) mice. We therefore generated postnatal forebrain-restricted *APP/APLP1/APLP2* cKO mice, in which all three genes are inactivated in excitatory neurons of the adult hippocampus, to investigate the role of APP family in the central synapse. We performed electrophysiological recordings in the Schaffer collateral (SC) pathway using acute hippocampal slices of *APP/APLP1/APLP2* cKO and control mice at 3 months of age. We found that short-term plasticity, including paired-pulse and frequency facilitation, is substantially enhanced at SC synapses of *APP/APLP1/APLP2* cKO mice, whereas long-term potentiation is decreased. Interestingly, selective inactivation of *APP/APLP1/APLP2* in excitatory neurons of hippocampal area CA1 only also resulted in increased synaptic facilitation at SC synapses. Importantly, whole-cell recording of hippocampal CA1 pyramidal neurons of *APP/APLP1/APLP2* cKO mice revealed deficits in intrinsic membrane properties, such as more depolarized resting membrane potential, lower threshold for action potential (AP) firing, shorter duration of the AP onset and upward shift of the frequency-current relationship, providing further evidence of hyper-excitability in the absence of APP family. We also found that CA1 pyramidal neurons of *APP/APLP1/APLP2* cKO mice exhibited higher frequencies of spontaneous excitatory postsynaptic currents (sEPSCs) than control neurons. Our latest findings from electrophysiological analysis of *APP/APLP1/APLP2* cKO mice on the synaptic function of APP family in adult mouse hippocampus will be presented.

Disclosures: S. Lee: None. **A. Ho:** None. **H. Watanabe:** None. **J. Kang:** None. **V.Y. Bolshakov:** None. **J. Shen:** None.

Poster

208. Synaptic Deficits in Alzheimer's Disease and Neurodegeneration I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 208.13/G9

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

Support: Tata Trusts

Title: Synapse-specific role of Akt kinases in Alzheimer's disease

Authors: R. GOWAIKAR[1], *V. RAVINDRANATH[1,2]
[1]Indian Inst. of Sci., Bangalore, India; [2]Ctr. for Brain Res., Bangalore, India

Abstract: Akt (protein kinase B), a serine threonine kinase, is an important upstream kinase that regulates several signaling pathways involved in diverse functions including cell growth and survival. Specifically, Akt-mTOR pathway is vital for proper functioning and maintenance of dendritic spines including protein translation via mTORC1, particularly during synaptic plasticity. Akt1, Akt2 and Akt3 are 3 forms of Akt that are coded by different genes and are not functionally redundant. Specific functions of Akt kinases in the brain in general, and at the synapse, in particular are poorly understood. We have demonstrated earlier the deficiency of synaptic Akt1 in AD mouse model (APP/PS1) leading to defective activity dependent translation (Ahmed et al 2016). We, further examined the status of the other forms of Akt at the synapse in young APP/PS1 mice with a view to determine their relative roles in pathogenesis of AD. We found that Akt2 is the most abundant Akt kinase in synaptosomes, followed by Akt3 and Akt1 in WT mouse. Synaptosomes prepared from APP/PS1 mice at 1 month of age showed decreased kinase activity of AKt1 and Akt2, while Akt3 was unaffected indicating that the Akt kinases were differentially affected in AD. These observations were sustained up to 9 months of age when the behavioural and pathological features emerged. Our results indicate that the activity of synaptosomal Akt1 and Akt2 are affected early in the pathogenesis of AD. Akt kinases are involved in a variety of important synaptic functions including activity dependent translation, therefore their perturbation early in the disease process could potentially affect synaptic function including plasticity promoting the progression of the disease.

Disclosures: R. Gowaikar: None. **V. Ravindranath:** None.

Poster

208. Synaptic Deficits in Alzheimer's Disease and Neurodegeneration I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 208.14/G10

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

Support: Tata Trusts

Title: Synaptosomal F-actin loss mediates early behavioural deficits in Alzheimer's Disease mouse model

Authors: *S. KARUNAKARAN[1], R. KOMMADDI[1], D. DAS[1], A. RAY[1], D. BENNETT[2], V. RAVINDRANATH[1,3]
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Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder that slowly impairs memory and higher cognitive functions. At the cellular level, AD is characterized by synaptic dysfunction including synapse loss, hyperphosphorylated Tau and extensive neurodegeneration. Synaptic dysfunction is seen as loss of dendritic spines in mouse models of AD and as decreased glucose utilization (FDG-PET imaging) in human subjects, and precedes clinical features of the cognitive dysfunction. However, the mechanisms underlying synaptic dysfunction including loss of spines is poorly understood. Dendritic spines along the neurites are the primary sites for receiving information and are also the cellular substrates for synaptic plasticity. Loss of spines often results in defective synaptic transmission. Filamentous actin (F-actin), the major cytoskeleton protein in spines is important for defining dendritic spine morphology, more so in synaptic plasticity. We examined the status of F-actin in dendritic spines in mouse model of AD. F-actin levels were decreased in synaptosomes from APP/PS1 mice starting at 1 month of age indicating that the cytoskeletal organization of F-actin in spines was perturbed. Further, at 2 months of age APP/PS1 mice showed impaired recall upon contextual fear conditioning (cFC), which could be reversed by actin polymerizing agent, jasplakinolide. Conversely, latrunculin A, an actin depolymerizing agent induced cFC deficit indicating that F-actin was important for consolidation and/or recall of memory. Further, F-actin levels were decreased in synaptosomes from AD postmortem cortex and significant correlation was seen between decrease in synaptosomal F-actin and poor performance in memory and other cognitive tasks in subjects with MCI and AD indicating that loss of F-actin at the synapse may also contribute to the disease progression in humans.

Disclosures: S. Karunakaran: None. **R. Kommaddi:** None. **D. Das:** None. **A. Ray:** None. **D. Bennett:** None. **V. Ravindranath:** None.

Poster

208. Synaptic Deficits in Alzheimer's Disease and Neurodegeneration I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 208.15/H1

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

Support: NIH Grant K08 NS069811

NIH Grant 5P50AG005134

Title: Modulation of ocular dominance plasticity by Amyloid Precursor Protein and Amyloid-beta

Authors: *C. M. WILLIAM[1], M. A. STERN[3], L. SAQRAN[3], X. PEI[2], M. P. FROSCH[4], B. T. HYMAN[3]
[1]Neuropathology Service, Dept. of Pathology, [2]Dept. of Pathology, New York Univ. Sch. of

Med., New York, NY; [3]MassGeneral Inst. for Neurodegeneration, Massachusetts Gen. Hosp., Charlestown, MA; [4]Neuropathology Service, Dept. of Pathology, Massachusetts Gen. Hosp., Boston, MA

Abstract: Amyloid precursor peptide (APP) and its proteolytic cleavage product, Amyloid-beta (Abeta), have been demonstrated to have positive and negative effects on synaptic plasticity in in vitro models. To explore the effects of these proteins on circuit-level synaptic plasticity in vivo, ocular dominance plasticity (ODP) was assessed in Abeta-expressing transgenic mice and in APP knock out mice. Mice that express Abeta in the absence of APP overexpression (BRI-Abeta40 or -Abeta42 mice; gifts of Todd Golde) demonstrate defects in ocular dominance plasticity (ODP), the plastic response to the loss of input from one eye (monocular deprivation, MD, via lid suture) that results in a shift of visual cortical responsiveness in favor of the non-deprived eye as well as an expansion in the cortical area responsive to the non-deprived eye. The shifts in ocular dominance index (ODI; the difference between contralateral and ipsilateral eye stimulation responses, divided by the sum of the responses) observed by intrinsic imaging in wild type mice fail to occur in BRI-ABeta42 mice (wild type pre-MD ODI %dF/F, 0.214 ± 0.055; post-MD ODI, -0.187 ± 0.084; BRI-Abeta42 pre-MD ODI, 0.139 ± 0.042; post-MD ODI, 0.020 ± 0.054; p=0.02, two-way ANOVA, n=7 per group). Following MD, expansions in the area of the visual cortex responsive to the non-deprived eye (ipsilateral to the non-deprived eye, measured using Arc immediate early gene induction), that occur in wild type mice fail to occur in transgenic mice. Mice that express the 40-amino acid-long species of Abeta, the species more typically produced during normal synaptic function, exhibit a similar defect in ODP, suggesting either species can inhibit plasticity. APP null mice demonstrate a defect in ODP following monocular deprivation (APP wild type pre-MD ODI %dF/F, 0.179 ± 0.019; post-MD ODI, -0.191 ± 0.080; knock out pre-MD ODI, 0.151 ± 0.026; post-MD ODI, 0.012 ± 0.079; p=0.04, two-way ANOVA, n=6-7 per group), suggesting that APP or a proteolytic cleavage product of APP plays a required role in basic cortical plasticity. Surprisingly, following monocular enucleation, APP knock out mice demonstrate a more robust plastic response than wild type mice, suggesting that in the context of a stronger challenge, the requirement for APP in producing a plastic response is bypassed and a second role for APP in limiting the plastic response is observed. These data suggest that APP function is required for OD plasticity, and that APP or a cleavage product, such as Abeta, also plays a role in limiting plasticity, raising the possibility that the ability of elevated levels of Abeta to suppress plasticity may relate to a normal role in modulating synaptic plasticity.

Disclosures: C.M. William: None. **M.A. Stern:** None. **L. Saqran:** None. **X. Pei:** None. **M.P. Frosch:** None. **B.T. Hyman:** None.

Poster

208. Synaptic Deficits in Alzheimer's Disease and Neurodegeneration I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 208.16/H2

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

Support: R01 AG053983 Cognitive Resilience to Alzheimer Neuropathologic Changes in the Honolulu-Asia Aging Study and the Nun Study

P50 AG005131 The Shiley Marcos Alzheimer's Disease Research Center

Title: Calcium channel blockers and Alzheimer's disease: Evidence of interaction with Apolipoprotein E

Authors: *S. D. EDLAND[1], R. P. GELBER[2], L. J. LAUNER[3], L. R. WHITE[2]
[1]UCSD, La Jolla, CA; [2]Pacific Hlth. Res. and Educ. Inst., Honolulu, HI; [3]Lab. of Epidemiology and Population Sci. Intramural Res. Program, Natl. Inst. on Aging, Bethesda, MD

Abstract: Background. Epidemiologic data suggest a protective effect of blood pressure medications on risk of later life neurodegenerative disease. Calcium channel blockers (CCBs) in particular have been associated with reduced risk in Parkinson's disease [Am J Epidemiol. 2012;175(7):627–635], and have been proposed as a preventive treatment for Alzheimer's disease [Reviews in the Neurosciences. 25(2):231-246]. The protective effect may be specific to persons with an Apolipoprotein E E4 genetic risk allele based on hippocampal slice culture models showing that ApoE E4, but not ApoE E3, increases post-synaptic Ca++ influx through calcium channels and induces post-synaptic Ca++ cellular stress.
Methods. We investigated the association between CCB exposure and impaired cognition and brain lesion density in the autopsy sub-study of the Honolulu Asia Aging Study (HAAS; n=852 Japanese-American men age 71-93 at CCB assessment and age 73-106 at death). Time to first evidence of mild cognitive impairment (74 or less on the CASI) was examined using Cox proportional hazards models. Lesion density at autopsy was compared using non-parametric Wilcoxon tests.
Results. Among persons with the APOE E4 Alzheimer risk allele, CCBs predicted a significantly lower instantaneous risk of incident cognitive impairment (hazard ratio = 0.24, p=0.02 versus untreated normotensive persons). Similar associations were not observed in persons without the APOE E4 risk allele. Brain weight and Alzheimer lesion density was comparable, although there was a non-significant trend toward lower amyloid load in E4 carriers on CCBs (p=0.15).
Conclusions. These data suggest that CCBs may protect against or confer resilience to the Alzheimer neuropathological process in persons with an APOE E4 risk allele. CCBs may

selectively protect against post-synaptic Ca++ stress in APOE E4 carriers, suggesting CCBs as a precision medicine intervention for this high risk population.

Disclosures: **S.D. Edland:** None. **R.P. Gelber:** None. **L.J. Launer:** None. **L.R. White:** None.

Poster

208. Synaptic Deficits in Alzheimer's Disease and Neurodegeneration I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 208.17/H3

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

Support: Synapsis Foundation, Switzerland

Title: Using uncoupling in mitochondria of astrocytes to promote neuroprotection in Alzheimer's disease

Authors: *N. ROSENBERG[1], A. B. ROCHER[2], M. BRIQUET[2], Y. BERNARDINELLI[3], J.-Y. CHATTON[2]
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Abstract: Oxidative stress has been associated with apoptosis and cell death in aging and neurodegenerative diseases such as Alzheimer's disease (AD). However, the nature of the stress causing cellular injury is not yet precisely known. It has been established in neuron-astrocyte co-culture experiments that uncoupling proteins (UCPs) endogenously expressed by astrocytes decreased peroxide production from astrocytes, increased glycolysis and lactate release, and enhanced survival rate of neurons. Lactate exerts beneficial effects in cerebral ischemia and has a non-metabolic modulatory effect on neuronal activity. Furthermore, in neurons, lactate is involved in the potentiation of NMDA receptors that are key players in synaptic plasticity and long-term memory consolidation. We aimed to investigate the contribution of UCP-mediated mild mitochondrial uncoupling in astrocytes of the hippocampus of 3xTg-AD mice by viral gene delivery of UCP4. Adeno-associated virus (AAV) containing UCP4 alone, or UCP4 in combination with mCherry as a fluorescent reporter under the short astrocytic GFAP promoter were stereotaxically injected in two sites of the hippocampus of wild-type and 3xTg-AD mice. GFAP and HA immunostaining showed a highly selective infection of CA1 and CA3 astrocytes as well as the expression of UCP4 in astrocytes. We are assessing the cognitive status of 3-months old mCherry vs. mCherry-UCP4 injected mice by performing passive avoidance and spatial recognition tasks. We are comparing the morphological properties of electrophysiologically characterized CA1 pyramidal cells by using whole-cell patch clamp recordings in the same animals. Preliminary findings reveal and validate the effectiveness of AAV infection and injection. Further experiments will allow us to tackle the question of whether

astrocytic UCP4 influences lactate and ROS production in vivo and impact on the function and health of vulnerable neurons of AD-associated pathologies.

Disclosures: **N. Rosenberg:** None. **A.B. Rocher:** None. **M. Briquet:** None. **Y. Bernardinelli:** None. **J. Chatton:** None.

Poster

208. Synaptic Deficits in Alzheimer's Disease and Neurodegeneration I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 208.18/H4

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

Support: NIH/NIA Grant 1R01AG042890

Amon Carter Foundation

Title: Oligomers of tau and amyloid beta synergistically converge onto calcineurin to disrupt synaptic plasticity and memory function

Authors: ***G. TAGLIALATELA**[1], B. KRISHNAN[1], W. ZHANG[1], R. KAYED[1], M.-A. MICCI[2]
[1]Neurol., Univ. of Texas Med. Br. Dept. of Neurol., Galveston, TX; [2]Anesthesiol., UTMB, Galveston, TX

Abstract: Alzheimer’s disease (AD) is the most common and severe age-associated neurodegenerative dementia of our times for which there is no cure. Synaptic dysfunction induced by the dysfunctional targeting of toxic oligomers of both amyloid beta (Aβ) and Tau (the two hallmark amyloids in AD) is recognized as one of the earliest events in AD, driving initial cognitive decline and clinical manifestation, and preventing it would thus be an effective therapy for AD. However, a strategy to achieve this important goal remains elusive. In the present work we began to address this critical knowledge gap by testing the hypothesis that activation of the CNS-rich phosphatase calcineurin (CN) mediates the synergistic effect of Aβ and tau oligomers on synapses and that CN inhibition is an effective approach to block such combined toxicity. CN is abnormally increased the brain of AD patients and mouse models of AD, and inhibition of CN with FK506 (an FDA-approved immunosuppressant) protects synapses from Aβ oligomers and restores memory in mice. Most notably, we showed that the incidence of AD in solid organ transplant recipients chronically treated with FK506 is dramatically reduced as compared to the general population, further suggesting a central role of CN in those cellular events that drive AD onset/progression. Here we used *in vitro*, *ex vivo* and *in vivo* approaches to test whether abnormal CN activation mediates the cellular, synaptic and behavioral impact of tau oligomers, alone or in combination with Aβ oligomers. We found that the effect of tau oligomers in

promoting cell death in human neuroblastoma cells, opposing synaptic plasticity in hippocampal slices, and disrupting memory function in mice are all accompanied by activation of CN and fully prevented by its inhibition with FK506. Most importantly, when ineffective doses of tau and Aβ oligomers were combined together, they synergized to suppress expression of synaptic long term potentiation (LTP) in hippocampal slices and this effect was also fully blocked by CN inhibition. Taken together, these results document a previously unappreciated role of CN as the point of molecular convergence of the toxic Aβ and tau oligomers and illustrate the beneficial effects of FK506 in preventing their combined toxicity. Our results also suggest an innovative treatment concept for AD centered on simultaneous blockade of tau and Aβ toxic species, a strategy expected to be effective in humans as suggested by the resilience to AD of transplanted patients chronically treated with FK506.

Disclosures: G. Taglialatela: None. **B. Krishnan:** None. **W. Zhang:** None. **R. Kayed:** None. **M. Micci:** None.

Poster

208. Synaptic Deficits in Alzheimer's Disease and Neurodegeneration I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 208.19/H5

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

Support: NIH/NIA R03 AG047537

NIH/NIA R01 AG042890

Title: NSC-derived exosomes reduce hippocampal synapses vulnerability to the dysfunctional impact of both amyloid beta and tau oligomers

Authors: *M.-A. MICCI[1], B. KRISHNAN[2], R. KAYED[2], W.-R. ZHANG[2], E. BISHOP[1], G. TAGLIALATELA[2]
[1]Anesthesiol., [2]Mitchell Ctr. for Neurodegenerative Diseases; Dept. of Neurol., UTMB, Galveston, TX

Abstract: Alzheimer’s disease (AD) is the most common and severe age-associated neurodegenerative dementia. Although there is ample consensus that an effective treatment should target the synaptic damaging impact of oligomers of both amyloid beta (Aβ) and tau, that synergistically converge onto synapses to drive, together, early synaptic dysfunction in AD, a strategy to achieve these goals remains unresolved. The recent discovery that certain individuals remain cognitively intact despite the presence of neuropathology associated with a fully symptomatic stage of the disease suggests that there is a way for the brain to evade dementia even in the face of AD. We have discovered that brain synapses in these unaffected subjects are

resistant to the disruptive binding of toxic Aβ and tau oligomers and that this resistance is associated with the presence of higher numbers of neural stem cells (NSC) in the hippocampus. It follows that understanding the mechanism(s) involved in such extraordinary resistance would reveal targets for the development of a novel, effective therapeutic concept based on inducing cognitive resilience in anyone challenged with AD neuropathology. We have recently shown that NSC-derived exosomes (NSC-exo; small secreted vesicles containing cell-specific cargos of proteins, lipids and genetic material) promote synaptic resistance to Aβ oligomers binding, and associated synaptic and cognitive deficits, using both *in vivo* and *in vitro* models. Here we set up to study whether, in addition to providing protection to Aβ oligomers, NSC-exo can promote synaptic resistance to tau oligomers toxicity. We found that hippocampal slices prepared from animals treated intracerebroventricularly with NSC-exo were significantly less vulnerable to tau oligomers binding than the ones isolated from animals treated with mature neuron-derived exosomes (MN-exo; used as control). We further found that tau oligomers-induced suppression of long-term potentiation (LTP) was abolished in hippocampal slices isolated from NSC-exo-treated mice. These results further points to NSC-exo as modulators of synaptic susceptibility to the dysfunctional impact of both Aβ and tau oligomers and unmask a novel therapeutic target for AD based on the delivery of NSC-exo or their bioactive cargoes.

Disclosures: M. Micci: None. **B. Krishnan:** None. **R. Kayed:** None. **W. Zhang:** None. **E. Bishop:** None. **G. Taglialatela:** None.

Poster

208. Synaptic Deficits in Alzheimer's Disease and Neurodegeneration I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 208.20/H6

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

Support: The Mitchell Center for Neurodegenerative Diseases

NIA R01 AG042890

Title: Increased synaptic sensitivity to Aβ and tau oligomers in aging CNS as a function of decreasing neural stem cells

Authors: *B. KRISHNAN, D. BRILEY, R. KAYED, G. TAGLIALATELA, M. A. MICCI
Dept. of Neurol., Univ. of Texas Med. Br. At Galveston, Galveston, TX

Abstract: Alzheimer’s disease (AD) is the most common and severe neurodegenerative dementia for which there is no cure. While aging is the most significant risk factor for AD, synaptic dysfunction is one of the earliest key events in AD, where oligomers of both Aβ and tau (the two hallmark amyloids in AD) can target and disrupt synapses causing memory

dysfunctions via converging synergistic mechanisms. Interestingly, AD pathology can occur years before symptoms become manifest, suggesting that aging renders synapses more vulnerable to the detrimental action of oligomers. However, the involved mechanisms remain unresolved. In the present work, we tested the hypothesis that aged synapses are more sensitive to the detrimental impact of oligomers and that such increased vulnerability is accompanied by reduction of hippocampal neural stem cells (NSC). We found that oligomers of Aβ and tau (alone or in combination) significantly reduced long-term potentiation (LTP) using high frequency stimulation (HFS) in both young (2-month) and old (18-month) C57Bl/6 mice hippocampi in an age-dependent manner. Notably, doses of the oligomers that do not induce LTP deficits in the young mice, effectively suppressed LTP in the older mice, suggesting a more detrimental impact of the toxic oligomeric species with increase in the age-dependent synapse vulnerability. We further found that this age-dependent synaptic vulnerability paralleled a significant reduction in the number of NSC in the hippocampus dentate gyrus (DG) and that was rescued by treating the aged animals with NSC-derived exosomes (small released vesicles containing genetic material and miRNA capable of modulating the physiology of target cells) intracerebroventricularly. Collectively, our results indicate an age-dependent increase in synaptic vulnerability to toxic Aβ and tau oligomers, a phenomenon possibly mediated by decreasing levels of hippocampal NSC and NSC-derived exosomal signaling within the hippocampus. Our data further suggest that promoting brain natural defenses via delivery of NSC-derived exosomes (or their specific content) may provide an unprecedented strategy to halt ongoing synaptic damage in the aging AD brain.

Disclosures: B. Krishnan: None. **D. Briley:** None. **R. Kayed:** None. **G. Taglialatela:** None. **M.A. Micci:** None.

Poster

209. Parkinson's Disease: Neuroprotective Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 209.01/H7

Topic: C.03. Parkinson’s Disease

Title: Characterisation of zebrafish CDNF mutant throughout the lifespan

Authors: *Y.-C. CHEN, S. SEMENOVA, M. SUNDVIK, P. PANULA
Univ. of Helsinki, Helsinki, Finland

Abstract: Cerebral dopamine neurotrophic factor (CDNF) belongs to the evolutionarily conserved novel CDNF/MANF family, which has a potential therapeutic role in neurodegenerative diseases such as Parkinson’s disease. Up to date, little research has been done on the molecular mechanism of CDNF in neurogenesis or its role in disease pathogenesis. To study the biological functions of CDNF, we generated a loss-of-function *cdnf* mutant fish (*cdnf* $^{-/-}$

) with a fourteen-nucleotide deletion causing a premature stop codon on exon2 of *cdnf* locus using the CRISPR/Cas9 system in zebrafish. The *cdnf* $^{-/-}$ fish was viable with no obvious gross phenotype or locomotor behavioral impairment in the lifetime. We analyzed the mRNA levels of angiogenic factors, neurotrophic factors, markers for neural proliferation and differentiation as well as markers for dopaminergic and histaminergic neurons using 8-dpf larvae, 8-month-old and 19-month-old *cdnf* mutant brains. Remarkably, a significant downregulation of *tek receptor tyrosine kinase* (*tek*) and *sex determining region Y-box2* (*sox2*) mRNA was found in 19-month-old *cdnf* $^{-/-}$ brains compared with those of wild type and heterozygous siblings. An upregulation of tyrosine hydroxylase 2 was found from the larval to aging stage of *cdnf* $^{-/-}$ brains although the catecholamine levels did not differ significantly. Nonetheless, dramatic reductions of the dopamine metabolite 3-methoxytyramine and homovanillic acid and the serotonin metabolite 5-hydroxyindoleacetic acid were detected in 19-month-old *cdnf* $^{-/-}$ brains, suggesting that loss of CDNF has a considerable impact on neurotransmitter systems at aging stages of the zebrafish.

Disclosures: Y. Chen: None. **S. Semenova:** None. **M. Sundvik:** None. **P. Panula:** None.

Poster

209. Parkinson's Disease: Neuroprotective Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 209.02/H8

Topic: C.03. Parkinson’s Disease

Support: Women's Advancement Inititaive Faculty Grant

College A&S University of Hartford

Title: ERK5 is expressed in ventral midbrain neurons and may regulate nurr1 transcriptional activity

Authors: *P. SACCHETTI[1], S. DELVECCHIO[2]
[1]Biol. Sci., [2]Neurosci. Program - Biol., Univ. of Hartford, West Hartford, CT

Abstract: The nuclear receptor nurr1 (NRA4A2) plays an essential role in inducing and maintaining proper expression of marker genes in developing and adult ventral midbrain dopamine neurons. In addition to gene regulation, expression of nurr1 seems to confer neuroprotection to these neurons. Differently from other members of the nuclear receptor superfamily of transcription factors, nurr1 transcriptional activity does not seem to be ligand-dependent. Despite efforts, the quest for nurr1 modulators has provided no specific insights into the mechanisms governing the activation and inactivation of this important transcription factor. The Extracellular signal-Regulated Kinase 5 (ERK5; MAPK7) signaling pathway is implicated in neuronal differentiation and cell survival in response to environmental stressors in different

cell types. Our previous studies showed that Erk5 directly interacts and phosphorylates nurr1, and it is thus capable of enhancing nurr1 transcriptional activity. However, the role of this regulatory interaction has not been addressed *in vivo* yet. The present study aims at mapping the expression of ERK5 in the ventral midbrain across developmental stages to adulthood. Using conventional and quantitative PCR, our data show that ERK5 is present in this tissue from embryonic day 11.5, and its expression levels are elevated by birth and peak in adulthood. Additionally, ERK5 was detected in tissue extracts positive for tyrosine hydroxylase and nurr1, two essential markers of ventral midbrain dopamine neurons. Experiments are underway to precisely map the cell population(s) expressing ERK5 in the midbrain at different developmental stages. Our data points to the presence of ERK5 in ventral midbrain neurons, reinforcing the hypothesis of an *in vivo* role for the ERK5 signaling pathway in differentiation and protection of dopamine neurons. ERK5 could exert these functions *in vivo* by phosphorylating nurr1 and affecting its transcriptional activity. The identification of proteins capable of modulating nurr1 activity would be very useful tools to clarify the mechanisms of action of this essential player implicated in the development and protection of dopamine neurons. This could provide new research avenues to battle neuronal degeneration in Parkinson's disease.

Disclosures: P. Sacchetti: None. **S. DelVecchio:** None.

Poster

209. Parkinson's Disease: Neuroprotective Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 209.03/H9

Topic: C.03. Parkinson's Disease

Support: NIH Grant AG040261

Parkinson's Disease Foundation

Title: Nigral GFR alpha1 expression as mediator of striatal GDNF impact: Evidence from aged and 6-OHDA lesioned rats

Authors: *M. F. SALVATORE[1], E. A. KASANGA[2], C. OWENS[3], F. P. MANFREDSSON[4], A. D. RICHARD[5], B. S. PRUETT[3], M. CANTU[2], L. MCDIVITT[3], C. TAN[2], A. GAJEWSKI[2], B. LATIMER[3]
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Abstract: The striatum can be targeted by growth factors to restore or preserve motor impairment. Striatal delivery of glial cell line-derived trophic factor (GDNF) can increase motor function in aging and PD models, and, in some studies, Parkinson's disease patients. However, despite evidence of motor improvement, many preclinical studies report little to no increases in tyrosine hydroxylase or DA content in striatal regions. Therefore, if increased dopamine function influences motor outcomes, the nigrostriatal compartment involved may be outside of striatum. Motor outcomes in human subject recipients of GDNF reveal two possible clues to further understand the molecular basis and nigrostriatal compartment for GDNF impact on motor function. First, bilateral improvements are reported following unilateral delivery in the putamen. Second, the motor effects of GDNF endure for months following cessation of its delivery in putamen. We have previously reported that nigral delivery of purified GDNF family receptor, GFRα1, increases TH expression and DA content in the substantia nigra (SN) alone in conjunction with a transient increase in locomotor activity. Here, we evaluated whether GFRα1 expression in the nigrostriatal pathway could be affected by unilateral GDNF delivery in striatum over time in aged rats. Second, we evaluated whether GFRα1 alone, delivered to the striatum or SN could affect TH expression in the 6-OHDA model. GDNF (30 µg) was delivered unilaterally into striatum and DA content and GFRα1 expression were determined in 3 groups reflecting 3 time points after delivery. GDNF increased DA in the SN at 4 weeks, without effect at 1 day or 1 week post-infusion. No differences in striatal DA were observed at any time interval post-infusion. GDNF produced a bilateral increase in GFRα1 expression in the nigra at 4 wks post-infusion. After induction of 6-OHDA lesion, infusion of purified GFRα1 (1 ng) into the SN reduced TH protein loss in the SN, but not striatum. Infusion of GFRα1 to striatum did not confer protection against TH loss in either striatum or SN. Taken together, we conclude that increased nigral GFRα1 expression may mediate long-term effects of striatal GDNF and that GFRα1 expression in the SN may mediate protection against loss of TH therein.

Disclosures: **M.F. Salvatore:** None. **E.A. Kasanga:** None. **C. Owens:** None. **F.P. Manfredsson:** None. **A.D. Richard:** None. **B.S. Pruett:** None. **M. Cantu:** None. **L. McDivitt:** None. **C. Tan:** None. **A. Gajewski:** None. **B. Latimer:** None.

Poster

209. Parkinson's Disease: Neuroprotective Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 209.04/H10

Topic: C.03. Parkinson's Disease

Support: Instituto de Salud Carlos III, i-PFIS fellowship IFI14/00016

Centro de Investigacion Biomedica en Red, Enfermedades Neurodegenerativas (CIBERNED)

Marcelino Botín Foundation

BBVA Foundation

Title: Molecular insights into the endogenous GDNF expression in striatal parvalbumin neurons: A possible tool for neuroprotective therapy for Parkinson's disease?

Authors: *D. ENTERRÍA-MORALES, I. LÓPEZ-LÓPEZ, J. LÓPEZ-BARNEO, X. D´ANGLEMONT DE TASSIGNY
Cell. Neurobio. and Biophysics, Inst. De Biomedicina De Sevilla, Sevilla, Spain

Abstract: Parkinson's disease (PD) is a neurodegenerative disorder caused by the loss of several populations of central and peripheral neurons. However, the most disabling motor symptoms (tremor, rigidity and bradykinesia) are mainly due to the progressive death of nigrostriatal dopaminergic (DA) neurons. Neuroprotective approaches, mainly based on the exogenous administration of the glial cell line-derived neurotrophic factor (GDNF), held high expectation from preclinical studies but their application in clinical trials proved more problematic. Previous work from our laboratory has suggested that GDNF, which is mostly produced by parvalbumin (PV) GABAergic interneurons in the mouse striatum, is essential for the survival and maintenance of adult mesencephalic DA neurons. However, this view has been challenged by others and therefore the role played by brain GDNF in neuroprotection of the nigrostriatal pathway is a matter of debate. Clarification of this question has fundamental translational relevance, as stimulation of endogenous striatal GDNF production could be a potential therapy for PD. In this work we sought: 1) to clarify the role of GDNF produced in the striatum, and 2) to determine what makes the PV neurons the selective supply (>90% of the Gdnf expressing cells) of striatal GDNF. We have generated transgenic mouse models carrying conditional deletions of the *Gdnf* gene. Our data indicate that GDNF is able to provide survival clues to the DA neurons until low levels are reached. However, decrease of striatal GDNF below a threshold level (~20% wild-type level) results in dramatic loss of DA neurons. Additionally, a FACS and microarray supported transcriptomic analysis of striatal PV neurons (versus the developmentally related cortical PV neurons that do not produce GDNF) showed specific intracellular pathways (e.g. PI3K-Akt or cAMP signaling) and unique receptors (e.g. GPR83, EGFR, c-KIT, or TACR3) to the striatal PV population. The relevance of these receptors and pathways on GDNF production is currently under investigation.
These data bring us closer to unravel the cellular/molecular pathways that drive *Gdnf* expression, and to identify potential pharmacological targets to specifically stimulate striatal GDNF synthesis.

Disclosures: D. Enterría-Morales: None. **I. López-López:** None. **J. López-Barneo:** None. **X. d´Anglemont de Tassigny:** None.

Poster

209. Parkinson's Disease: Neuroprotective Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 209.05/H11

Topic: C.03. Parkinson’s Disease

Support: Academy of Finland Grant 293392

Academy of Finland Grant 287843

TEKES 3iRegeneration

Title: Elucidating the molecular mechanisms of enoxacin and CDNF-mediated protection of dopaminergic neurons

Authors: J. KONOVALOVA, P. CHMIELARZ, *A. DOMANSKYI
Univ. of Helsinki, Helsinki, Finland

Abstract: MicroRNAs (miRs) are small non-coding regulatory RNAs that control gene expression by binding to specific mRNA targets and regulating their translation. Disruption in miR biogenesis contributes to multiple pathological conditions, including neurodegenerative diseases, such as amyotrophic lateral sclerosis and Parkinson’s disease (PD). Motor symptoms of PD are caused by age-related progressive degeneration of dopaminergic (DA) neurons in the substantia nigra. Despite many years of extensive research, currently there are no available treatments that would stop or slow down degeneration of DA neurons and PD progression. Therefore, novel targets for its treatment and management are required.
We have recently demonstrated the crucial importance of miR biogenesis in dopaminergic (DA) neuron maintenance by showing that selective depletion of miR processing enzyme Dicer in adult DA neurons causes their progressive loss and development of PD-like phenotype in mice. Furthermore, treatment of cultured primary DA neurons with enoxacin known to enhance processing of miR precursors significantly increases survival of DA neurons and attenuates their vulnerability to endoplasmic reticulum stress. Another promising strategy in PD treatment utilizes cerebral dopamine neurotrophic factor (CDNF), known to alleviate endoplasmic reticulum stress and showing neuroprotective and neurorestorative effects in animal PD models. However, precise molecular mechanisms of enoxacin or CDNF action on DA neurons are still elusive.
Here we show that intrastriatal and intranigral CDNF injections in mice affected the expression levels of several miRs in the ventral midbrain. Utilizing 3’UTR luciferase reporter assay, we identified several miRs as potential regulators of CDNF and mesencephalic astrocyte-derived neurotrophic factor (MANF). To uncover the molecular mechanisms of enoxacin neuroprotection, we are currently analyzing changes in the levels of selected miRs and mRNAs

in primary DA neurons after enoxacin treatment. We have also developed lentiviral vectors for the expression of selected miRs under control of human *synapsin1* promoter, which allows specific and efficient targeting of DA neurons both *in vitro* and *in vivo* to test the neuroprotective effect of several miR candidates.
Our results suggest that miRs may have potential neuroprotective effect that can be utilized as new therapeutic approach for PD treatment.

Disclosures: J. Konovalova: None. **P. Chmielarz:** None. **A. Domanskyi:** None.

Poster

209. Parkinson's Disease: Neuroprotective Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 209.06/H12

Topic: C.03. Parkinson’s Disease

Support: KIST

Title: The neuroprotecive role of cAMP signaling pathway in *Drosophila* model of parkinson’s disease

Authors: S. ISMAEL, *D. LEE
Ohio Univ., Athens, OH

Abstract: Parkinson’s Disease (PD) is a progressive movement disorder associated with loss of dopaminergic neurons in substantia nigra pars compacta and cytoplasmic proteinous aggregates called Lewy bodies. PD is characterized by several symptoms in the patient, such as tremors, rigidity, bradykinesia and postural abnormality. Currently levodopa, dopamine precursor, and Dopamine type-2 receptor agonists are the most effective therapeutic drugs for ameliorating PD symptoms and providing patients a better life, but none of them yet prevents PD progression. As several PD models and post mortem brain tissue of PD patients have shown disruption of cAMP signaling pathway, we hypothesize manipulation of this signaling pathway may give another therapeutic target. To model PD, third-instar larvae and primary neuronal culture of Drosophila melanogaster were subjected to an environmental PD toxin rotenone. Larval locomotor behaviors such speed, pause and angular velocity were quantified as they are different ways to examine various PD-like motor symptoms. Additionally, neuronal culture was used to see dopaminergic neurodegeneration. We found that rotenone-treated larvae show decreased locomotion speed, increased angular velocity and pause time, and rotenone degenerates dopaminergic neurons in *Drosophila* embryonic neuronal culture. Furthermore, mutant *Dunce*, encoding *Drosophila* phosphodiesterase, rescued rotenone-mediated larval locomotion, while mutant rut1, encoding *Drosophila* adenylyl cyclase, showed no effects. This data suggests elevation of cAMP has neuroprotective effect against rotenone toxicity. Using designer receptors exclusively activated

by designed drugs (DREADDs), up-regulation of cAMP specifically in dopaminergic neurons was achieved in a crossed line TH-Gal4 X UAS-rM3BDs, which activates G αs when 100 μM or 1 μM clozapine-N-Oxide was applied for larval locomotion assay or primary neuronal culture, respectively. Our results show stimulation of cAMP pathway in dopaminergic neurons reduces rotenone-induced effects on locomotion speed by 68% and DA neurodegeneration by 71%. These results strongly support that there is disruption in cAMP signaling pathway in *Drosophila* PD model. Our work will lead to enhance our understanding of neuroprotection and help to identify the new potential therapeutic targets that can slow PD progression. This work was funded by Korea institute of Science and Technology.

Disclosures: S. Ismael: None. **D. Lee:** None.

Poster

209. Parkinson's Disease: Neuroprotective Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 209.07/I1

Topic: C.03. Parkinson’s Disease

Support: NIH Grant ES021656

NIH Grant ES021656-S1

NIH Grant NS096841

Title: Nurr1 regulates inflammatory activation of glia in a model of Parkinson's disease

Authors: *S. L. HAMMOND
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Abstract: Parkinson’s disease (PD) is characterized by the degeneration of dopaminergic neurons of the ventral midbrain and activation of microglia and astrocytes. The orphan nuclear receptor Nurr1 (NR4A2) regulates inflammatory gene expression in glial cells, as well as genes associated with homeostatic and trophic function in dopaminergic neurons. Despite these known functions of Nurr1, an endogenous ligand has yet to be discovered. We postulated that activation of Nurr1 would suppress activation of glia and thereby protect against loss of dopamine (DA) neurons following subacute lesioning with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). We previously demonstrated that a synthetic Nurr1 ligand, 1,1-bis(3′-indolyl)-1-(p-chlorophenyl) methane (C-DIM12), suppresses inflammatory gene expression in primary astrocytes and induces a dopaminergic phenotype in neuronal cultures. Pharmacokinetic analysis of C-DIM12 in mice by LC-MS depicts approximately three-times more compound concentrated in brain than in plasma. Through computational modeling of Nurr1 we have identified high binding affinity interactions between the Nurr1 co-activator domain and C-DIM12. Mice were

treated with 4 doses of MPTP + probenecid over 14 days and monitored for neurobehavioral function, loss of dopaminergic neurons and glial activation. Using 3D design-based stereology, C-DIM12 protected against loss of DA neurons in the substantia nigra pars compacta (SNpc). Western blot analysis also depicts preservation of Nurr1 regulated proteins TH, DAT and VMAT2 of the striatum. High throughput morphometric analysis revealed that C-DIM12 preserved a ramified morphological phenotype in microglia of the SNpc and suppressed activation of astrocytes. Finally, overexpression of Nurr1 in astrocytes in the SNpc using adeno-associated virus (AAV) conferred protection against MPTP-induced loss of DA neurons. These data demonstrate that activation of Nurr1 in glial cells suppresses neuroinflammation and thereby protects DA neurons against MPTP-induced neurodegeneration.

Disclosures: S.L. Hammond: None.

Poster

209. Parkinson's Disease: Neuroprotective Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 209.08/I2

Topic: C.03. Parkinson’s Disease

Support: Yale Kavli Institute for Neuroscience

Title: Mechanisms of GHSR-mediated protection of Substantia nigra dopamine neurons

Authors: *B. STUTZ[1,2], C. NASRALLAH[2], M. NIGRO[3], Z.-W. LIU[2], X.-B. GAO[2], J. D. ELSWORTH[4], L. MINTZ[5], T. L. HORVATH[2]
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Abstract: Parkinson’s Disease (PD) occurs worldwide affecting approximately 5 million individuals and is expected to affect around 10 million by 2030. In the US, 1 million individuals have PD, and 60,000 new cases are diagnosed every year, causing a rapidly expanding social, medical and financial burden. The growth hormone secretagogue 1 receptor / ghrelin receptor (GHSR) was demonstrated to be involved in *substantia nigra* (*SN*) dopamine (DA) neurons survival, which degeneration are the main cause of PD. Ghrelin activation of GHSR has been shown to protect *SN* DA neurons against 1-methyl-4-phenyl-1,2,5,6 tetrahydropyridine (MPTP) treatment. Here, we report that a human isoform of the ghrelin gene (Dln101) displays equivalent neuroprotective factor. However, while exogenous administration of mouse ghrelin electrically activates *SN* DA neurons increasing neuronal firing, dopamine output to the dorsal striatum, as well as animal locomotion; the human isoform significantly suppressed *SN* DA neuronal firing and decreased dopamine output to the dorsal striatum, with associated decrease in animal motor behavior. These data suggests a possible role of Dln101 as an inverse agonist/antagonist of the

GHSR. Moreover, genetic ablation of GHSR completely prevents both ghrelin and Dln101 effects over *SN* DA neurons. In further characterizing the neuroprotection mechanism elicited by Dln101, we found that MPTP-induced microglia activation was partially prevented with Dln101 pre-treatment as well as was the MPTP-induced increase in gene expression of inflammation markers, such as TNF alpha, CD68 and CCL-2. In addition, animals treated with Dln101 displayed increased levels of antioxidative genes, including SOD-2 and catalase, as well as positive trends for increased UCP expression, and decreased reactive oxygen species in *SN* DA neurons following MPTP exposure. Altogether, our data suggest a better maintenance of cell redox state and decreased inflammatory tonus promoted by Dln101. Central to the pathophysiology of PD, mitochondrial function is compromised in PD leading to altered dynamics and decreased ATP production. Activation of GHSR by Dln101 was shown to regulate mitochondrial fusion as a plausible mechanism underlying *SN* DA survival, through the activity of mitochondrial outer membrane protein mitofusin 2, which emerges as a potential therapeutic target in PD clinical research in the near future.

Disclosures: **B. Stutz:** A. Employment/Salary (full or part-time):; Biogen. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Dia Lean. **C. Nasrallah:** None. **M. Nigro:** None. **Z. Liu:** None. **X. Gao:** None. **J.D. Elsworth:** None. **L. Mintz:** None. **T.L. Horvath:** None.

Poster

209. Parkinson's Disease: Neuroprotective Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 209.09/I3

Topic: C.03. Parkinson’s Disease

Title: Mirtazapine exerts astrocytes-mediated dopaminergic neuroprotection

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Abstract: Background: In Parkinson's disease, dopaminergic neurons are degenerated by various factors. Oxidative stress is well known to be involved in neurodegeneration. We previously reported that serotonin 1A (5-HT1A) receptor full agonist 8-OH-DPAT protected dopaminergic neurons by promoting astrocyte proliferation and up-regulation of antioxidative molecule metallothionein (MT) in astrocytes. Anti-depressant drug mirtazapine has been known to activate 5HT1A receptors indirectly. Therefore, mirtazapine has a possibility to protect dopaminergic neurons by targeting astrocytes. Object: In this study, we examined whether mirtazapine can protect dopaminergic neurons by promoting MT expression and proliferation of astrocytes.

Methods: We examined neuroprotective effects of mirtazapine by in vivo animal experiments and in vitro culture studies. The hemi-parkinsonian mice produced by 6-OHDA injections into the right side of striatum were administrated with mirtazapine (5 or 16 mg/kg, i.p) for 8 days. Immunohistochemical analysis was performed using brain sections. As in vitro experiments, primary cultured neurons and astrocytes were prepared from the mesencephalon and striata of Sprague-Dawley rat embryos at 15 days gestation. Mesencephalic neurons or neuron-astrocyte co-cultures were treated with mirtazapine. Results: In the animal experiment, the reduction of dopaminergic neurons on the lesioned side of the substantia nigra in parkinsonian mice was ameliorated by the administrations of mirtazapine for 8 days. The treatment with the drug significantly increased MT expression in GFAP- or S100β-positive astrocytes in the striatum of parkinsonian mice. These effects were annulled by simultaneous treatment with a 5-HT1A antagonist. In vitro study using primary cultured neurons and astrocytes, mirtazapine protected dopaminergic neurons against 6-OHDA neurotoxicity in neuron-astrocyte co-cultures, but not in enriched neuronal cultures. In addition, mirtazapine promoted astrocyte proliferation and up-regulated MT expression in the striatal astrocytes, which were mediated by secreted molecules from mesencephalic neurons. Conclusion: These results suggested that mirtazapine exerts possible disease-modifying neuroprotective property by up-regulation of MT in astrocytes via 5-HT1A receptors.

Disclosures: R. Kikuoka: None. **I. MIyazaki:** None. **N. Kubota:** None. **M. Maeda:** None. **D. Kagawa:** None. **M. Moriyama:** None. **A. Kume:** None. **S. Murakami:** None. **Y. Kitamura:** None. **M. Asanuma:** None.

Poster

209. Parkinson's Disease: Neuroprotective Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 209.10/I4

Topic: C.03. Parkinson’s Disease

Support: NMRC-TCR

CBRG

NGS Scholarship

Title: The AMPK-PGC-1α axis in neuroprotection - implications for energy deficits in Parkinson's disease

Authors: *L. HANG[1,2], C.-H. NG[1], A. H. BASIL[1], J. L. THUNDYIL[1], K.-L. LIM[1,2,3,4]
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Abstract: Emerging studies implicate energy dysregulation as an underlying trigger for Parkinson's disease (PD), suggesting that a better understanding of the molecular pathways governing energy homeostasis could help elucidate therapeutic targets for the disease. Supporting this, we have recently demonstrated that activation of AMP kinase (AMPK), a master regulator of cellular energy homeostasis, rescues the pathological phenotypes of *Drosophila* models of PD (Ng et al., 2012 J. Neurosci.). Using the *Drosophila* system, we showed here that AMPK-mediated neuroprotectionrequires PGC-1α, a downstream target of AMPK that functions as a key regulator of mitochondrial biogenesis. Consistent with this, we found that expression silencing of *Drosophila* PGC-1α results in PD-related phenotypes in flies. Importantly, we further found that genetic or pharmacological activation of the *Drosophila* PGC-1α is sufficient to rescue the disease phenotypes of several genetic fly models of PD (Ng et al., 2017 Neurobiol. Aging, accepted). Notwithstanding the above findings, whether they are relevant to the mammalian context were unclear. As an initial attempt to clarify this, we examined the expression of AMPK in rodent brains and found that phospho-AMPK (pAMPK), i.e. the activated form of AMPK, is disproportionately distributed in the adult mouse brain, being high in the ventral midbrain where the substantia nigra (affected in PD brains) resides and relatively lower in regions such as the cortex - reflecting perhaps the unique energy demands of midbrain dopaminergic neurons. Importantly, the physiologically higher level of midbrain pAMPK is significantly reduced in Parkin-deficient mice; the loss of function of which in humans causes recessive Parkinsonism. Not surprisingly, the expression of PGC-1αmirrors the expression pattern of pAMPK. Finally, we showed that treatment of mice with metformin (an AMPK activator)promotes the level of midbrain pAMPK, which potentially represents a viable strategy to restore energy dysregulation in PD brains.

Disclosures: L. Hang: None. **C. Ng:** None. **A.H. Basil:** None. **J.L. Thundyil:** None. **K. Lim:** None.

Poster

209. Parkinson's Disease: Neuroprotective Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 209.11/I5

Topic: C.03. Parkinson's Disease

Support: Spanish Ministry of Economy and Competitivity: Project SAF2014-57160-R

Funds were also obtained via a crowdfunding campaign via Goteo.org and sponsored by Mememtum: early detection of neurological disorders and Portal d'Avall S.L.

Title: Role of RTP801 in neuronal plasticity and motor learning

Authors: *L. PÉREZ-SISQUÉS[1,2], N. MARTÍN-FLORES[1,2], A. LLOBET[1], M. CANAL[1], J. ROMANÍ-AUMEDES[1,3], M. MASANA[1,4,5,2], M. LACHÉN-MONTES[6], E. SANTAMARÍA[6], J. FERNÁNDEZ[6], J. GILBERT[7], H. MAN[7], E. FEINSTEIN[8], D. WILLIAMSON[9], X. GASULL[1,2], D. SOTO[1,2], J. ALBERCH[1,4,5,2], C. MALAGELADA[1,2]
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Abstract: RTP801/REDD1 is a stress-regulated protein that is elevated in cellular and animal models of Parkinson's disease (PD), Huntington's disease (HD) and also in human postmortem PD and HD brains. RTP801 is pro-apoptotic by sequentially inhibiting mTOR and Akt via the tuberous sclerosis complex (TSC1/2). RTP801 also has a regulatory role in cortical development, neuronal differentiation and peripheral nervous system myelination.In our preliminary results we observed that RTP801 is enriched at the synapses of both murine models and human postmortem brains. Here, we investigated whether RTP801 has a role in neuronal plasticity by using both cellular and animal models. We first characterized the RTP801 knock out (KO) mice versus wild type (WT) animals at 2 months of age at a behavioral, histological, electrophysiological and biochemical level.RTP801 KO animals showed no significant differences in locomotor activity or hippocampal memory. However, KO mice performed better in tasks involving motor learning. In line with this, RTP801 KO mice showed differences in spine density in specific brain areas.To investigate in further detail, we also performed electrophysiological analysis in primary cortical cultures from RTP801 KO and WT mice. Moreover, we performed proteomic analysis of cortical synaptosomes from RTP801 KO and WT mice.Altogether, these results suggest that RTP801 has an important role in modulating neuronal plasticity and motor learning.

Disclosures: L. Pérez-Sisqués: None. **N. Martín-Flores:** None. **A. Llobet:** None. **M. Canal:** None. **J. Romaní-Aumedes:** None. **M. Masana:** None. **M. Lachén-Montes:** None. **E. Santamaría:** None. **J. Fernández:** None. **J. Gilbert:** None. **H. Man:** None. **E. Feinstein:** None. **D. Williamson:** None. **X. Gasull:** None. **D. Soto:** None. **J. Alberch:** None. **C. Malagelada:** None.

Poster

209. Parkinson's Disease: Neuroprotective Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 209.12/I6

Topic: C.03. Parkinson's Disease

Support: NIH CA161882

MJ Fox 11551

Title: Molecular cloning of a novel 69 kDa brain-specific isoform of Regulator of G protein Signaling 6 (RGS6)

Authors: *K. E. AHLERS-DANNEN[1], A. STEWART[2], J. YANG[1], J. G. KOLAND[1], R. A. FISHER[1]
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Abstract: RGS proteins modulate the magnitude and duration of G protein coupled receptor (GPCR) signaling by facilitating heterotrimeric G protein inactivation. RGS proteins terminate G protein signaling through GTPase-activating (GAP) activity, bestowed by their semiconserved RGS domain, towards Gα subunits. We have demonstrated that RGS6 ($G\alpha_{i/o}$-specific GAP), a member of the R7 RGS protein subfamily, is critically involved in several CNS disorders for which RGS6 may be a novel therapeutic target. Remarkably, $RGS6^{-/-}$ mice have reduced anxiety and depression, exhibit diminished alcohol seeking/reward behaviors, and develop late-onset Parkinson's disease (PD). The role of RGS6 in these disorders is dependent on its ability to inhibit signaling of various brain GPCRs, including: cortical and hippocampal $5\text{-}HT_{1A}$Rs (anxiety/depression), $GABA_B$Rs in mesolimbic dopaminergic neurons (alcoholism), and D2Rs in dopaminergic neurons of the substantia nigra pars compacta (SNc, PD). Potentially key to RGS6's ability to regulate numerous GPCRs are previously unidentified domains arising via alternative mRNA splicing. Our initial cloning effort identified 36 distinct RGS6 mRNAs in human brain encoding proteins ≤ 56 kDa. Recently, we identified, in mouse and human, at least two additional brain-specific RGS6 isoforms that are larger (~61, 69 kDa) than the ubiquitously expressed 56 kDa RGS6L forms. The function of these RGS6 isoforms and how they arise is unknown, but they may be critical for CNS pathology as both are highly expressed in the brain regions affected by the disorders described above. Here we report PCR amplification and cloning of six novel RGS6 cDNAs from a human brain library that arise by alternative mRNA splicing and novel exon inclusion. One of these novel cDNAs exhibits near exclusive CNS expression, encodes a 69 kDa protein that co-migrates with the large (69 kDa) brain-specific RGS6 protein, and has a C-terminal extension near the RGS domain that may be a novel regulatory domain. This novel RGS6 splice-form may be important for PD progression as its expression is up-

regulated in the human SNc during neurodegeneration while other RGS6L isoforms are down-regulated. Other identified RGS6 cDNAs include those with novel exons encoding early stop codons yielding RGS6 proteins lacking all but the N-terminus and those with novel 3' exons generating RGS6 proteins with unique C-termini. Interestingly, several of the newly identified exons are shared primarily between humans and other primates. Together, this research lays the foundation for experiments to elucidate the functional significance of RGS6 alternative mRNA splicing in normal brain function and pathology.

Disclosures: K.E. Ahlers-Dannen: None. **A. Stewart:** None. **J. Yang:** None. **J.G. Koland:** None. **R.A. Fisher:** None.

Poster

209. Parkinson's Disease: Neuroprotective Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 209.13/I7

Topic: C.03. Parkinson's Disease

Support: ALF Vasterbotten

Parkinsonfonden

SLS

Title: Exploring the role of locus coeruleus in Parkinson's disease and its importance for nigral dopaminergic cell survival

Authors: A. VIREL[1], R. LATERVEER[1], I. DUDKA[2], S. OLMEDO-DIAZ[1], R. STENMARK PERSSON[1], A. BARKANDER[1], N. KARALIJA[1], *S. AF BJERKEN[1]
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Abstract: Locus coeruleus (noradrenaline; NA) has been suggested to be part of the early pathological process in neurodegenerative disorders such as Alzheimer's and Parkinson's disease. NA suppresses neuroinflammation by affecting microglia production of proinflammatory cytokines, and seems to act as a protector for substantia nigra dopamine neurons. Herein, we explore the impact of NA on the nigral dopamine neurons using the DSP4 [N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine] rat model. Sprague-Dawley rats have been injected with repeated DSP4 injections (50 mg/kg), causing a selective noradrenergic denervation. Functional evaluation using *in vivo* chronoamperometry demonstrated significantly increased striatal dopamine release in DSP4 treated rats compared to controls. Also, at 6 months following DSP4-lesion, stereological cell counting demonstrated significantly reduced numbers of tyrosine hydroxylase (TH)-positive cells in locus coeruleus and interestingly also a significantly reduced number of TH-positive cells in the substantia nigra. To further stress the

idea of NA acting as an immunosupressor and protector for nigral dopamine cells, we have now also administered a subthreshold dose of lipopolysaccharide (LPS; 2,5 mg/kg) to DSP4 rats (NA deficient). The potential neuroinflammatory process, in both DSP4 and DSP4/LPS-treated rats, is evaluated at different time points following drug administration using metabolomics. Also, one set of DSP4/LPS animals have been subjected to coerulean and nigral stereological cell counting.

Disclosures: A. Virel: None. **R. Laterveer:** None. **I. Dudka:** None. **S. Olmedo-Diaz:** None. **R. Stenmark Persson:** None. **A. Barkander:** None. **N. Karalija:** None. **S. Af Bjerken:** None.

Poster

209. Parkinson's Disease: Neuroprotective Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 209.14/I8

Topic: C.03. Parkinson’s Disease

Title: Serum quantification of glp-1 induced by ileal interposition in wistar male rats

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Abstract: Introduction: Glucagon-like peptide 1 (GLP-1) is a hormone synthesized in the gut by L-cells in the brain by preproglucagon neurons, located in a specific receptor with ubiquitous localization and with multiple effects. GLP-1 secretion is induced by the presence of bolus in the intestine and by indirect activation of neuroendocrine mechanisms. Several studies have shown that early exposure of the bolus to the ileum, caused by ileal interposition surgery, increased GLP-1 levels. In turn, GLP-1 is being studied as a neuroprotective factor in various models of brain injury. Objective: To standardize the surgical technique of illicit interposition and model to achieve an increase of GLP-1. **Methodology**: Performing ileal interposition surgery on male Wistar rats and determination of GLP-1 levels by immunoassay enzyme kit GLP-1 rat. **Results:** The results associated with the level of GLP-1 levels after ileal interposition surgery are shown. **Discussion:** The counter with an endogenous expression model of GLP-1 allows us to analyze the role of this protein in the models of neuronal injury in animals.
Key words: ileal Ileal, model, GLP-1

Disclosures: M.S. Salgado: None.

Poster

210. Parkinson's Disease: Preclinical Therapeutic Development

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 210.01/I9

Topic: C.03. Parkinson's Disease

Support: MnDRIVE Postdoctoral Fellowship in Neuromodulation

NIH grant R01 NS037019

NIH grant R01 NS077657

Title: Effects of parkinsonism and therapeutic deep brain stimulation on phase-synchronization across the subthalamic nucleus, globus pallidus, and primary motor cortex

Authors: *D. ESCOBAR SANABRIA[1], L. A. JOHNSON[1], J. ZHANG[1], S. NEBECK[1], M. D. JOHNSON[2], G. F. MOLNAR[1], J. L. VITEK[1]
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Abstract: Increased phase-synchronization of neural activity across the subthalamic nucleus (STN), internal segment of the globus pallidus (GPi), and motor cortical regions has been hypothesized to contribute to motor dysfunction in Parkinson's disease (PD). This hypothesis is based on the observation that levodopa decreases phase-synchronization across these structures in PD patients monitored using MEG/EEG and recordings from implanted deep brain stimulation (DBS) leads. How phase-synchronization changes from the normal to parkinsonian condition and during therapeutic DBS in the STN and GPi, however, remains unknown. In this study, we characterized changes in phase-synchronization across the STN, GP, and motor cortex (M1) of two rhesus macaques in the normal and parkinsonian condition, with and without therapeutic DBS. Each animal was implanted with a DBS lead in both STN and GPi and a Utah array in M1. Spontaneous local field potentials were collected in the awake resting state before and after animals were rendered parkinsonian by injections of the neurotoxin MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine). Static and dynamic measurements of phase-locking indicated that phase-synchronization between the STN and GPi centered at 12 Hz increased in the parkinsonian condition of both subjects and decreased during therapeutic STN and GPi DBS. We also observed changes in STN-M1 and GPi-M1 synchronization in the parkinsonian condition, although changes were not consistent across animals. These data suggest that increased phase-synchronization across STN and GPi is associated with development of parkinsonism, while reductions are associated with improvements in motor signs. The relationship between changes in phase-synchronization across subcortical and cortical structures is less clear and the topic of further study. Overall, these results further support the hypothesis that abnormal synchronization between nodes in the basal ganglia-cortical network underlies motor deficits in Parkinson's

disease, and that one of the therapeutic mechanisms of DBS is to disrupt pathological synchronization.

Disclosures: D. Escobar Sanabria: None. **L.A. Johnson:** None. **J. Zhang:** None. **S. Nebeck:** None. **M.D. Johnson:** None. **G.F. Molnar:** None. **J.L. Vitek:** None.

Poster

210. Parkinson's Disease: Preclinical Therapeutic Development

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 210.02/I10

Topic: C.03. Parkinson's Disease

Support: Boston Scientific

NIH Grant NS037019

NIH Grant NS058945

NIH Grant NS077657

Parkinson's Disease Foundation Postdoctoral Fellowship PDF-FBS-1550

Title: Critical parameters determining efficacy of coordinated reset stimulation of subthalamic nucleus and related changes in behavior and primary motor cortical local field potentials in a parkinsonian monkey

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Abstract: Coordinated reset deep brain stimulation (CR DBS) has been reported to be an effective therapy for the treatment of Parkinson's disease (PD), however, a systematic examination of the CR parameter space and the associated changes in cortical activity has not been explored. In this study, we investigated three CR stimulation paradigms and the corresponding changes in the M1 local field potentials in a non-human primate (NHP) model of PD. A NHP (female, 6 kg) was trained to do a standard reach/retrieval task and rendered parkinsonian. The animal was implanted with an 8-contact DBS lead in the subthalamic nucleus (STN) and a 96-channel Utah array in the arm area of M1. Three CR stimulation paradigms with distinct spatial activation profiles were studied, with each paradigm being delivered over five consecutive days for 4 hours per day. The Unified Parkinson's Disease Rating Scale modified for

NHPs (mUPDRS) and movement during the task were assessed before, multiple times during, and after DBS, with M1 LFPs recorded before and immediately after DBS. Power spectral density and phase-amplitude coupling (PAC) analysis was performed to investigate the changes in LFP activity. The mUPDRS and task related data showed sensitivity to CR paradigms with two out of the three activation profiles demonstrating a therapeutic effect acutely, sub-acutely with long-term carryover marked by reduced mUPDRS, retrieval and reaction times. Although there was some acute improvement in rigidity with the third activation profile, both retrieval and reaction times were increased and overall task performance was worse. The power of beta oscillation in M1 LFPs was correlated with the mUPDRS. Although beta power was also correlated with M1 beta/gamma PAC, the PAC modulation index did not correlate with parkinsonian symptoms. This study is the first to explore different CR paradigms in the NHP model of PD which demonstrated the significant role of the CR DBS spatial activation profile on therapeutic efficacy, and, interestingly, showed a stimulation pattern which can worsen motor function. The changes in M1 PAC and beta oscillation observed in this study further demonstrated the fluctuating character of PAC which questions the role of M1 PAC as a biomarker for PD motor signs. Exploration of CR stimulation paradigms may also provide a novel approach in delineating the pathophysiological basis underlying the motor signs of PD.

Disclosures: **J. Wang:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Boston Scientific Neuromodulation, 25155 Rye Canyon Loop, Valencia, CA USA. **S. Nebeck:** None. **D. Escobar:** None. **L.A. Johnson:** None. **J. Zhang:** None. **S. Fergus:** None. **S. Kulkarni:** A. Employment/Salary (full or part-time):; Boston Scientific Neuromodulation, 25155 Rye Canyon Loop, Valencia, CA USA. **A. Featherstone:** A. Employment/Salary (full or part-time):; Boston Scientific Neuromodulation, 25155 Rye Canyon Loop, Valencia, CA 91355. **H. Bokil:** A. Employment/Salary (full or part-time):; Boston Scientific Neuromodulation, 25155 Rye Canyon Loop, Valencia, CA USA. **M.D. Johnson:** None. **G.F. Molnar:** None. **J.L. Vitek:** None.

Poster

210. Parkinson's Disease: Preclinical Therapeutic Development

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 210.03/J1

Topic: C.03. Parkinson’s Disease

Support: NIH Grant NS081118

NIH Grant NS094206

NIH Grant NS098573

NIH Grant P41-EB015894

NIH Grant P30-NS057091

MICROBRADAM

UEF-Brain Pool

Title: Advanced stimulation patterns to increase therapeutic windows for deep brains stimulation applications

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Abstract: Pulse patterns used in deep brain stimulation (DBS) therapy are thought to induce largely non-specific axonal activation surrounding active electrodes. Given the proximity of active electrodes to regions implicated in side effects of DBS as well as the high levels of anisotropy within and surrounding DBS targets, there is a need for more selective stimulation approaches. Previous work has shown orientation selectivity of stimulation by varying the electrode shape and controlling the primary electric field direction using multichannel electrodes. In this work, we introduce a spatiotemporal approach based on Rotating Field Phase Steering (RFPS) paradigms for enhancing orientation selectivity of axonal activation. We evaluated these RFPS approaches using computational tissue conductance models developed in COMSOL and coupled with axonal models in NEURON to estimate axon activation thresholds for (1) a Medtronic 4-annular-contact channel DBS lead and (2) an Abbott 8-contact array with two annular contacts separated by two rows of 3 segmented contacts. Stimulation was applied in varying electrode combinations using phase-offset (0-2π) sinusoids, pulse delayed (0-500 μs) sinusoids, and biphasic square pulses. Axonal activation thresholds were analyzed for axons radially distributed 1 mm adjacent to the central axis of the leads. Sinusoids, applied through two adjacent cathodes on the Medtronic lead with no phase-offset and no pulse delay, resulted in lower activation thresholds for axons perpendicular versus parallel to the lead (**1:1.65** for sinusoids, **1:1.53** for square pulses). In contrast, sinusoids with a phase-offset of π, pulse delay of 500 μs, and bipolar square pulses between two adjacent contacts revealed lowest thresholds for parallel axons with a threshold ratios of **5.86:1, 5.75:1, and 5.58:1** respectively. Coupling the Abbott DBS lead to these novel stimulation paradigms using two diagonally-oriented segmented contacts improved orientation selectivity to axons with angles ±30° relative to the central axis of the lead. Thresholds ratios of 4.60:1 (phase offset = π) and 1:1.80 (phase offset = 0), were found for axons aligned antiparallel to the active contacts (+60° relative to the lead central axis) compared to axons parallel to the active contacts (-30°). This study provides a stimulation framework for generating orientation-selective activation with potential to widen the therapeutic window between stimulating pathways of interest and pathways implicated in side effects. RFPS combined with multichannel electrodes provides a wide spectrum of variables for more efficient, flexible, and selective neuromodulation.

Disclosures: **J. Slopsema:** None. **L. Lehto:** None. **S. Michaeli:** None. **M.D. Johnson:** None.

Poster

210. Parkinson's Disease: Preclinical Therapeutic Development

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 210.04/J2

Topic: C.03. Parkinson's Disease

Support: NIH Grant R01 NS077657

Title: Bilateral SMA and M1 LFP activity and connectivity is altered in the MPTP NHP model of Parkinson's disease

Authors: B. J. TITTLE[1], *C. M. HENDRIX[1], A. M. AMUNDSON[1], M. D. JOHNSON[2], G. F. MOLNAR[1], J. L. VITEK[1]
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Abstract: Optimizing therapy for patients with Parkinson's disease (PD) requires a deeper understanding of the mechanisms that underlie its motor signs. Pathologic synchronous oscillations within deep brain structures of the basal ganglia-thalamocortical (BGTC) network are implicated in PD pathology. Cortical involvement, however, is not well understood. In this study, we explore changes in cortical activity in parkinsonism during goal-directed motor behavior.
A non-human primate (NHP) was trained in a left-hand center-out reaching task. Local field potentials (LFP) were recorded over the bilateral supplementary motor area ($SMA_{L/R}$) and the right motor cortex ($M1_R$) in the naïve and mild hemi-parkinsonian state. Time-frequency response (TFR) characteristics were computed for each trial; Inference testing was performed on the resulting normalized power (z-score). Cluster-based statistics across states were examined as a function of time-locked frequency band desynchronization and modulatory coactivation within and between cortical structures.
In the naive state, high and low beta band desynchronization was time-locked to the go-cue, present in both SMA_R and SMA_L, and absent in $M1_R$. In the parkinsonian state, both high and low beta band desynchronization was markedly reduced in $SMA_{L/R}$, while high beta band desynchronization emerged in $M1_R$. When comparing the relative power between SMA_L/SMA_R, we found that asymmetry in the time and amplitude of desynchronization present in the naive state was lost in the PD state. Asymmetry in relative power between $SMA_R/M1_R$ in the naive state was reversed in the PD state.
LFP modulation in SMA time-locked to the instructional go-cue likely reflects the role of SMA in motor planning. In the parkinsonian condition, loss of SMA desynchronization with the emergence of $M1_R$ high-beta desynchronization suggests a fundamental change in the relationship between the SMA and M1 during movement planning. Desynchronization of $M1_R$ in

the parkinsonian state may be a compensatory mechanism for the changes that occur in SMA or contribute to the motor dysfunction observed in these animals. More detailed studies correlating the changes in SMA and M1 activity to individual motor signs as well as to specific task epochs will be required to elucidate the causal or epiphenomenal role of these changes in cortical activity to the motor dysfunction that occurs in PD.

Disclosures: B.J. Tittle: None. **C.M. Hendrix:** None. **A.M. Amundson:** None. **M.D. Johnson:** None. **G.F. Molnar:** None. **J.L. Vitek:** None.

Poster

210. Parkinson's Disease: Preclinical Therapeutic Development

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 210.05/J3

Topic: C.03. Parkinson’s Disease

Support: P50-NS-098573

R01-NS-085188

P41-EB-015894

P30-NS-076408

U54-MH-091657

Title: Multi-objective particle swarm optimization with subject-specific models facilitate spatially targeted programming in subthalamic nucleus deep brain stimulation

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Abstract: Recent developments in deep brain stimulation (DBS) technology have enhanced the spatial, temporal, and surgical precision of stimulation. With respect to spatial precision, the introduction of multi-source directional stimulation devices has enabled finer current steering capabilities. One remaining challenge to spatially steering current is the need to balance multiple objectives during programming in order to maximize activation of one or more therapeutic targets while minimizing side effects. An additional challenge involves efficiently traversing the expanded range of possible combinations of contacts and amplitudes in order to fully leverage the precision afforded by multi-source directional DBS devices. We have previously shown that computational models coupled with optimization algorithms are well suited to facilitate such

contact and amplitude selection in theoretical DBS programming examples. Here, we present a multi-objective particle swarm optimization (MOPSO) algorithm implemented on detailed subject-specific models of human subjects with subthalamic nucleus DBS. In this retrospective modeling study, the MOPSO programming approach efficiently evaluated combinations of contacts and current amplitudes, identifying a range of optimal combinations that provide maximal activation of the regions of interest (e.g. motor STN, superior cerebellar peduncle) while minimizing activation of non-target regions (e.g. medial lemniscus, internal capsule). Across subjects, there were a range of therapeutic effects and side effects, each corresponding to activation of different tracts, such as 18% medial lemniscus activation at paresthesia occurrence in one subject. Such variability in lead placement and activation in the associated brain regions were accounted for by the multiobjective algorithm. The MOPSO algorithm, coupled with subject-specific models, provides an efficient programming platform for spatial optimization of multi-source directional DBS.

Disclosures: E. Peña: None. **S. Zhang:** None. **R. Patriat:** None. **N. Harel:** None. **M.D. Johnson:** None.

Poster

210. Parkinson's Disease: Preclinical Therapeutic Development

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 210.06/J4

Topic: C.03. Parkinson’s Disease

Support: NSF IGERT DGE-1069104

NIH R01-NS094206

NIH P50-NS098573

NSF CBET-1264432.

Title: Reinforcement learning for phasic disruption of pathological oscillations in a computational model of Parkinson's disease

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Abstract: Deep brain stimulation (DBS) is an effective therapy for motor symptoms of PD. However, programming these devices is difficult, and therapy is limited by side effects and partial efficacy. Furthermore, traditional continuous DBS (cDBS) does not account for fluctuations in motor symptoms caused by factors such as sleep, attention, stress, etc., and as the patient’s state changes, so does the need for stimulation. Current cDBS strategies are incapable

of adapting to the needs of patients: once the clinician sets the parameters, they do not change until the next programming visit. *In this study, we have created a reinforcement learning (RL) DBS algorithm capable of learning online how best to stimulate to reduce pathological oscillations* in silico.

We have developed the RL-DBS algorithm for tuning DBS parameters, and have tested it on a biophysically realistic model of the basal ganglia-thalamocortical system, simulating parkinsonian neural activity. The RL-DBS algorithm decides when to deliver stimulus pulses based upon the real-time amplitude and phase of the pathological oscillation in order to reduce the amplitude of that oscillation. The algorithm learns which actions lead to the highest cumulative reward (i.e. reduction of oscillation amplitude).

After training on the model, the RL-DBS algorithm is able to learn both phase and amplitude selectivity to optimally reduce the oscillation. The algorithm learns the expected reward for both actions (not stimulating and stimulating) as a function of the phase/amplitude of the oscillation (**Fig. 1a/b**). The algorithm then decides which action to execute based upon the action difference (**Fig. 1c**). Additionally, the algorithm learns to deliver bursts of stimulation phase-locked to the oscillation.

We created an adaptive RL-DBS algorithm capable of learning on-line how to reduce the power of a pathological oscillation in a computation model of PD. The algorithm has the potential to deliver individualized, adaptive DBS therapy that can improve the quality of life for PD patients.

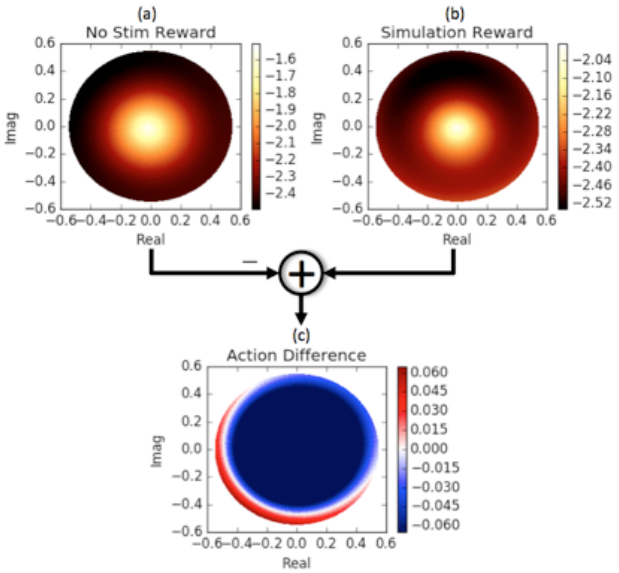

Fig. 1. Learned reward maps (a), (b) and action difference (c) as a function of the phase and amplitude of the oscillation. (a) and (b) show the learned reward for no stimulation and stimulation respectively, while (c) shows the action difference. The algorithm selects the action that with the highest expected reward. The action difference reveals that the algorithm learns both phase- and amplitude-selective stimulation.

Disclosures: **L. Grado:** None. **M.D. Johnson:** None. **T.I. Netoff:** None.

Poster

210. Parkinson's Disease: Preclinical Therapeutic Development

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 210.07/J5

Topic: C.03. Parkinson's Disease

Support: NIH Grant R01 NS077657

NIH Grant R01 NS058945

Title: Parkinsonism alters directional tuning in primary motor cortex

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Abstract: *Background* Primary motor cortex (M1) is a critical node in the basal ganglia thalamo-cortical circuit for encoding movement and abnormal neuronal activity in M1 may contribute to the motor symptoms of PD. Recent studies suggested that parkinsonism may influence the encoding of kinetic parameters of active movement in M1. We hypothesize that directional tuning, a fundamental coding principle in M1, is altered in PD, and address this issue with a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) non-human primate (NHP) model. *Method* A NHP was trained to make arm movements in 8 directions (at 45º intervals) to reach and retrieve treats from a two-dimensional Klüver board in the normal, parkinsonian without (drug-off) and with L-DOPA (drug-on) state. The task completion rate, reach time, retrieval time and the maximum speed during movement were measured, and the modified Unified Parkinson's Disease Rating Scale (mUPDRS) was performed in each state to assess severity of the animal. The activity of single cells was recorded by a Utah array implanted in the arm region of M1 while the animal was performing active movement in each state. The preferred direction and the directional tuning curve during the movement for each neuron was calculated. The modulation index for the preferred direction and the sector width of the tuning curve, a measure of the dispersion of the pattern of the neuronal discharge about the preferred direction, were also estimated to indicate the specificity of directional tuning during movement. *Result* Induction of parkinsonism worsened motor function, as reflected by increased mUPDRS and lower task completion rate. L-DOPA significantly improved the motor function, though there was no significant difference in the reach time, retrieval time and maximum speed between the drug-on and drug-off state. Although there was no significant difference between the ratio of direction-modulated neurons in normal, drug-on and drug-off states, during movement the preferred direction for the same neuron shifted in a random pattern with lower modulation index, and the sector width of the tuning curves was significantly larger in the drug-off state. In general, these

changes were more likely to occur in the retrieval phase of the movement.*Conclusion* In the parkinsonian state, there was a loss of specificity of the directional modulation of neuronal firing in M1 which improved with L-DOPA. Observations in this study support the hypothesis that encoding process in M1 is altered and likely plays an important role in the dysfunction of PD. These data provide new insight into the directional information encoding process in M1 and how it is changed in parkinsonian state.

Disclosures: Y. Yu: None. **L. Johnson:** None. **S. Nebeck:** None. **J. Zhang:** None. **M.D. Johnson:** None. **G.F. Molnar:** None. **J.L. Vitek:** None.

Poster

210. Parkinson's Disease: Preclinical Therapeutic Development

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 210.08/J6

Topic: C.03. Parkinson's Disease

Support: Udall grant P50-NSO98573

R01-NS094206

Michael J. Fox

Title: A particle-swarm optimization algorithm for predicting deep brain stimulation settings that improve parkinsonian motor signs

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Abstract: Introduction: Deep brain stimulation (DBS) is an effective surgical therapy used to treat several neurological disorders. However, surgical targeting errors and the high-dimensionality of the stimulation parameter space often result in less than ideal therapy levels in patients. In this study, we investigated the hypotheses that (1) increasing segmentation of electrodes along and around the DBS lead and (2) using a semi-automated particle swarm optimization algorithm to identify stimulation settings that more precisely target the sensorimotor subthalamic nucleus (STN) would enable stronger therapy levels on parkinsonian akinesia, bradykinesia, and gait dysfunction than what would otherwise be available with brute-force programming of stimulation settings through standard DBS leads with a stack of four cylindrical electrode contacts.
Methods: A non-human primate was implanted unilaterally with a DBS array targeting the STN and was rendered parkinsonian with systemic MPTP. The DBS array (600µm diameter) consisted of four columns and eight rows of electrodes (NeuroNexus Technologies). Akinesia

and bradykinesia were assessed by investigators blinded to the stimulation settings, whereas gait kinematics were evaluated using an HR Walkway 4 VersaTek System gait mat. DBS was applied for half an hour through five different stimulation settings: through 'grouped' contacts that mimic the cylindrical electrode of a standard DBS lead (C0-C3), or through contacts identified by the PSO algorithm to most precisely target the sensorimotor STN while avoiding the associative/limbic STN and the corticospinal tract of internal capsule.
Results: The PSO-generated stimulation setting resulted in the largest improvement in gait kinematics as compared to no stimulation or a monopolar review. No stimulation resulted in the subject ambulating 16 gait cycles/minute, the highest grouped contact stimulation resulted in 57 gait cycles/minute and PSO stimulation resulted in 74 gait cycles/minute. In blinded evaluations of motor function during locomotion, akinesia scores (range 0-3) went from an average score of 1.0 during no stimulation to a score of 0.57 during PSO stimulation. Bradykinesia scores went from an average score of 1.0 without stimulation to a score of 0.60 during PSO stimulation.
Conclusions: Higher density DBS arrays as well as semi-automated programming algorithms can enable higher levels of therapy than what is available with existing technology. The PSO approach was able to identify the most therapeutic monopolar electrode group configuration and achieved a higher degree of therapy in terms of gait kinematics, akinesia, and bradykinesia.

Disclosures: A.M. Doyle: None. **S. Zhang:** None. **E. Peña:** None. **M. Yeatts:** None. **M.D. Johnson:** None.

Poster

210. Parkinson's Disease: Preclinical Therapeutic Development

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 210.09/J7

Topic: C.03. Parkinson's Disease

Title: Antiparkinsonian effect of caffeine in unilateral 6-OHDA-lesioned rat model: Comparison with selective A_{2A} antagonist drugs

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Abstract: Selective adenosine A_{2A} receptor antagonists have been proposed as potential novel non-dopaminergic therapies for the symptomatic treatment of Parkinson's disease (PD). One selective A_{2A} antagonist, Tozadenant, is currently in phase III clinical trials, while another, Istradefylline, is approved in Japan as add-on treatment to L-Dopa [1]. Interestingly, the psychostimulant caffeine, which is itself a non-selective adenosine receptor antagonist, was also shown to potentiate the antiparkinsonian effects of L-Dopa in a randomized controlled clinical trial [2].

The objective of this study was to evaluate the antiparkinsonian effects of caffeine in the 6-OHDA lesioned rat model and to compare them to those of two selective A_{2A} antagonists, Tozadenant and Preladenant. The doses of caffeine were selected in order to be comparable to those achieved by regular coffee intake in adult subject (200 mg). The study aimed firstly, at evaluating the acute antiparkinsonian effects of caffeine when given alone or when co-administered with L-Dopa and secondly, at determining if chronic caffeine treatment would induce pharmacological tolerance.
6-OHDA lesioned rats were treated with either caffeine (3-100 mg/kg), Tozadenant (3-60 mg/kg) or Preladenant (0.1-1 mg/kg) either alone or in combination with a low active dose of L-Dopa (25 mg/kg). When the drugs were given in the absence of L-Dopa, efficacy was assessed by measuring the level of general activity (distance and rearing), when they were given along with L-Dopa their efficacy was determined by their ability to enhance the contralateral rotations. The results demonstrated that an acute administration of caffeine was able to dose-dependently increase the distance traveled by the animals and that the magnitude of this effect was comparable to that observed in animals that were treated with the selective A_{2A} antagonists. Furthermore, caffeine significantly potentiated the effects of L-Dopa when it was used in an acute setting as add-on treatment, indeed, it potentiated L-Dopa to a greater extent than either Tozadenant or Preladenant. What was more remarkable was that chronic (10 d.) caffeine treatment either with or without L-Dopa did not induce tolerance, while chronic treatment with A_{2A} antagonists led to pharmacological tolerance.
In conclusion, this study demonstrates that caffeine has strong antiparkinsonian properties when given to 6-OHDA lesioned rats and that, unlike selective A_{2A} antagonists which displayed marked pharmacological tolerance, the behavioural effects of caffeine were sustained even in chronic treatment paradigms. 1. Oertel WH (2017). F1000Res 6: 260. 2. Postuma RB, et al. (2012) Neurology 79.

Disclosures: **A. Michel:** A. Employment/Salary (full or part-time):; UCB Biopharma. **J. Nicolas:** A. Employment/Salary (full or part-time):; UCB Biopharma. **C. De Wolf:** A. Employment/Salary (full or part-time):; UCB Biopharma. **F. Hustadt:** A. Employment/Salary (full or part-time):; UCB Biopharma. **M. Citron:** A. Employment/Salary (full or part-time):; UCB Biopharma. **P. Downey:** A. Employment/Salary (full or part-time):; UCB Biopharma.

Poster

210. Parkinson's Disease: Preclinical Therapeutic Development

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 210.10/J8

Topic: C.03. Parkinson’s Disease

Support: The presented work was commissioned by the MJFF Parkinson's Disease Research Tools Consortium

Title: Assay development and validation of a high content-based high-throughput assay to measure α-synuclein aggregation in dopaminergic human neurons differentiated *In vitro*

Authors: F. VERKAAR[1], T. N. MARTINEZ[2], A. JENSEN[1], *T. D. WOLINSKY[3], D. F. FISCHER[4], J. DEGROOT[1], B. MILLE-BAKER[1]
[1]Discovery, Charles River Labs., Leiden, Netherlands; [2]Res. Programs, The Michael J. Fox Fndn. For Parkinson's Res., New York, NY; [3]Discovery from Charles River, Wilmington, MA; [4]Discovery, Charles River, Saffron Walden, United Kingdom

Abstract: Rare genetic aberrations linked to Parkinson's disease (PD) are situated in the gene encoding α-synuclein. Such α-synuclein mutations result in the formation of fibrillary aggregates. Inhibition of α-synuclein aggregation is widely perceived as a viable option for therapeutic intervention of PD progression. However, an ongoing challenge in PD research is a general lack of high-quality, reproducible, cellular models to probe α-synuclein biology. Here, we describe the development of a cellular assay to measure α-synuclein aggregation in dopaminergic human neurons differentiated from a neuronal progenitor cell line (ReNcell VM) following adenovirus-mediated delivery of α-synuclein and high-content-based detection of α-synuclein aggregation using an aggregate-specific antibody. The assay was automated and miniaturized to 384-well format to enable high-throughput screening, followed by a proof-of-concept pilot screen in which 1,000 compounds were evaluated for their ability to inhibit α-synuclein aggregation. Twenty-three hit compounds were found to specifically inhibit α-synuclein aggregation without affecting cellular viability or influencing total α-synuclein expression levels. These hit molecules may provide the basis for new chemical lead series for the development of α-synuclein aggregation-targeting therapeutics, which validates the α-synuclein aggregation assay as a high-throughput platform for the identification of novel chemical starting points to target PD.

Disclosures: F. Verkaar: None. **T.N. Martinez:** None. **A. Jensen:** None. **T.D. Wolinsky:** None. **D.F. Fischer:** None. **J. DeGroot:** None. **B. Mille-Baker:** None.

Poster

210. Parkinson's Disease: Preclinical Therapeutic Development

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 210.11/J9

Topic: C.03. Parkinson's Disease

Support: NIH (NINDS) R01NS073125

Title: A closed loop brain machine interface for Parkinson's disease using dorsal column electrical stimulation

Authors: *A. YADAV, M. A. NICOLELIS
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Abstract: Parkinson's Disease (PD) is a neurodegenerative disorder affecting lives of millions of people across the world, resulting in life-altering motor, sensory, and cognitive deficits. Although electrical stimulation has been proposed as an alternative therapeutic procedure for PD, current methods such as deep brain stimulation are available for only a small percentage of PD patients. Recently, we demonstrated that electrical stimulation of the dorsal columns of the spinal cord, or Dorsal Column Stimulation (DCS), a semi-invasive procedure, is beneficial in alleviating the cardinal symptoms of PD. Subsequently, multiple clinical studies employing continuous high frequency DCS have shown efficacy in treating the symptoms associated with PD. Here, we demonstrate a closed loop stimulation strategy for PD in the 6-hydroxydopamine (6-OHDA) rat model of PD. Rats were implanted with recording microelectrodes in motor cortex and striatum, and stimulating electrodes in the spinal cord, and then injected with 6-OHDA to induce intrastriatal lesions that resulted in akinetic symptoms. Closed-loop DCS driven by oscillatory spiking activity of cortical and striatal neurons in the beta frequency range resulted in alleviation of akinetic behavior in rats. Preliminary results indicate that closed-loop DCS is superior to open-loop DCS for ameliorating PD symptoms. We propose that closed-loop DCS may provide effective management of PD symptoms by modulating the pathological oscillatory activity in the cortico-basal ganglia neural circuits.

Disclosures: A. Yadav: None. **M.A. Nicolelis:** None.

Poster

210. Parkinson's Disease: Preclinical Therapeutic Development

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 210.12/J10

Topic: C.03. Parkinson's Disease

Title: Effect of amantadine on L-DOPA-induced cortical gamma oscillations in the 6-OHDA rat

Authors: *B. POUYATOS, A. EVRARD, R. MAURY, C. ROUCARD, Y. ROCHE, V. DUVEAU
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Abstract: Parkinson's disease (PD) is among the most prevalent of neurodegenerative disorders. Motor symptoms observed in PD are mainly due to a dysfunction of the cortico-basal ganglia resulting from the death of dopaminergic neurons in the *substantia nigra pars compacta*. A hypersynchronization of beta frequency oscillatory activity in these circuits has been observed in both parkinsonian patients and animal models of the disease. This abnormal beta oscillation is suppressed by dopaminergic treatments along with motor symptoms. In addition, chronic L-

DOPA treatment induced a prominent gamma resonant oscillation associated with abnormal involuntary movements (AIMs) in the motor cortex of both hemiparkinsonian rats (Halje et al. 2012) and patients (Oswal et al. 2013). More recently an exaggerated phase amplitude coupling (PAC) between β-phase (13-30 Hz) and γ-amplitude (50-200 Hz) has been characterized in the motor cortex of PD patients (de Hemptinne et al., 2013). The aim of this study was to investigate the effect of the antidyskinetic drug amantadine on the cortical beta band, phase amplitude coupling and the L-DOPA-induced gamma oscillations and AIMs in the 6-OHDA rat. Unilaterally 6-OHDA-lesioned rats were implanted with a bipolar electrode in the motor cortex ipsilateral of the lesion. Rats were treated daily with 20mg/kg L-DOPA to induce stable gamma oscillations, which were monitored at day 1, 3 and 5 using EEG recordings. The effects of pre-treatments with either vehicle or amantadine (45 or 90mg/kg) 120 min before L-DOPA injection was then evaluated on gamma oscillations and L-DOPA induced abnormal involuntary movements (AIMS). We identified a prominent beta oscillation and a strong coupling between the amplitude of high gamma (80-160Hz) and the phase of theta (4-6Hz) in the motor cortex in the 6-OHDA model of PD. These EEG biomarkers are stable, reliable, can be quantified objectively and are transiently modulated by dopaminergic agonists. Chronic L-DOPA (20mg/kg) treatment induces a transient switch of EEG activities from beta (~30Hz) to gamma (~90Hz) resonant oscillations, along with a decrease of the PAC index and the appearance of AIMs. Amantadine administration induces (1) a decrease of the power of the L-DOPA-induced gamma band, (2) a drop in AIM score and (3) an increase of the duration of the L-DOPA-induced decline of the PAC index. This EEG biomarker brings a significant added value to drug development as a stable, quantifiable, reliable and objective endpoint for the development of new antiparkinsonian and antidyskinetic molecules.

Disclosures: **B. Pouyatos:** A. Employment/Salary (full or part-time):; SynapCell. **A. Evrard:** A. Employment/Salary (full or part-time):; SynapCell. **R. Maury:** A. Employment/Salary (full or part-time):; Synapcell. **C. Roucard:** A. Employment/Salary (full or part-time):; Synapcell. **Y. Roche:** A. Employment/Salary (full or part-time):; Synapcell. **V. Duveau:** A. Employment/Salary (full or part-time):; Synapcell.

Poster

210. Parkinson's Disease: Preclinical Therapeutic Development

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 210.13/J11

Topic: C.03. Parkinson’s Disease

Support: Academy of Finland Grant 253840

Title: GDNF, CDNF and MANF have divergent effects on γ-aminobutyric acid neurotransmission and dopamine neurochemistry in rats

Authors: *J.-M. RENKO, A. KONTTI, I. REENILÄ, P. PIEPPONEN, M. SAARMA, R. K. TUOMINEN
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Abstract: Neurotrophic factors (NTFs) are secreted proteins which support the survival and recovery of neurons. Therefore NTFs hold potential for disease-modifying therapies for neurodegenerative disorders like Parkinson´s disease. Glial cell line-derived neurotrophic factor (GDNF), cerebral dopamine neurotrophic factor (CDNF) and mesencephalic astrocyte-derived neurotrophic factor (MANF) have shown neuroprotective and restorative effects on dopaminergic neurons in animal models of Parkinson´s disease. However, critical gaps in the knowledge of the pharmacological effects of these NTFs exist: to date their effects on γ-aminobutyric acid (GABA) neurotransmission within the basal ganglia of living rats and central dopamine neurochemistry regulating enzymes have remain obscure. Here we report the effects of GDNF, CDNF and MANF on GABAergic neurotransmission and tyrosine hydroxylase (TH)-activity *in vivo*, as well as, the effect of GDNF on catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO) activity. NTFs were unilaterally injected into the striatum of intact male Wistar rats. Microdialysis experiments with high-potassium stimulation were performed one and three weeks after the treatment in freely-moving animals. Striatal tissue samples were collected one week after the treatment for enzyme activity measurements. NTFs did not have significant effects on stimulus-evoked GABA release within the lateral globus pallidus one week after the injection. Three weeks after the injection, however, stimulus-evoked release of GABA was significantly elevated in CDNF treated animals. GDNF, unlike CDNF or MANF, increased striatal tissue TH-activity one week after the injection. Furthermore, GDNF significantly increased COMT-activity and decreased MAO-A-activity. The results show that the NTFs studied here have divergent effects on GABAergic neurotransmission, and dopamine synthetizing and metabolizing enzymes. Although the cellular mechanisms remain to be clarified, knowing the biological effects of exogenously administrated NTFs in the intact brain is an important step towards developing novel neurotrophic treatments for degenerative brain diseases.

Disclosures: J. Renko: None. **A. Kontti:** None. **I. Reenilä:** None. **P. Piepponen:** None. **M. Saarma:** None. **R.K. Tuominen:** None.

Poster

210. Parkinson's Disease: Preclinical Therapeutic Development

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 210.14/J12

Topic: C.03. Parkinson’s Disease

Support: Air Liquide Santé International

Title: Inhaling xenon ameliorates gait in the MPTP macaque model of Parkinson disease

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Abstract: Parkinson disease (PD) is symptomatically treated with L-DOPA, but this treatment often leads to disabling dyskinesia. We have recently shown that xenon gas exposition (i) normalises transmission and reverses maladaptive plasticity of corticostriatal glutamatergic projections associated with L-DOPA-induced dyskinesia and (ii) ameliorates dyskinesia in rat and nonhuman primate models of PD-related symptomatology. While the alleviation of dyskineia is critically important for patients, the anti-dyskinetic action should not be accomplished at the expense of the anti-akinetic action of L-DOPA.
To quantify a possible interference of xenon with L-DOPA effects, we conducted kinematic analysis of gait in 4 monkeys that were trained to walk along a straight corridor. The monkeys behaved freely without any constraints to ensure the ecological relevance of the testing conditions. We used video recordings (100Hz) of markers painted onto hindlimb and forelimb joints to reconstruct whole-body kinematics in three dimensions.
In most animals, 50% of the optimal L-DOPA dose was the most effective concentration to reduce gait-cycle duration (i.e. to alleviate bradykinesia) and increase step length (short steps being a key feature of PD). Instead, the optimal 100% L-DOPA dose that improved classic parkinsonian features often failed to further improve gait parameters, and often worsened locomotor performance compared to the baseline (no L-DOPA and no xenon intake).
Unexpectedly, not only xenon inhalation for 1 hr prior observation had no delayed sedative effect, but it mediated a synergistic improvement of gait parameters. This synergy peaked when combining xenon with the 50% dose of L-DOPA. Xenon inhalation thus alleviated L-DOPA-induced dyskinesia in dyskinetic MPTP-treated macaques, thus further improving gait quality.
To the best of our knowledge, this is the first example of an anti-dyskinetic strategy that also improves a motor behaviour otherwise refractory to dopamine replacement therapy. These findings highlight the robust clinical relevance of xenon inhalation as an anti-dyskinetic treatment.

Disclosures: **E. Bezard:** 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.; Air Liquide Sante International. **T. Mikelovic:** None. **E.M. Moraud:** None. **S. Sun:** None. **D.W. Ko:** A. Employment/Salary (full or part-time):; Motac neuroscience. **Q. Li:** A. Employment/Salary (full or part-time):; Motac neuroscience. **A. Millet:** A. Employment/Salary (full or part-time):; Air Liquide Santé International. **G. Farjot:** A. Employment/Salary (full or part-time):; Air Liquide Santé International. **E. Pioli:** A. Employment/Salary (full or part-time):; Motac neuroscience. **G. Courtine:** None. **B. Bessiere:** A. Employment/Salary (full or part-time):; Air Liquide Santé International.

Poster

210. Parkinson's Disease: Preclinical Therapeutic Development

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 210.15/K1

Topic: C.03. Parkinson's Disease

Support: Weston Brain Institue

Title: Determination of the pharmacokinetic profiles of the mGluR2 positive allosteric modulator LY-487,379 and of the mGluR2 orthosteric agonist LY-354,740, in the rat and the common marmoset

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Abstract: Activation of metabotropic glutamate receptor 2 (mGluR2) represents a promising approach to alleviate a breadth of neuro-psychiatric disorders, from schizophrenia to Parkinson's disease, both as a symptomatic therapy and potential disease-modifying paradigm.
Here, we have determined the pharmacokinetic (PK) profile of the prototypical and highly-selective mGluR2 positive allosteric modulator LY-487,379 in the rat and the common marmoset as well as the PK profile of the clinically-ready mGluR2/3 orthosteric agonist LY-354,740 in the common marmoset. Because it had previously been published, the PK profile of LY-354,740 in the rat was not determined here.
In rats, blood was drawn at 10 different time points, at baseline and following sub-cutaneous (sc) administration of LY-487,379 0.1, 1 and 10 mg/kg. For marmosets, we have used a sparse sampling technique, where minimal blood volume was sampled at 10 different time points, from a limited number of animals, at baseline and following sc administration of LY-487,379 and LY-354,740, both 1 mg/kg, with additional samplings conducted at maximal plasma concentration time (Tmax) with LY-487,379 0.1 and 10 mg/kg, and LY-354,740 0,1, 0.3 and 10 mg/kg. Plasma levels of LY-487,379 and LY-354,740 were determined by liquid chromatography and tandem mass spectrometry (LC-MS/MS). Compartmental analysis was used to determine PK parameters such as Tmax, maximal plasma concentration (Cmax) and half-life (T1/2).
In rats, Tmax occurred 15 min following administration of LY-487,379, while T1/2 was 115 min, regardless of the dose administered. Cmax was variable, depending on the dose injected.
In marmosets, Tmax was also 15 min after administration of LY-487,379, but T1/2 was 90 min, which is slightly shorter than in the rat; a linear relationship was observed between Cmax values and the dose administered. For LY-354,740 in marmosets, Tmax occurred 60 min following

administration, while T1/2 was observed at 67 min. A linear relationship was observed between Cmax values and the dose administered. Administration of LY-354,740 1 mg/kg and lower led to plasma levels comparable to those that were well-tolerated in the clinic.
To the best of our knowledge, the PK profile of LY-487,379 has not been published in human and, whether the plasma levels achieved here would be well-tolerated in clinical settings is unknown. However, our results with LY-354,740 in the marmoset indicate that experiments assessing its therapeutic potential in this small primate should employ doses not higher than 1 mg/kg sc, to maximise the chances of success when undertaking clinical trials.

Disclosures: D. Bédard: None. **A. Hamadjida:** None. **F. Gaudette:** None. **S.G. Nuara:** None. **J.C. Gourdon:** None. **F. Beaudry:** None. **P. Huot:** None.

Poster

210. Parkinson's Disease: Preclinical Therapeutic Development

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 210.16/K2

Topic: C.03. Parkinson’s Disease

Support: Weston Brain Institute

Title: The selective metabotropic glutamate receptor 2 orthosteric agonist LY-354,740 alleviates L-DOPA-induced dyskinesia in the 6-OHDA-lesioned rat model of Parkinson's disease

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Abstract: L-3,4-dihydroxyphenylalanine (L-DOPA) is the most effective symptomatic treatment for Parkinson’s disease (PD). However, upon chronic administration, L-DOPA leads to the development of motor complications such as dyskinesia. We have recently demonstrated that activation of metabotropic glutamate receptor 2 (mGluR2) with the prototypical positive allosteric modulator LY-487,379 reduces the expression of established, and attenuates the development of, L-DOPA-induced dyskinesia, in the 6-hydroxydopamine (6-OHDA)-lesioned rat. Here, we have assessed the effect of mGluR2 activation through orthosteric stimulation on reduction and prevention of dyskinesia, using the clinically-ready orthosteric agonist LY-354,740.
Rats were rendered hemi-parkinsonian by stereotaxic injection of 6-OHDA into the right medial forebrain bundle. Following a recovery period, degree of parkinsonism was assessed using the cylinder test and two studies were then performed. In the first set of experiments, rats were primed with chronic L-DOPA administration to induce axial, limbs and oro-lingual (ALO)

abnormal involuntary movements (AIMs), after which L-DOPA was administered, in combination with LY-354,740 (vehicle, 0.1, 1 and 10 mg/kg), in to a randomised Latin square design. In the second set of experiments, rats were administered a daily treatment of LY-354,740 (0.1 or 1 mg/kg) or vehicle, started concurrently with L-DOPA, for 22 days. After a 3-day washout period, an acute challenge of L-DOPA was administered and ALO AIMs severity was assessed. The effect of LY-354,740 on L-DOPA anti-parkinsonian action was subsequently determined by the cylinder test.
In combination with L-DOPA, LY-354,740 0.1 mg/kg, significantly diminished the severity of established ALO AIMs duration, by 17% ($P<0.05$), and of ALO AIMs amplitude, by 18% ($P<0.05$, compared to L-DOPA/vehicle. LY-354,740 0.1 mg/kg, when started concurrently with L-DOPA, attenuated the priming process leading to the development of dyskinesia. Thus, in the acute L-DOPA challenge performed following the priming phase, ALO AIMs were significantly lower (by 67% in the LY-354,740 0.1 mg/kg group, $P<0.05$, and by 58% in the LY-354,740 1 mg/kg group, $P<0.05$) when compared to L-DOPA/vehicle. The anti-dyskinetic action of LY-354,740 did not impair L-DOPA anti-parkinsonian action. Our results suggest that selective $mGluR_2$ activation through orthosteric stimulation is an effective and promising therapeutic strategy to alleviate the severity of established, and prevent the development of dyskinesia.

Disclosures: **A. Hamadjida:** None. **I. Frouni:** None. **C. Kwan:** None. **V. Nafade:** None. **D. Bédard:** None. **C. Rouillard:** None. **P. Huot:** None.

Poster

210. Parkinson's Disease: Preclinical Therapeutic Development

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 210.17/K3

Topic: C.03. Parkinson’s Disease

Support: Weston Brain Institute

Title: The clinically-ready metabotropic glutamate receptor 2 orthosteric agonist LY-354,740 alleviates both psychosis and dyskinesia in the MPTP-lesioned marmoset model of Parkinson's disease

Authors: *P. HUOT[1], S. G. NUARA[2], J. C. GOURDON[2], A. HAMADJIDA[3]
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Abstract: Psychosis and dyskinesia cause significant morbidity to as many as 50-95% of patients with advanced Parkinson’s disease (PD). Recently, studies have indicated that activators of metabotropic glutamate receptor 2 (mGluR2) may be useful in the treatment of neuro-psychiatric disorders, including psychosis. Based on their interaction with serotonin 2A (5-

HT2A) receptors, we hypothesised that mGluR2 activation would effectively alleviate psychosis and dyskinesia in PD, and have recently demonstrated that mGluR2 activation with the highly-selective positive allosteric modulator LY-487,379 effectively alleviates both psychosis and dyskinesia, in the parkinsonian primate. Here, we have assessed the anti-psychotic and anti-dyskinetic potential of the selective and clinically-ready mGluR2 orthosteric agonist LY-354,740 in the gold-standard animal model of PD, the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned primate.
Six common marmosets (*Callithrix jacchus*) were rendered parkinsonian by MPTP injection. Stable and reproducible psychosis-like behaviours (PLBs) and dyskinesia were induced by administration of L-3,4-dihydroxyphenylalanine (L-DOPA)/benserazide (henceforth termed L-DOPA). LY-354,740 (vehicle, 0.1, 0.3 and 1 mg/kg) was then administered to the animals in combination with L-DOPA, according to a randomised Latin square design, after which its effects on PLBs, dyskinesia and parkinsonism were determined.
In combination with L-DOPA, LY-354,740 1 mg/kg significantly reduced PLBs severity, by 34% ($P<0.05$), when compared to L-DOPA alone. Moreover, LY-354,740 1 mg/kg significantly reduced duration of on-time with disabling PLBs, when compared to L-DOPA/vehicle (by 65%, $P<0.001$). LY-354,740 1 mg/kg also reduced dyskinesia severity, by 46%, when compared to L-DOPA alone ($P<0.05$). Accordingly, LY-354,740 1 mg/kg significantly reduced duration of on-time with disabling dyskinesia, by 87% ($P<0.001$), when compared to L-DOPA/vehicle. Beneficial effects on both PLBs and dyskinesia were also obtained with lower doses of LY-354,740. Importantly, LY-354,740 did not alter the anti-parkinsonian effect of L-DOPA.
These results suggest that mGluR2 activation with an orthosteric agonist is a promising therapeutic strategy to alleviate both psychosis and dyskinesia in PD. Moreover, inasmuch as it has already been tested in the clinic, with well-documented safety and tolerability profiles, LY-354,740 could be advanced rapidly to proof-of-concept clinical trials in the PD population.

Disclosures: **P. Huot:** None. **S.G. Nuara:** None. **J.C. Gourdon:** None. **A. Hamadjida:** None.

Poster

210. Parkinson's Disease: Preclinical Therapeutic Development

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 210.18/K4

Topic: C.03. Parkinson’s Disease

Support: MJFF Grant 10197

Title: A novel mGluR4 PAM alleviates motor symptoms in primate models of Parkinson's disease

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Abstract: Background. Parkinson's Disease (PD) is a neurodegenerative disorder affecting more than six million people worldwide. Available treatments mainly consist in replacing the missing dopamine that is responsible for dysfunction of the basal ganglia (BG) motor circuit. Levodopa remains the gold standard for PD. As the disease progresses, these treatments become less effective and produce debilitating side effects, including motor fluctuations and levodopa-induced dyskinesia (LID). Over the past decade, modulation of presynaptic metabotropic glutamate receptor 4 (mGluR4) has been proposed as a promising approach to normalize the BG circuitry in PD.
Objective. Objective was to assess the potential of our novel mGluR4 positive allosteric modulator (PAM), foliglurax, as an anti-parkinsonian treatment in non-human primate (NHP) models.
Methods. Foliglurax (PXT002331) was tested in three models of MPTP-induced parkinsonism in macaques: early stage parkinsonism (CLD-MPTP), motor fluctuations and LID. In parallel, brain penetration of the compound was assessed using PET imaging in macaques.
Results. Foliglurax demonstrated consistent anti-parkinsonian efficacy in all models. Coadministration of foliglurax and a low sub-optimal dose of levodopa resulted in a robust and dose-dependent reversal of parkinsonian motor symptoms in macaques. Moreover, foliglurax strongly decreased dyskinesia induced by levodopa, thus having therapeutic efficacy on both aspects: parkinsonian motor symptoms and LID.
Conclusion. This is the first demonstration that a mGluR4 PAM can alleviate the motor symptoms of PD and the motor complications induced by levodopa in non-human primates. Supported by its unique preclinical profile, foliglurax has been the first mGluR4 PAM entering the clinics and is now being tested in Phase IIa studies.

Disclosures: D. Charvin: A. Employment/Salary (full or part-time):; Prexton Therapeutics. 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.; MJFF. **T. Di Paolo:** 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.; Prexton Therapeutics. **E. Bezard:** 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.; Prexton Therapeutics. **C. Halldin:** 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.; Prexton Therapeutics. **G. Duvey:** A. Employment/Salary (full or part-time):; Prexton Therapeutics. **L. Grégoire:** 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.; Prexton Therapeutics. **A. Takano:** 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.; Prexton Therapeutics. **E. Pioli:** 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.; Prexton Therapeutics. **R. Medori:** A. Employment/Salary (full or part-time):; Prexton Therapeutics. **F. Conquet:** A. Employment/Salary (full or part-time):; Prexton Therapeutics.

Poster

210. Parkinson's Disease: Preclinical Therapeutic Development

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 210.19/K5

Topic: C.03. Parkinson’s Disease

Support: NIH Grant #T35HL007479 (MJB)

Yamamura Fellowship (MJB)

ARCS Scholar Award (AJF)

Title: BDNF and mTOR contribute to the suppression of L-DOPA-induced dyskinesia by sub-anesthetic ketamine

Authors: *A. J. FLORES[1,2], M. J. BARTLETT[7,3,2], H. K. DOLLISH[4], K. P. DOYLE[5,2], S. J. SHERMAN[2,1], T. FALK[2,4,6,1,3]
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Abstract: Sub-anesthetic infusions of ketamine are an effective therapy for the treatment of depression, posttraumatic stress disorder, and refractory chronic migraine. In each of these disorders hypersynchronous electrical activity between brain regions has been reported. This is a shared commonality with Parkinson’s disease (PD) and L-DOPA-induced dyskinesia (LID), where hypersynchrony occurs in the cortico-striatal network. Ketamine is known to alter oscillatory brain activity. In prior work, we have shown a long-term therapeutic effect, with reduced LID and improved on-time, in PD patients (Sherman SJ et al., *Case Rep. Neurol.* 2016; 8:53-58). In a preclinical model, we have also reported that established LID, as measured by

abnormal involuntary movements (AIMs), can be reduced in a dose-dependent manner by a low-dose ketamine infusion (Bartlett MJ et al., *Neurosci. Lett.* 2016; 612:121-125). Here, we show low-dose ketamine suppresses development of LID and that the sustained anti-dyskinetic effect is inhibited by blocking the brain-derived neurotrophic factor (BDNF) receptor tropomyosin receptor kinase B (TrkB).

Male Sprague Dawley rats were unilaterally injected with 6-hydroxydopamine at two sites (10 micrograms/site) in the medial forebrain bundle. In a first cohort (n=9), rats were primed for 4 weeks with escalating daily L-DOPA doses (6 mg/kg - 12 mg/kg; *i.p.*), and treated for 10 hours with ketamine once per week (5x *i.p.* injections of 20 mg/kg, 2 hours apart; 5^{th} injection was paired with L-DOPA). AIMs were scored every 3-4 days to determine the severity of LID. Ketamine treatment led to a significant reduction in AIMs development throughout the 4-week study. Striatal tissue was harvested and demonstrated increases in mTOR phosphorylation in both lesioned (*$p<0.05$) and unlesioned (*$p<0.001$) hemispheres after ketamine (two-tailed Student's *t*-tests). Further mechanistic studies will evaluate the Erk1/2 and Akt pathways. In a second cohort, the rats were primed with daily injections of L-DOPA (6 mg/kg; *i.p.*) for 14 days. On days 0 and 7, rats were treated with ketamine (as above), ketamine plus the TrkB antagonist, ANA-12 (0.5 mg/kg; *i.p.*), or vehicle. On day 11, rats treated with ketamine showed a 50% reduction in their total limb, axial, and oral AIMs scores as compared to controls. However, this sustained effect of ketamine was lost in rats co-treated with ANA-12 (One-way ANOVA, Tukey post-hoc tests; *$p<0.05$; n=9-10).

Combined, this data both suggests a novel use for low-dose ketamine as an early therapy to prevent the development of LID and that ketamine’s effects may result from an increase in BDNF combined with changes in synaptic plasticity mediated via mTOR.

Disclosures: **A.J. Flores:** None. **M.J. Bartlett:** None. **H.K. Dollish:** None. **K.P. Doyle:** None. **S.J. Sherman:** None. **T. Falk:** None.

Poster

210. Parkinson's Disease: Preclinical Therapeutic Development

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 210.20/K6

Topic: C.03. Parkinson’s Disease

Support: MINECO grant SAF2014-55700-P

MINECO/ISCIII grant PIE14/00034

Catalan government grant 2014 SGR 1054

Fundació la Marató de TV3 grant 20152031

IWT grant SBO-140028

Title: Optical control of Parkinsonism using a photoactive adenosine A_{2A} receptor antagonist

Authors: *F. CIRUELA[1,2], J. TAURA[1,2], E. G. NOLEN[3], G. CABRÉ[4], J. HERNANDO[4], M. LÓPEZ-CANO[1,2], V. FERNÁNDEZ-DUEÑAS[1,2], K. A. JACOBSON[5]
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Abstract: G protein-coupled adenosine receptors are promising therapeutic targets for a wide range of pathological conditions, such as Parkinson's disease. However, the ubiquity of adenosine receptors and eventual lack of selectivity of most of adenosine-based drugs have frequently diminished their therapeutic potential. Optopharmacology is a novel approach that may help sorting out this issue, since it allows the spatiotemporal control of receptor functioning. We have developed the first generation of light-sensitive caged adenosine A_{2A} receptor ($A_{2A}R$) ligands: MRS7145 is a SCH442416 (an $A_{2A}R$ antagonist) derivative that is coumarin-blocked at the 5-amino position. First, MRS7145 was photochemically characterized by *in vitro* spectroscopy, monitoring SCH442416 release upon violet light illumination (405 nm). Next, the light-dependent pharmacological profile of MRS7145 was assessed in living cells (HEK-293T cells permanently expressing the receptor). Thus, upon photoactivation, MRS7145 precluded $A_{2A}R$ ligand binding and agonist-induced cAMP accumulation. Thereafter, the ability of MRS7145 to block $A_{2A}R$ in a light dependent manner was assessed *in vivo*. To this end, $A_{2A}R$ antagonist-mediated locomotor activity potentiation was evaluated in brain (striatum) fiber-optic implanted mice. Upon light irradiation (405 nm) of the dorsal striatum, MRS7145 induced significant hyperlocomotion. Finally, the efficacy of MRS7145 motor impairment reversal was evaluated in an animal model of movement disorders, namely the hemiparkinsonian 6-OHDA lesioned mouse. Thus, photoactivated MRS7145 was able to potentiate the number of contralateral rotations induced by L-3,4-dihydroxyphenylalanine (L-DOPA). Overall, MRS7145 is a new light-operated $A_{2A}R$ antagonist with potential utility for the treatment of Parkinson's disease.

Disclosures: F. Ciruela: None. **J. Taura:** None. **E.G. Nolen:** None. **G. Cabré:** None. **J. Hernando:** None. **M. López-Cano:** None. **V. Fernández-Dueñas:** None. **K.A. Jacobson:** None.

Poster

210. Parkinson's Disease: Preclinical Therapeutic Development

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 210.21/K7

Topic: C.03. Parkinson's Disease

Support: CAPES

DFG

Title: 50-kHz ultrasonic vocalizations can induce paradoxical kinesia in cataleptic rats: A new animal model and its possible mechanisms

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Abstract: Parkinson's disease is a neurodegenerative basal ganglia disease which leads to a global deterioration in motor function, such as brady- or akinesia as one of the most characteristic clinical features. Such patients, however, may become able to make quick movements, such as catching a ball or running, when excited by external stimuli. There are several reports of this phenomenon called paradoxical kinesia which refers to a sudden transient ability of akinetic Parkinsonian patients to perform motor tasks they are otherwise unable to perform. The mechanisms underlying this phenomenon are unknown due to a paucity of valid animal models that faithfully reproduce it. Our aim was to develop a new method to evaluate paradoxical kinesia in cataleptic rats by presenting species-relevant signals, namely rat ultrasonic vocalizations (USV). To test the effects of USV in cataleptic animals, male rats received haloperidol (0.5mg/kg, IP), and 60 min after injection, the bar test was performed during which a given rat was exposed to different playback presentations of appetitive 50-kHz USV or relevant acoustic controls. The bar test consists of gently placing the rat with its forepaws on a horizontal bar. The time until it steps down with both forepaws is measured. When quantifying catalepsy time, only 50-kHz USV playback substantially reduced step-down latencies. Importantly, this effect was consistently observed in four independent groups of rats and irrespective of whether 50-kHz USV were presented during the 1^{st}, 2^{nd}, 3^{rd} or 4^{th} playback presentation, with the effects being most prominent during the 1^{st} presentation. Importantly, the rats not only stepped down when exposed to 50-kHz USV, but explored the zone proximal to the active ultrasonic speaker. In contrast, the few rats that managed to step down from the bar during relevant acoustic controls did not exhibit such exploratory behavior or any preference for the sound source. In a second experiment, we provide first evidence for a possible brain mechanism of this effect. We selected the inferior colliculus as a target area since it is known to serve not only as an acoustic relay station, but can also modulate haloperidol-induced catalepsy. We found that intracollicular microinjection of the glutamatergic agonist NMDA prevented the effectiveness of 50-kHz USV to induce paradoxical kinesia without blocking basic acoustic processing. Together, our animal model fulfills the criterion of face validity and provides a completely new approach for studying paradoxical kinesia which might be useful for uncovering the mechanisms behind this phenomenon and for improving behavioral therapies for Parkinson's disease.

Disclosures: R.K. Schwarting: None. **L.C. Tonelli:** None. **M. Wöhr:** None. **L. Melo-Thomas:** None.

Poster

210. Parkinson's Disease: Preclinical Therapeutic Development

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 210.22/K8

Topic: C.03. Parkinson's Disease

Support: Michael J Fox Foundation for Parkinson's Research

Title: A pharmacokinetic study of orally administered nilotinib in chronically catheterized beagle dogs to assess its partitioning into the cerebrospinal fluid and brain tissue

Authors: *K. MERCHANT[1,2], C. S. VENUTO[3], A. FRICKE[3], B. SIDDIQI[4], B. FISKE[4]
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Abstract: Nilotinib, a BCR-Abl tyrosine kinase inhibitor, is approved for treatment of chronic myeloid leukemia. A recent open-label study of nilotinib in individuals with Parkinson's disease (PD) and Dementia with Lewy Body provided preliminary evidence of its safety and tolerability along with its potential to reduce motor and cognitive symptoms (Pagan et al., 2016). The clinical study was rationalized on the basis of several rodent PD model studies in which nilotinib reduced α-synuclein pathology and dopamine neuronal loss (Hebron et al., 2013; Senthilkumar et al., 2014). However, a rigorous characterization of nilotinib's pharmacokinetics (PK) in the periphery versus central compartments has been lacking. The present study was conducted at MPI Research (Michigan, USA) using 8 male beagle dogs with indwelling intrathecal and venous catheters to enable serial sampling of the cerebrospinal fluid (CSF) over 12h and serum over 48h, respectively. Nilotinib was administered orally once daily for 14 days at 20 or 50 mg/kg to target exposures obtained in the clinical PD study. In addition, paired serum and brain tissue were collected at necropsy following saline perfusion to assay nilotinib concentrations at 2h, the predicted time to maximum serum concentration (T_{max}) in the dog. The table summarizes the average (standard deviation) PK exposure parameters in the serum, CSF and brain tissue for total nilotinib levels. Consistent with the previous dog toxicokinetic study at 5 mg/kg, the observed median T_{max} in the serum was 2 hours. The mean CSF/serum C_{max} or $AUC_{0\text{-}12h}$ ratios ranged from 0.005 to 0.008 for both 25 and 50 mg/kg doses indicating CSF penetration of nilotinib to be <1.0%. These data are consistent with the reported protein binding of 98.3% in the dog (Xia et al., 2012). The average brain tissue:serum partition coefficient for total nilotinib concentration ranged from ~1.5 to 3.0, indicating lipophilic properties of nilotinib. Studies are underway to determine whether pharmacologically effective concentrations of nilotinib were attained in the brain and CSF *via* assessment of pharmacodynamic responses.

Nilotinib Pharmacokinetic Parameter	Serum		CSF		Brain exposures (2 h)	
	20 mg/kg (n=4)	50 mg/kg (n=4)	20 mg/kg (n=4)	50 mg/kg (n=4)	20 mg/kg (n=4)	50 mg/kg (n=4)
C_{max} (total), ng/mL	1,672 (1,752)	2,438 (2,271)	14.3 (14.8)	14.7 (13.7)	4,132 (4,158)	3,355 (1,392)
$AUC_{0-\tau}$, ng*h/mL	10,024 (11,134)	25,171 (27,356)	81.4 (85.1)	130 (75)	NA	NA

Disclosures: **K. Merchant:** None. **C.S. Venuto:** None. **A. Fricke:** None. **B. Siddiqi:** None. **B. Fiske:** None.

Poster

210. Parkinson's Disease: Preclinical Therapeutic Development

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 210.23/K9

Topic: C.03. Parkinson’s Disease

Support: CIHR

Title: mGluR5 modulation as a neuro-recovery strategy for Parkinson’s disease

Authors: ***K. FARMER**[1], T. FORTIN[1], A. DERKSEN[1], E. ROWE[1], N. PROWSE[1], A. THOMPSON[1], C. RUDYK[1], Z. DWYER[1], S. S. G. FERGUSON[2], S. P. HAYLEY[1]
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Abstract: We tested the effects of a specific negative allosteric modulator of mGluR5 in a 6-OHDA model of Parkinson’s disease (PD). Both acute and chronic administration of the drug improved motor functioning. With chronic administration we were able to completely rescue 6-OHDA induced motor and cognitive impairments. While mGlur5 modulation did not influence the 6-OHDA induced loss dopaminergic neurons in the substantia nigra, it did increase dopaminergic terminal coverage in the striatum. Similarly, mGluR5 modulation appeared to influence motor cortex striatal signaling (as indicated by FosB staining) in the lesioned mice. Interestingly, the mGluR5 drug had brain region specific signaling effects that differed between the motor cortex and striatum. Together our data, underline the importance of the glutamatergic

signaling in the symptomatic profile of PD, and suggests that specific and targeted modulation of the mGluR5 system may be beneficial in promoting neural recovery.

Disclosures: K. Farmer: None. **T. Fortin:** None. **A. Derksen:** None. **E. Rowe:** None. **N. Prowse:** None. **A. Thompson:** None. **C. Rudyk:** None. **Z. Dwyer:** None. **S.S.G. Ferguson:** None. **S.P. Hayley:** None.

Poster

210. Parkinson's Disease: Preclinical Therapeutic Development

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 210.24/K10

Topic: C.03. Parkinson’s Disease

Support: Schulich School of Medicine and Dentistry

Michael J Fox Foundation for Parkinson's Research

Title: A novel substrate for preclinical models of cell-based therapy for Parkinson’s disease

Authors: S. M. BENOIT[1], S. SCHMID[2], *M. O. HEBB[3]
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Abstract: Introduction: Decades of research, including many clinical trials, have looked into the potential of using cell-based therapies for neurodegenerative diseases (e.g., Parkinson’s Disease). While many technical improvements have led to advances in the field, researchers have yet to define an ideal substrate for transplantation. Previously, work from our lab has shown that small volume biopsies from human neurosurgical patients can generate an expandable population of brain-derived progenitor cells (BDPC). The neural origin, immunological properties and endogenous expression of neurotrophic factors (NTF), render BDPCs a favourable substrate for transplantation, but a preclinical transplant model is needed to evaluate this potential. The goal of this study was to test our hypothesis that BDPCs can be generated from rodent cortical tissue using the protocol established for human samples and will exhibit a similar phenotype to their human analogues. **Methods:** Small cortical tissue samples from adult Fischer rats were processed and cultured using our previously described protocol for human samples. Using Western Blot and immunocytochemistry we evaluated expression of a broad panel of lineage-specific markers as well as several neurotrophic factors. Neurotrophic factor expression was further evaluated using PCR for NTF-specific messenger RNA. **Results:** Rodent BDPCs were apparent one week after culture of primary cortical tissue and were readily passaged. Cells expressed multiple proteins characteristic of neural and glial progenitor lineages as well multiple NTFs in both media and whole cell preparations. Robust mRNA expression for the NTFs was

also detected. **Conclusions:** Isolation of BDPC from adult rat brain tissue is feasible and provides a renewable source of neural cells with characteristics favourable to long-term therapeutic function and survival in the brain. These rodent BDPC share attributes of those generated previously from human cortical brain biopsies, which offers the opportunity to study viability, integration and function in a preclinical syngeneic transplant model. This model is expected to provide valuable insight on the therapeutic potential of BDPCs as a personalized autologous substrate for cell-based therapy in neurodegenerative disease.

Disclosures: S.M. Benoit: None. **S. Schmid:** None. **M.O. Hebb:** None.

Poster

210. Parkinson's Disease: Preclinical Therapeutic Development

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 210.25/K11

Topic: C.03. Parkinson’s Disease

Support: Focused Ultrasound Foundation

Title: Focused ultrasound enhancement of intranasal delivery of GDNF hDNA nanoparticles to rat brain

Authors: *A. E.-E. ALY[1], T. SUN[3], Y. ZHANG[4], O. SESENOGLU-LAIRD[5], L. PADEGIMAS[5], M. J. COOPER[5], N. MCDANNOLD[4], B. L. WASZCZAK[2]
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Abstract: The blood-brain barrier (BBB) prevents therapeutic proteins and the genes encoding them from entering the brain. We have previously shown that intranasal administration of PEGylated lysine 30-mer (CK30PEG10K) compacted plasmid DNA nanoparticles (NPs) encoding glial cell line-derived neurotrophic factor (GDNF), developed by Copernicus Therapeutics, Inc., can transfect brain cells in vivo, induce transgene expression, and provide neuroprotection of substantia nigra (SN) dopamine neurons in the rat 6-hydroxydopamine model of Parkinson’s disease (PD). We have also shown with double-label immunohistochemistry (DL-IHC) that transgene expression occurs throughout the rat brain primarily in cells located immediately abluminal to the vascular endothelium, presumably pericytes. This localization is consistent with distribution of the nasally-administered NPs by perivascular transport. Focused ultrasound (FUS) with circulating microbubbles has been proposed as a means of transiently disrupting the BBB to permit localized delivery of biomolecules to specific brain regions. Since the intranasal route provides no inherent means of targeting, we sought to determine if combining focused ultrasound (FUS) with intranasal administration of pGDNF NPs could

enhance delivery, improve tissue penetration, and enrich transgene expression in the sonicated regions. Two sites, one in the right forebrain and one in the right midbrain, were sonicated with circulating microbubbles just before and after intranasal administration of the NPs. One week later, transgene expression in the brain was assessed by ELISA and DL-IHC. FUS-mediated disruption of the BBB resulted in a shift in the distribution of transgene expression to the sonicated brain regions and hemisphere relative to the unsonicated (left) side, but there was no net change in total whole brain expression relative to rats given the same intranasal dose of NPs without FUS. DL-IHC showed that FUS also altered cellular transfection patterns. At the sonication sites, large numbers of cells other than pericytes were transfected, and they were located deeper in the parenchyma than at non-sonicated sites. These cells were not astrocytes or neurons. At non-sonicated sites on both sides of the brain, a larger percentage of transfected cells were located within 15 µm of neurons than in rats not subjected to FUS. These results demonstrate that FUS with circulating microbubbles combined with intranasal administration of our DNA NPs increases delivery to the sonicated brain areas, improves tissue penetration, and enriches transgene expression locally at the targeted location(s) in brain.

Disclosures: **A.E. Aly:** None. **T. Sun:** None. **Y. Zhang:** None. **O. Sesenoglu-Laird:** None. **L. Padegimas:** None. **M.J. Cooper:** None. **N. McDannold:** None. **B.L. Waszczak:** None.

Poster

210. Parkinson's Disease: Preclinical Therapeutic Development

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 210.26/K12

Topic: C.03. Parkinson’s Disease

Title: The c-Abl inhibitor, Radotinib, protects dopaminergic neurons in a preclinical model of sporadic Parkinson's disease

Authors: *S. LEE[1,2], Y. PARK[3], S. KIM[1,2], D. KIM[4], J. SHIN[4], D. CHO[4], G. LEE[4], H. JU[4], H. YUN[4], S. LEE[3,5], H. KO[1,2,6,7,5]
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Abstract: c-Abl is a nonreceptor tyrosine kinase that is activated in human postmortem brains of patients with Parkinson's disease (PD) in the striatum and substantia nigra. Accumulating evidence suggests that c-Abl inhibition might be beneficial in PD and α-synucleinopathies. Recently, Nilotinib, a c-Abl inhibitor, showed improved motor and cognitive symptoms in PD

patients. However, the lack of selectivity and safety issues still remain. Here we show the neuroprotective efficacy of Radotinib, a brain penetrant c-Abl inhibitor, in the α-synuclein preformed fibrils (PFFs)-induced model of sporadic PD. Radotinib is also a selective Bcr-Abl kinase inhibitor and have greater pharmacokinetic properties and safety profiles and the blood-brain barrier (BBB) penetration compared to Nilotinib and other c-Abl inhibitors. Interestingly, in vitro studies demonstrate that the treatment of Radotinib protects the α-synuclein PFFs-induced neuronal toxicity, reduces the PFFs-induced LB/LN-like pathology, and inhibits the PFFs-induced c-Abl activation in neurons. Furthermore, administration of Radotinib prevents dopamine (DA) neuron loss and behavioral deficits following α-synuclein PFFs-induced toxicity in vivo. Taken together, our findings indicate that Radotinib has beneficial neuroprotective effects in PD and provides a strong evidence that selective and brain permeable c-Abl inhibitors can be potential therapeutic agents for the treatment of PD and α-synucleinopathies.

Disclosures: S. Lee: None. **Y. Park:** None. **S. Kim:** None. **D. Kim:** None. **J. Shin:** None. **D. Cho:** None. **G. Lee:** None. **H. Ju:** None. **H. Yun:** None. **S. Lee:** None. **H. Ko:** None.

Poster

210. Parkinson's Disease: Preclinical Therapeutic Development

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 210.27/L1

Topic: C.03. Parkinson’s Disease

Support: NIH R21 NS085539

Branfman Family Foundation

Title: Characterization of microrecordings in the Substantia Nigra pars reticulata for the accurate placement of deep brain stimulation electrodes

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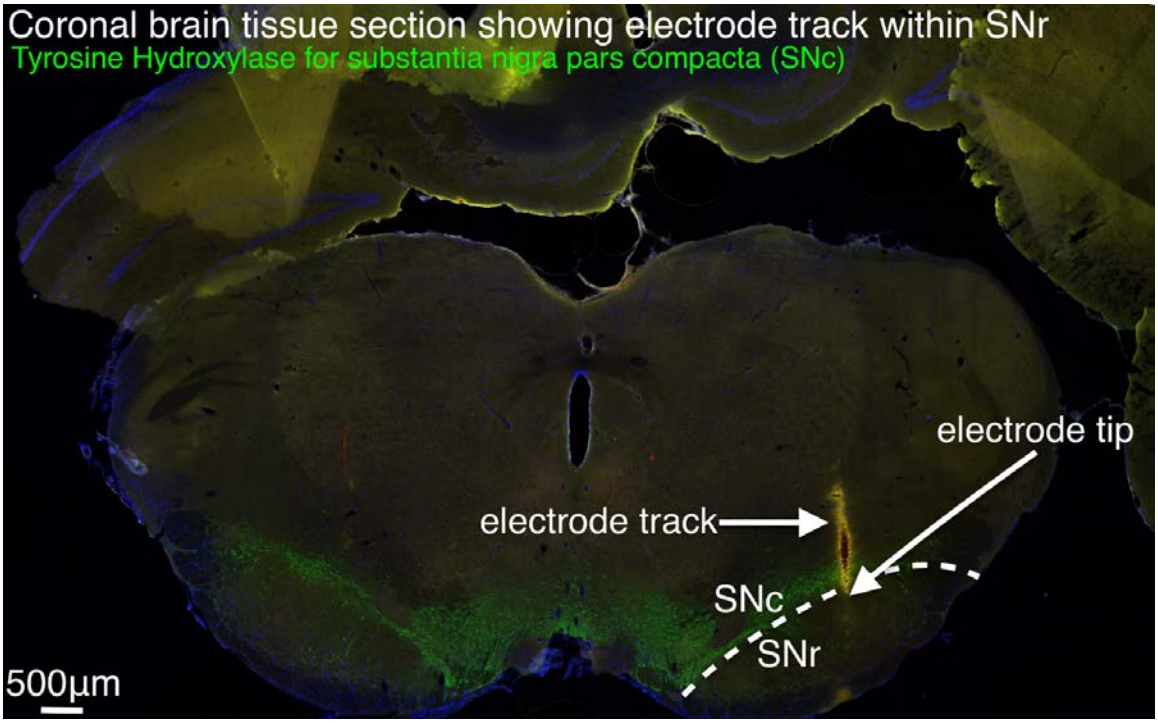
Abstract: Deep brain stimulation (DBS) is an effective treatment for tremor, rigidity and bradykinesia in Parkinson’s disease. However, gait and postural disturbances can worsen with disease progression and there is currently no effective pharmacological treatment. DBS at the Substantia Nigra pars reticulata (SNr) is a promising treatment for the gait and postural disturbances of Parkinson’s, however, the neural basis is unclear. We analyzed intraoperative neural recordings - spikes and local field potentials (LFPs) - and immunohistochemistry in anesthetized rats to identify electrophysiological features that are correlated with accurate microelectrode placement in SNr to develop a preclinical rat model to investigate the neural basis

of SNr DBS. Microelectrode tracks were indicated by dip coating the electrode with a fluorescent dye to precisely identify the microelectrode tip within the brain. Histology confirmed that all microelectrodes were within the SNr (see figure). Single unit activity from sites located within the SNr was 25.65 ± 3.92 spikes/s, an increase in firing rate from no spikes at 0.1 mm dorsal to SNr ($p < 0.05$), and an increase in background noise level 0.1 mm dorsal to SNr ($p < 0.05$), but not 0.2 mm dorsal to SNr. Further, the power spectrum of LFPs within SNr showed increased power in the 1.5-30 Hz band compared to dorsal 0.1 mm and 0.2 mm to SNr. The location of SNr indicated by immunohistochemistry compared to changes in neural activity differed by 0.5 mm with potential causes including brain edema during surgery and shrinkage during fixation, and highlights an advantage of using intraoperative recordings to determine depth of implant location in contrast to basing implant depth solely on a rat brain atlas. Our results suggest that intraoperative microelectrode recordings are a useful technique to identify the SNr for preclinical studies of SNr DBS.



Disclosures: **H. Li:** None. **G.C. McConnell:** None.

Poster

210. Parkinson's Disease: Preclinical Therapeutic Development

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 210.28/L2

Topic: C.03. Parkinson’s Disease

Title: *In vivo* imaging of cortical activity elicited by STN DBS during the acute response to electrode implantation

Authors: *A. J. SUMINSKI[1], S. SALEH[1], J. NOVELLO[3], J. YE[1], S. K. BRODNICK[3], J. PISANIELLO[3], J. NESS[2], A. M. DINGLE[4], J. C. WILLIAMS[5], W. B. LAKE[1]
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Abstract: Deep brain stimulation (DBS) is an established adjunctive method of alleviating symptoms for various movement disorders including Parkinson's Disease (PD). Despite intraoperative testing for optimal placement and efficacy of the stimulating electrodes, optimization of the stimulation parameters (i.e. pulse amplitude, frequency and phase duration) to effectively treat the symptoms of PD is a weeks to months-long process for many patients. The length of the programming period is thought to be due, in part, to the inflammatory response to electrode implantation. To investigate the effect of inflammation on current delivery, transgenic mice, expressing Thy1-GCaMP6f (a genetically-encoded calcium sensor), were anesthesized with isoflurane (1- 2.5%) and implanted with a unilateral, concentric DBS electrode (125um diameter) in the subthalamic nucleus (STN) using stereotaxy (-1.7mm AP, -1.5mm ML, -4.5mm DV from bregma). After the surgical procedure, anesthesia was switched from isoflurane to a ketamine (25-100mg/kg)/dexmedetomidine(0.05-0.1mg) cocktail as isoflurane ablates nearly all cortical signals. Next, high frequency electrical stimulation of the STN was performed using trains of 10 biphasic pulses (cathodal-first, 100-200 uA; 100us per phase, 150Hz) initiated at pseudorandom intervals (varying between 3-4 seconds). We imaged changes in fluorescence (10Hz frame rate) elicited by stimulation to characterize the response of cortical neurons to STN DBS. We observed a widespread wave of depolarization on the cortical surface resulting from stimulation. Initial analyses show that this neural activity emanated from the site where the DBS electrode entered the parenchyma. This result is consistent with the idea that the acute inflammatory response during the perioperative and early postoperative periods shunt current away from the desired target compared to the chronic inflammatory state weeks later. Further understanding the local parenchymal effects of lead implantation will help in the development of methods to reduce the inflammatory response during this process. This effort may result in more predictable DBS outcomes and a shorter time to optimal therapeutic benefit.

Disclosures: A.J. Suminski: None. **S. Saleh:** None. **J. Novello:** None. **J. Ye:** None. **S.K. Brodnick:** None. **J. Pisaniello:** None. **J. Ness:** None. **A.M. Dingle:** None. **J.C. Williams:** None. **W.B. Lake:** None.

Poster

210. Parkinson's Disease: Preclinical Therapeutic Development

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 210.29/L3

Topic: C.03. Parkinson’s Disease

Support: MJFF Grant 6120.01

Title: General amyloid interaction motif (GAIM) reduces misfolded alpha synuclein inclusions formation in cell-to-cell transmission model

Authors: *C. H.-Y. CHUNG, E. ASP, J. LEVENSON, C. ROCKWELL-POSTEL, K. MCDOWELL, M. LULU, J. WRIGHT, M. PROSCHITSKY, R. KRISHNAN, R. FISHER
Proclara Biosci., Cambridge, MA

Abstract: Lewy bodies and Lewy neurites are the pathological hallmarks found in Parkinson’s disease patients and they are mainly composed of aggregated alpha synuclein. Recent studies have shown that alpha synuclein pathology can propagate from neuron-to-neuron, and multiple *in vitro* and *in vivo* models have been established to recapitulate this process. General amyloid interaction motif (GAIM) is the amyloid binding fragment derived from filamentous bacteriophage M13, which reduces assembly and aggregation of fibrillar misfolded proteins, such as amyloid beta, tau, and α-synuclein. A GAIM-human immunoglobulin (GAIM-Ig) fusion protein, which displays 2 copies of GAIM, remodels various amyloid aggregates in vitro and reduce amyloid plaque and insoluble tau in transgenic animals. In this study, over 100 variants of GAIM-Ig fusions were generated and Ig-fusions which show improved binding to amyloid aggregates, reduced non-specific binding, and improved neo-natal receptor (FcRn) binding were screened. In addition, these mutants were designed to reduce immunogenicity potential by eliminating possible T-cell epitopes of GAIM. We then tested if these variants could differentially mitigate inclusion formation in a previously established *in vitro* primary neuronal model of alpha synuclein cell-to-cell transmission. Briefly, alpha synuclein pre-formed fibrils (PFFs), incubated with or without GAIM-fusions, were transduced in primary mouse hippocampal neurons, and inclusion formation, as indicated by immunostaining of phospho-alpha synuclein serine 129, was quantified. One of the lead compounds from our screening campaign, NPT189, was further tested in a PFF injection mouse model. Wildtype mice received intrastriatal injection of alpha synuclein PFFs and were treated with NPT189 via intraperitoneal administration weekly for 3 months. Motor functions were tested monthly by wire hang test and grip strength meter, and neuropathology (pS129) was evaluated at the end of our study. Our data show that GAIM-Ig fusions can reduce inclusion formation in a primary neuronal model of cell-to-cell transmission and rescues behavioral deficits in an alpha synuclein transmission mouse model.

Disclosures: **C.H. Chung:** A. Employment/Salary (full or part-time):; Proclara Biosciences. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Proclara Biosciences. **E. Asp:** A. Employment/Salary (full or part-time):; Proclara Biosciences. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Proclara Biosciences. **J. Levenson:** A. Employment/Salary (full or part-time):; Proclara Biosciences. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Proclara Biosciences. **C. Rockwell-Postel:** A. Employment/Salary (full or part-time):; Proclara Biosciences. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Proclara Biosciences. **K. McDowell:** A. Employment/Salary (full or part-time):; Proclara Biosciences. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Proclara Biosciences. **M. Lulu:** A. Employment/Salary (full or part-time):; Proclara Biosciences. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Proclara Biosciences. **J. Wright:** A. Employment/Salary (full or part-time):; Proclara Biosciences. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Proclara Biosciences. **M. Proschitsky:** A. Employment/Salary (full or part-time):; Proclara Biosciences. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Proclara Biosciences. **R. Krishnan:** A. Employment/Salary (full or part-time):; Proclara Biosciences. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Proclara Biosciences. **R. Fisher:** A. Employment/Salary (full or part-time):; Proclara Biosciences. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Proclara Biosciences.

Poster

211. Parkinson's Disease: Human Therapeutic Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 211.01/L4

Topic: C.03. Parkinson’s Disease

Support: NYIT COM internal grant

Title: Effect of osteopathic manipulative medicine on constipation and the gut microbiota in Parkinson's disease

Authors: *J. D. MANCINI[1], L. R. MARTINEZ[2], G. TORRES[2], E. CHEN[3], S. JACOB[3], J. SAMUEL[3], T. LI[1]
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Abstract: Parkinson's disease (PD) impairs both motor and nonmotor function, including constipation, which may present prior to motor symptoms. The gut microbiome appears to be significantly different in PD and may play a critical role in its pathophysiology. Osteopathic manipulative medicine (OMM) is the diagnosis and treatment of the neuromusculoskeletal system anatomy to improve body mechanics of muscle tone, circulation, body fluids, and nervous impulses utilizing non-invasive, manual techniques. Previous studies have demonstrated that OMM improved constipation in cerebral palsy and those who were otherwise healthy. The purpose of this study is to determine whether or not a pre-defined OMM experimental protocol will (a) improve motility time and constipation symptoms and severity, and (b) lead to pertinent differences in gut microbiota after four weekly OMM treatments. Subjects (n=3) with PD and constipation underwent Movement Disorders Society-Unified PD rating scale and 10 weeks of monitoring for severity of constipation using questionnaires validated for diagnosis, symptom severity, and quality of life in constipation. The Bristol stool chart was used to monitor motility. Biweekly stool and mouth samples were analyzed for microbiota. In weeks 5-8, each subject underwent 30 minute intervention with an OMM protocol once per week to address areas of autonomic nervous system and somatic dysfunction associated with gastrointestinal function. Stool samples before and after OMM treatments showed the following bacterial mean abundance for Prevotellaceae (0.115 and 0.074%), Lachnospiraceae (15.835 and 18.753%), Lactobacillacae (0.827 and 1.411%), Verrucomicrobiacae (12.171 and 3.118%), Bradyrhizobiacae (0.040 and 0.002%), Ruminococcicae (7.328 and 11.164%), and Enterobacteriaceae (1.357 and 1.845%) families. The mean abundance for Bacteroidetes phylum was 40% before and 34% after OMM. The Cleveland constipation scoring, Bristol stool scale, and patient assessment of constipation-symptom and –quality of life scale scores tended to improve with this OMM procedure. Our findings are consistent with previous gut microbiota studies in PD. Although more subjects are necessary to determine significance, OMM may have a beneficial effect on constipation and gut microbiota in PD.

Disclosures: J.D. Mancini: None. **L.R. Martinez:** None. **G. Torres:** None. **E. Chen:** None. **S. Jacob:** None. **J. Samuel:** None. **T. Li:** None.

Poster

211. Parkinson's Disease: Human Therapeutic Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 211.02/L5

Topic: C.03. Parkinson’s Disease

Support: NINDS K23-NS067053-5

Brain Research through Advancing Innovative Neurotechnologies® (BRAIN) Initiative 1UH3NS100553-01

Medtronic

Title: Stimulus-evoked cortical physiology identifies corticospinal tract activation by subthalamic deep brain stimulation

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Abstract: Background: Although DBS is effective for motor symptoms of Parkinson's disease, improvement varies substantially in individuals. Motor side effects constrict the therapeutic window, limit efficacy, and can worsen speech and gait. Non-invasive methods to identify capsular activation could be used to tailor outcomes and guide directional steering, adaptive stimulation, and other emerging technologies.
Aims: We evaluated whether the latency of scalp potentials elicited by subthalamic DBS predicts motor side effect thresholds at a given stimulation site.
Methods: We measured event related potentials elicited by 20 Hz DBS with high density electroencephalography in 7 participants (8 hemispheres, 32 electrodes). We reversed bipolar DBS contact pairings to minimize the stimulus artifact, calculated event related potentials, and correlated response latency with motor side effect thresholds during 160 Hz stimulation using one-way ANOVA at alpha of 0.05.
Results: DBS elicits cortical activation at approximately 1 millisecond after stimulus onset at sites with and without motor side effects. In a voltage-dependent manner, cortical activation occurs at shorter latencies at sites with capsular side effects versus those chosen for clinical therapy ($F = 12.2$ and $p < 0.001$, ANOVA).
Conclusions: The precise timing of cortical activation by DBS predicts clinically relevant motor side effects, suggesting distinct cortical projections into effective versus ineffective stimulation sites. These findings provide a non-invasive framework to guide emerging technologies such as directional and closed loop stimulation.

Disclosures: H.C. Walker: A. Employment/Salary (full or part-time):; University of Alabama at Birmingham. 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.; Medtronic. **A. Romeo:** None. **C.L. Gonzalez:** None. **G. Cutter:** None. **B.L. Guthrie:** None.

Poster

211. Parkinson's Disease: Human Therapeutic Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 211.03/L6

Topic: C.03. Parkinson's Disease

Title: Transcranial direct current stimulation augmented individualized gait training targeted at freezing of gait in Parkinson's Disease: A case description

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Abstract: Background:
Fifty to 70% of people with Parkinson's Disease (PD) experience freezing of gait (FOG). Freezing episodes are significantly correlated with the risk of falling, which can lead to injury, fear of falling, decreased activity levels and increased functional impairments. Current treatments for PD, such as pharmacologic agents and deep brain stimulation have a variable effect on FOG, making treatment options limited. Recent evidence demonstrates disrupted cortical networks in individuals who exhibit FOG, with alterations in the supplementary motor area (SMA) and executive function disorder. Transcranial direct current stimulation (tDCS) can modulate cortical excitability non-invasively, and may be a useful adjuvant to gait training in individuals who freeze. Our objective is to report on a case study assessing feasibility and preliminary efficacy of an individualized gait training targeting FOG and augmented with tDCS.
Methods:
The participant was a female with Hoehn and Yahr stage II PD with FOG, and initial unified Parkinson's disease rating scale (UPDRS) motor sub score of 29. An assessment battery was performed in the "on" phase at baseline and following the 3-week CMCLT protocol. Feasibility was assessed by measuring the percentage of adherence and occurrence of adverse events. Preliminary efficacy was assessed with the outcome measures: the freezing of gait questionnaire (FOG-Q) to assess freezing, Timed up-and-go (TUG) and TUG with dual-task (TUG-DT) to assess walking function and cognitive reserve, and the Montreal Cognitive Assessment (MOCA) for used for global cognition. The intervention was comprised of 45-minute training sessions, 3x per week for 3 weeks, where the individual performed tasks specifically designed to provoke and train freezing, increasing in complexity throughout the training and incorporating motor and cognitive dual-tasks. TDCS (1mA) was applied to the SMA concomitantly with training.
Results:
Adherence to the protocol was 100% without any adverse events reported. The participant

demonstrated: a decrease in severity and frequency of freezing episodes (FOG-Q baseline=15, posttest= 8); improved walking function (TUG baseline=19.69s, posttest= 17.14s); cognitive reserve (mean TUG-DT baseline=25.52s, posttest=23.07s); and improved global cognition MOCA (baseline=16, posttest=26).
Conclusions:
The results of the present study demonstrate safety and preliminary efficacy of an individualized gait training protocol augmented by tDCS in an individual in Stage II Hoehn and Yahr who experiences FOG. Our results suggest further examination of this protocol in a larger sample.

Disclosures: J. Rice: None. **A. Swarowsky:** None. **K. Cai:** None. **S. Aldraiweish:** None. **J. Gomes-Osman:** None.

Poster

211. Parkinson's Disease: Human Therapeutic Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 211.04/L7

Topic: C.03. Parkinson's Disease

Title: Endurance exercise improves function in individuals with parkinson's disease: A meta-analysis

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Abstract: Current evidence has shown that exercise can reduce symptoms of Parkinson's disease (PD). However, previous studies indicated mixed results, possibly because of variability in terms of the nature of the exercise interventions. The purpose of this study was to perform a meta-analysis of current evidence from endurance exercise intervention studies for effects on the United Parkinson's Disease Rating Scale (UPDRS) in individuals with PD. A systematic literature search in six electronic databases was performed and two independent reviewers screened the title and abstract of 1,106 records captured by the initial search. Inclusion criteria for full-text review were (A) peer-reviewed English-language publications, (B) randomized controlled trials that compared an endurance exercise intervention group to a non-exercising control group, and (C) an outcome measure which included the UPDRS total score or section III (motor) subscore. From the title/abstract screening, the same independent reviewers assessed 245 full-text articles for eligibility. Of the full-text articles reviewed 7 articles were included in our meta-analysis, 238 were excluded for the following reasons: 147 did not meet endurance exercise criteria, 53 were review/systematic reviews, 34 were conference abstracts or posters, 2 were

editorial or commentary, 1 was a study protocol, and 1 was unpublished. The d index was used to calculate the difference between means of different groups within individual studies, and a weighting factor or w was used to calculate the effect size across studies. Overall, d index was found to be -0.32 with 95% confidence interval, CI (-.09, -.56) found to be statistically significant indicating a positive effect of endurance exercise in UPDRS scores. In conclusion, this meta-analysis supports integrating endurance exercise training, as defined by ACSM, into treatment of PD.

Disclosures: S.O. Ahmad: None. **L. Jaegers:** None. **M. Krieger:** None. **E. Bixler:** None. **P. Kelly:** None. **E.P. Weiss:** None. **A. Flach:** None.

Poster

211. Parkinson's Disease: Human Therapeutic Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 211.05/L8

Topic: C.03. Parkinson’s Disease

Support: NYIT-COM Internal Grant Funding

Title: The effect of osteopathic manual treatments on motor and nonmotor aspects of camptocormia in parkinson's disease

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Abstract: Parkinson’s disease (PD) has motor and nonmotor symptoms, including dysregulation of the cardiovascular system by the autonomic nervous system (ANS). Camptocormia, an involuntary severe truncal flexion, is associated with more nonmotor symptoms than in PD alone. Current treatment recommendations for camptocormia are only moderately effective or high risk. Improvement in ANS balance in other illnesses has been demonstrated with particular osteopathic manual treatment (OMT) techniques, and there have been cases in which OMT was demonstrated to improve camptocormia posture. To determine if OMT applied to pre-defined anatomy can improve motor and nonmotor aspects of camptocormia in PD (NYIT-IRB-approved1130), men or women with PD with camptocormia and with PD, 50 to 90 years old were recruited. Outcome measures for motor and nonmotor function were performed before and after 8 weekly, 17-step, OMT sessions in PD with camptocormia and compared to no intervention in PD alone. Outcome measures included International Movement Disorder Society-Unified Parkinson's Disease Rating Scale MDS-UPDRS and postural measurements for motor function and the Non-motor Symptoms Scale (MDS-NMSS), SCOPA-AUT ANS scale for PD, and orthostatic heart rate variability (HRV) for nonmotor function. Outcome measures were

repeated 2 weeks post OMT. Two males with PD and camptocormia (PDC1 and PDC2) and 1 female with PD (PD1) were enrolled in the study to date. The PD1 NMSS and SCOPA-AUT scores were 27% and 11% less than the mean scores of PDC1 and 2. NMSS scores improved by 14% in PDC1 and 11% in PDC2 from before to after OMT. Two weeks post OMT scores further decreased by 6% in PDC1 and 3% in PDC2. The SCOPA-AUT score improved by 2% in PDC1 and 15% in PDC2 from before to after OMT. The two week post OMT scores decreased further by 9% in PDC1 and increased by 5% in PDC2. The change in sympathetic-vagal HRV ratio in response to orthostatic challenge before OMT was 0.4206, -0.9814, and -0.6303 for PDC1, PDC2, and PD1, respectively. The ratio after OMT was 1.3548 and 0.6886 for PDC1 and PDC2, respectively. The ratio 2 weeks post OMT was 0.0990 and 0.5385 for PDC1 and PDC2, respectively. Total MDS-UPDRS scores improved with OMT by 35% in PDC1 and 20% in PDC2. Head carriage improved by 2.3 inches in PDC1 and 0.3 inches in PDC2. Time able to stand unassisted increased by 104 sec and 92 sec for PDC1 and PDC2. The camptocormia in PD subjects had an increased sympathetic response to orthostatic challenge as well as a decreased severity of motor function and nonmotor function scores after 8 weekly treatments with the pre-defined OMT protocol. More subjects, including placebo-controls, are necessary to determine significant changes.

Disclosures: T.G. Ng: None. **D. Pasternack:** None. **A. Leder:** None. **J. Mancini:** None.

Poster

211. Parkinson's Disease: Human Therapeutic Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 211.06/L9

Topic: C.03. Parkinson’s Disease

Support: Micheal J Fox Foundation

Title: Long-term responsive deep brain stimulation for medically refractory freezing of gait in parkinson’s disease

Authors: *R. MOLINA[1], K. SOWALSKY[2], J. ROPER[2], J. B. SHUTE[6], E. OPRI[1], D. MARTINEZ-RAMIREZ[3], K. FOOTE[3], C. J. HASS[4], M. OKUN[3], A. GUNDUZ[5]
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Abstract: Background
Current treatment modalities for refractory freezing of gait (FoG) in Parkinson’s disease (PD) have been largely ineffective. FoG affects over 53% of PD patients, regardless of disease progression or medical therapy. Due to an unmet and pressing need, we developed a novel

therapeutic strategy to treat medically refractory FoG with responsive deep brain stimulation (DBS) targeting the pedunculopontine nucleus (PPN). Responsive DBS delivers stimulation therapy based on control signal. In this study, we utilize the brain's own electrophysiology as an input signal to the DBS stimulation controller.
We seek to identify neural electrophysiological features for real-time detection of gait events. Detection of gait events will be followed with responsive DBS stimulation to the target region, the PPN. Therefore, we seek to understand stimulation induced changes in gait and whether responsive PPN DBS can effecitvely reduce FoG episodes.

Methods

All participants must meet preset criterion on the FoG-Q and a minimum of 5 freezing episodes incited by provocation protocols. Five patients will receive bilateral globus pallidus interna (GPi) and PPN DBS electrode implantation with two Activa PC+S Neurostimulation system, (Medtronic, Minneapolis, MN), one for each region. These novel devices allow simultaneous stimulation and recording from the depth electrodes using the Medtronic Nexus-D system, an external device enabling real-time control and data. Neural data is concurrently collected from multiple EMG+acceleration sensors (Delsys, Inc., Natick, MA) and an 8-camera motion capture system (Vicon Peak, Oxford, UK over two-day monthly visits. GPI DBS will be programmed to current standard of care to provide treatment of PD's cardinal symptoms. PPN DBS paradigms will be designed using the extracted gait features. Final evaluation of the therapy's efficacy will also be measured through clinical scores, specifically the UPDRS III, the Parkinson's Disease Questionaire 39 and the Gait and Falls Questionaire.

Results

Acute testing of responsive stimulation was done in the gait lab. Once the detector was optimized from previously determined neural markers and thresholds held constant, subjects could be placed on long-term responsive stimulation. From a pool of 5 participants, 2 were eligible for long-term PPN DBS. Preliminary results show improvement from their monthly visit after long-term responsive DBS compared to their 6 month GPI DBS only therapy.

Conclusion

Our initial results are promising across the 2 patients who have undergone long-term responsive PPN DBS. There is current work in determining optimal stimulation parameters.

Disclosures: R. Molina: None. **K. Sowalsky:** None. **J. Roper:** None. **J.B. Shute:** None. **E. Opri:** None. **D. Martinez-Ramirez:** None. **K. Foote:** None. **C.J. Hass:** None. **M. Okun:** None. **A. Gunduz:** None.

Poster

211. Parkinson's Disease: Human Therapeutic Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 211.07/L10

Topic: C.03. Parkinson's Disease

Support: Michael J. Fox Foundation, Grant 9205

Title: Intracortical plasticity is preserved in de novo Parkinson's disease: A tSMS study

Authors: M. DILEONE[1], V. CATANZARO[1], A. OLIVIERO[2], J. A. OBESO[1,3], *G. FOFFANI[1,2]
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Abstract: In Parkinson’s disease, treatment-naïve (de novo) patients are characterized by absent corticospinal plasticity and reduced short-interval intracortical inhibition (SICI), a GABA-mediated inhibition in human motor cortex. We recently introduced transcranial static magnetic field stimulation (tSMS), a non-invasive brain stimulation technique that is able to induce a short-lasting reduction in corticospinal excitability and an increase in SICI in healthy controls. The objective of this study was use tSMS to test the intracortical plasticity of motor cortex de novo Parkinson’s disease (PD). We performed a single-blind study to assess cortical excitability before and immediately after 10-min of tSMS applied to the more affected motor cortex in de novo patients with Parkinson’s disease (N=18) and in healthy controls (N=9). No patients were on dopaminergic treatment. Corticospinal excitability was evaluated by the amplitude of motor evoked potentials (MEPs) elicited by single-pulse transcranial magnetic stimulation (TMS) and SICI was assessed by a paired-pulse TMS protocol. In healthy controls, tSMS significantly reduced MEP amplitudes while increasing SICI. In de novo PD patients, tSMS did not modulate MEP amplitudes, but - similarly to the healthy controls - significantly increased SICI. These results confirm that dopamine depletion leads to deficient corticospinal plasticity, but they show that intracortical plasticity - assessed by SICI - is preserved in de novo Parkinson’s disease.

Disclosures: M. Dileone: None. **V. Catanzaro:** None. **A. Oliviero:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cofounder of Neurek SL and inventor on tSMS-related patents. **J.A. Obeso:** None. **G. Foffani:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cofounder of Neurek SL and inventor on tSMS-related patents.

Poster

211. Parkinson's Disease: Human Therapeutic Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 211.08/M1

Topic: C.03. Parkinson’s Disease

Support: NIH Medical Scientist Training Program (CWL)

NSF Graduate Research Fellowship (KAM)

A. Alfred Taubman Medical Research Institute

Title: Electrophysiological signatures of clinically effective regions of subthalamic nucleus deep brain stimulation in Parkinson's disease

Authors: *K. A. MALAGA[1], C. W. LU[1], K. L. CHOU[2,3], P. G. PATIL[1,2,3]
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Abstract: The mechanisms of efficacy for deep brain stimulation (DBS) of the subthalamic nucleus (STN) for the treatment of Parkinson's disease are not clearly defined and analytical methods to optimize stimulation programming are lacking. In practice, clinicians largely rely on empirical examination to determine effective stimulation parameters, including contact choice and amplitude. Previous studies have identified promising associations between peak beta power and active contact location, but do not address the spatial extent of activation. The objective of this study was to more precisely predict optimal stimulation sites by utilizing patient-specific tissue activation models and identifying associations between regions of therapeutic activation and electrophysiological markers. Atlas-independent tissue activation models were generated using clinically determined DBS programming parameters and tissue properties derived from validated 3T diffusion tensor MRI. Electrophysiological features, including cross-frequency interactions, were extracted from microelectrode recordings obtained during lead placement surgery and then mapped to tissue activation models via direct visualization of the STN and DBS lead. Specific electrophysiological features were selected using LASSO regression techniques, which identified several predictive single and cross-frequency features in addition to beta power, such as high frequency band power and spike-field coherence, that mapped to clinically effective stimulation sites. A support vector machine using these features was able to correctly identify stimulation sites with greater accuracy than beta power alone. Our study suggests novel electrophysiological features of the STN region that may be useful to improve DBS programming and predict the optimal locus for STN DBS.

Disclosures: K.A. Malaga: None. **C.W. Lu:** None. **K.L. Chou:** None. **P.G. Patil:** None.

Poster

211. Parkinson's Disease: Human Therapeutic Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 211.09/M2

Topic: C.03. Parkinson’s Disease

Support: Gifts to the Brain Restoration Center

Tom Dupree for Parkinson's Disease Research

University of Kentucky start-up funds

National Center for Advancing Translational Sciences grant UL1TR000117

Title: Peripheral nerve grafts to the brain of patients with Parkinson's disease: Microscopic, biochemical, and immunohistochemical characterization

Authors: *A. S. WELLEFORD[1,2], C. G. VAN HORNE[1,2], J. QUINTERO[1,2], Y. AI[1], G. GERHARDT[1,2]
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Abstract: Currently two clinical trials (NCT01833364 and NCT02369003) are underway which feature the implantation of a peripheral nerve autograft to the brain (targeted either to the Substantia Nigra or the Nucleus Basalis of Meynert) in combination with Deep Brain Stimulation (DBS) for the treatment of patients with Parkinson's disease. This nerve tissue is harvested from the sural nerve, a cutaneous sensory nerve located in the lateral ankle, of patients undergoing DBS surgery. Two tissue samples per patient are collected for study (one during the Stage I surgery, another during the Stage II surgery 5-7 days later) in addition to the tissue used for the graft. As of 5/1/17, 43 patients have received a graft.
The character of the peripheral nerve tissue used in these clinical trials has yet to be described. This study examines several aspects of the peripheral nerve tissue; including microscopic appearance, levels of neurotrophic factors, morphology of Schwann Cells, and presence of macrophages. Techniques used include H&E and MCOLL histological staining, immunohistochemistry, and ELISA. Additional data regarding the sural nerve grafts derived from the study subjects will be presented. These results are supplemented by immunohistochemical analysis of the brain of non-human primates that have undergone an analogous procedure. The results of this model show growth of tyrosine hydroxylase-containing nerve fibers, which are a marker of dopamine-producing neurons, into the area of the peripheral nerve graft. In addition, results in this model show the presence of S100beta and GFAP co-staining cells within and surrounding the graft, which is a marker of peripheral nerve regeneration. These findings suggest that the nerve graft in human patients may also display a regenerative phenotype, which has the potential to alter the course of neurodegeneration in the brain.

Disclosures: A.S. Welleford: None. **C.G. van Horne:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Medtronic. **J. Quintero:** None. **Y. Ai:** None. **G. Gerhardt:** None.

Poster

211. Parkinson's Disease: Human Therapeutic Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 211.10/M3

Topic: C.03. Parkinson's Disease

Support: Funding provided by gifts to the Brain Restoration Center, Ann Hanley Parkinson's Research Fund, Tom Dupree for Parkinson's Disease Research, Pro's Players Fore Parkinson's

National Center for Advancing Translational Sciences, through grant UL1TR001998. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Title: A phase 1 trial evaluating the safety and feasibility of autologous peripheral nerve grafts in patients with Parkinson's disease

Authors: *C. G. VAN HORNE[1,2], J. E. QUINTERO[3,2], J. GURWELL[4,2], A. ANDERSON-MOONEY[4,2], A. S. WELLEFORD[3,2], J. R. LAMM[1,2], J. T. SLEVIN[4,2], G. A. GERHARDT[3,2]
[1]Neurosurg., [2]Brain Restoration Ctr., [3]Neurosci., [4]Neurol., Univ. of Kentucky Med. Ctr., Lexington, KY

Abstract: We present an ongoing open-label, Phase I trial, (NCT01833364 and NCT02369003), examining the safety and feasibility of grafting autologous peripheral nerve tissue to the substantia nigra (SN) in patients with Parkinson's disease (PD). Peripheral nerve tissue contains Schwann cells, which transdifferentiate after nerve injury or transection to become "repair cells" for regenerating neural tissue. The repair cells up-regulate and release a host of factors including GDNF, NGF, BDNF, and NT-3. For the trial, graft tissue is harvested from the sural nerve and deployed during routine deep brain stimulation (DBS) surgery. Immediately following DBS surgery (targeting subthalamic nucleus (STN) or globus pallidus internus (GPi)) a section of sural nerve is excised, stripped of the epineurium, cut into 1 mm pieces, and unilaterally delivered along 5 mm of the substantia nigra (SN) in the dorsal-ventral axis. The primary endpoint is safety. Secondary endpoints include Unified Parkinson's Disease Rating Scale (UPDRS) scores, non-motor symptom scale scores, changes in quality of life, and changes in ioflupane I-123 (DaTscan®) quantification. To date, 26 participants have received a single implantation to the SN. The overall adverse event profile is comparable to standard DBS surgery, with no serious adverse events related to the delivery of the graft. Nineteen participants who received a single graft to the SN unilaterally have reached the 1 year time point and have demonstrated a *decrease* of 7.6 points (considered a moderate clinically important difference) in the UPDRS motor scores off medication and off stimulation (27.6 ± 12.6 points, mean ± SD) compared to before surgery (35.0 ± 11.7 points). For comparison, 16 PD patients in our clinic who received only GPi DBS showed an *increase* of 0.3 ± 15.0 points in their mean UPDRS motor score (off medicine and stimulation) after about one year compared to before surgery. Our initial results indicate a safe and feasible means of delivering cell or biologic therapy with DBS and provide preliminary clinical evidence of potential baseline improvements at one year.

Disclosures: C.G. van Horne: None. **J.E. Quintero:** None. **J. Gurwell:** None. **A. Anderson-Mooney:** None. **A.S. Welleford:** None. **J.R. Lamm:** None. **J.T. Slevin:** None. **G.A. Gerhardt:** None.

Poster

211. Parkinson's Disease: Human Therapeutic Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 211.11/M4

Topic: C.03. Parkinson’s Disease

Support: Funding provided by gifts to the Brain Restoration Center, Ann Hanley Parkinson’s Research Fund, Tom Dupree for Parkinson's Disease Research, Pro's Players Fore Parkinson's

National Center for Advancing Translational Sciences, through grant UL1TR001998. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Title: Dose escalation of autologous peripheral nerve grafts at the time of deep brain stimulation surgery in patients with Parkinson's disease

Authors: J. E. QUINTERO[1,2], J. A. GURWELL[3,1], A. J. ANDERSON-MOONEY[3,1], A. S. WELLEFORD[2,1], J. R. LAMM[4,1], J. T. SLEVIN[3,1], *G. A. GERHARDT[2,1], C. G. VAN HORNE[4,1]
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Abstract: Our ongoing clinical trial (NCT02369003) assesses the safety and feasibility of implanting autologous peripheral nerve grafts to the substantia nigra (SN) in patients with Parkinson’s disease (PD) undergoing DBS surgery. Peripheral nerve tissue contains Schwann cells which transdifferentiate after nerve injury to become “repair cells”. Grafts are implanted during DBS surgery targeting the globus pallidus interna. The overall adverse event profile is comparable to standard DBS surgery, with no serious adverse events related to the unilateral delivery of one graft. Nineteen participants who received a single graft to the SN have reached the 1-year time point and have demonstrated a *decrease* of 7.6 points (considered a moderate clinically important difference) in the UPDRS III motor scores off medication and off stimulation compared to before surgery. Based on these results, we have increased the dosage of nerve grafts to the SN by making two separate nerve graft deployments unilaterally to the SN in 8 participants and three separate deployments (two in one SN and one in the contralateral SN) in one participant. The grafts are approximately 5mm in length and consist of fascicles from the sural nerve cut into 1mm segments. The segments are deposited separately along two trajectories in the dorso-ventral axis through the middle and posterior regions of the SN. Adverse events are continuously monitored. To date, nine participants have received multiple deployment of nerve grafts to the SN. The intraoperative and immediate postoperative adverse event profiles are comparable to standard DBS surgery with no adverse events related to the delivery of the graft.

There have been no episodes of confusion or cognitive dysfunction during the post-operative period and all subjects were discharged on post-op day 1. Early results show that multiple graft deployments unilaterally and bilaterally may be a safe and feasible means of increasing the nerve graft dosage to possibly further improve function of the SN.

Disclosures: J.E. Quintero: None. **J.A. Gurwell:** None. **A.J. Anderson-Mooney:** None. **A.S. Welleford:** None. **J.R. Lamm:** None. **J.T. Slevin:** None. **G.A. Gerhardt:** None. **C.G. van Horne:** None.

Poster

211. Parkinson's Disease: Human Therapeutic Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 211.12/M5

Topic: C.03. Parkinson's Disease

Support: NHLBI T35 HL094308

Title: DBStar: an open-source toolkit for reconstructing targets from deep brain stimulation procedures performed with patient-customized stereotactic platforms

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Abstract: Deep brain stimulation (DBS) is a neurosurgical intervention for treating neurological disorders such as Parkinson's disease. During the operation, microelectrode recordings are made along the implantation trajectory to map neural activity from the awake patient. Although final implantation locations are confirmed with post-operative imaging, patient-specific electrode arrays (e.g. STarFix, FHC Inc.) can have multiple parallel recording trajectories. As intra-operative neural data furthers our understanding of DBS's clinical efficacy and therapeutic mechanisms, it is important to understand the anatomical context of all recording trajectories. Here we describe a principled method for reconstructing intra-operative recording locations along multiple trajectories using the Analysis of Functional Neuroimages (AFNI) software toolkit, combining imaging (CT and/or MRI), the surgical plan, and recording depth values. Pre-, intra-, and post-operative images underwent rigid registration in the Waypoint planner software (FHC Inc.). These transformations were exported and applied to the original DICOM series to obtain a representation of the images in a common coordinate space. Electrode artifacts in intra- or post-operative images were isolated, and recording depth values were placed along the artifact's principal axis. Using surgical plan geometry, coordinates derived from this axis were shifted to parallel electrode trajectories (anterior, center, posterior, etc). To analyze

coordinates across patients, pre-operative T1-weighted MR images underwent non-rigid registration to a AFNI Talairach atlas volume (TT_N27).
Intra-operative recording and final implantation coordinates from three different DBS targets were analyzed: subthalamic nucleus (STN), ventral intermediate nucleus (VIM), or globus pallidus pars interna (GPi). Final DBS electrode coordinates (Medtronic 3387/3389, bottom of contact 0) for each target group in both patient-specific and atlas coordinate space (N=49 DBS electrodes) were calculated relative to the mid-commissural point. Results and inter-patient variability are shown to be consistent in both coordinate spaces.
To validate intra-operative microelectrode recording site locations, we compared STN recording sites (N=169) across patients. Specifically, we tested whether a recording coordinate was inside or within 1 mm of the TT_N27-defined STN border. 115 of the 169 recording coordinates (68%) were found to be within the STN, with a mean euclidean distance of 3.66 ± 1.24 mm from the STN center-of-mass.
Future work will focus on integration with electrophysiology, behavior, and diffusion MR datasets.

Disclosures: **P.M. Lauro:** None. **S. Lee:** None. **M. Ahn:** None. **A. Barborica:** A. Employment/Salary (full or part-time):; FHC inc.. **W.F. Asaad:** None.

Poster

211. Parkinson's Disease: Human Therapeutic Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 211.13/M6

Topic: C.03. Parkinson’s Disease

Title: Cholinergic enhancement of endogenous event-related potentials in Parkinson's patients with cognitive impairments

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Abstract: Cholinesterase inhibitors are the only group of drugs recommended for the treatment of dementia in Parkinson's disease. We investigated the cognitive effects of Rivastigmine by using clinical and electrophysiological characteristics of cognitive functions. Cognitive event-related potentials (ERP) were registered in 41 patients with Parkinson's disease (age 60-74, Hoehn and Yahr 2,5-3) with mild cognitive impairment (n=28) and dementia (n=13). Mini-mental state examination (MMSE), Montreal Cognitive Assessment (MoCA) and Frontal assessment battery (FAB) score were used to evaluate the cognitive function of patients. A half of the group (n=20) was treated with Rivastigmine (3-6 mg/day) for 12 weeks. ERP source localization was carried out using Low-resolution brain electromagnetic tomography (LORETA). In the control group no significant changes was found for cognitive scales or event-related brain

activity after 12 weeks of the standard antiparkinson medication treatment. Alternatively after a course of the Rivastigmine we found the significant ($p<0.05$) improvement of cognitive functions by scores on all outcome scales: MMSE from 25 [21; 26] to 26 [24; 28], MoCA from 21 [14; 23] to 22 [20; 26], FAB from 11 [9; 15] to 15 [11; 16]. Besides, we found the increase of the specific brain activity processes during cognitive load. An amplitude of the N2-P3 component increased widespread in the fronto-central neocortical areas (Fz: from 4 [3; 6] to 6 [6; 7] mkV). N2 peak latency decreased in the frontal, temporal and occipital areas of the left hemisphere (F7: from 304 [282; 316] to 258 [248; 310] ms). In the LORETA study we revealed a significant increase of the ERP generators after Rivastigmine treatment in the right inferior parietal lobule and middle temporal gyrus of left hemisphere. An enhancing of second source can explain a topography of component N2-P3 augmentation. These findings can confirm the positive effect of Rivastigmine on the structure of brain networks responsible for the cognitive processes. Activation of additional networks in the frontal and temporal lobe of the left hemisphere may play an important role for mechanisms of treatment effects of cholinesterase inhibitors on the cognitive and behavioral problems associated with Parkinson's disease.

Disclosures: S. Kryzhanovskyi: None. **O. Shalenko:** None. **N. Karasevych:** None. **I. Karaban:** None.

Poster

211. Parkinson's Disease: Human Therapeutic Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 211.14/M7

Topic: C.03. Parkinson’s Disease

Support: NIH Grant R01 NS075012

NIH Grant R01 NS052318

Title: Movement-related beta-band desynchronization in supplementary motor area is reduced by anti-parkinsonian medication and relates to the velocity of upper limb movement in parkinson’s disease

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Abstract: We investigated the effects of an acute dose of anti-parkinsonian medication on theta (3-7 Hz), alpha (8-12 Hz), and beta-band (13-30 Hz) oscillations in Parkinson’s disease (PD) using high-density 128 Channels electroencephalography (EEG) during an upper limb ballistic

movement. Further, we tested if blood oxygenation level dependent (BOLD) activity from functional magnetic resonance imaging (fMRI) in the putamen and subthalamic nucleus (STN) predicts the response to medication in cortical oscillations. Fifteen PD patients were included who had a positive response to anti-parkinsonian medication as measured by a reduction in the MDS-UPDRS-III. Each patient performed ballistic upper limb movements during high-density EEG, both OFF and ON medication state. PD OFF and PD ON testing was counter-balanced, and was performed one day apart. In addition, patients were studied using task-based fMRI in the OFF state. For EEG, we used an upper limb ballistic movement task that required patients to move their right arm from right to left in the horizontal plane as fast and accurately as possible. EEG data were processed by independent component analysis followed by measure projection analysis allowing statistical event-related spectral analysis in 3D source-space. For task-fMRI, we used a force control paradigm that required patients to produce grip force with their more affected hand. Percent signal change of BOLD activity during the force task was calculated for the putamen and STN contralateral to the hand tested. We found that upper limb movements in PD were significantly faster in the ON condition compared to the OFF condition. PD ON showed less movement-related desynchronization of beta-band (13-30 Hz) and more movement-related desynchronization of theta (3-7 Hz) and alpha (8-12 Hz) bands after the movement onset in supplementary motor area (SMA) than PD OFF. The velocity of movement during the task was positively associated with movement-related beta-band desynchronization after the movement onset in SMA. The BOLD fMRI signal in the contralateral putamen and STN predicted the difference in movement-related beta-band desynchronization between PD OFF and PD ON, indicating that patients with greater BOLD signal in the putamen and STN in the OFF state had the greatest response to medication in the cortex. In conclusion, movement-related beta-band desynchronization in SMA is reduced by an acute dose of anti-parkinsonian medication, and the BOLD activity in the basal ganglia predicts the anti-parkinsonian medication-related response in SMA movement-related beta-band desynchronization.

Disclosures: **J. Chung:** None. **R.G. Burciu:** None. **E. Ofori:** None. **M.S. Okun:** None. **C.W. Hess:** None. **D.E. Vaillancourt:** None.

Poster

211. Parkinson's Disease: Human Therapeutic Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 211.15/M8

Topic: C.03. Parkinson’s Disease

Support: CONACyT Grant 0114218-2009

Title: Tracts involved in the improvement subsequent to ablative neurosurgery of the subthalamus in Parkinson's disease

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Abstract: There is evidence of superior motor outcome improvement when surgical interventions for treating motor symptoms of Parkinson's disease (PD) are performed within the posterior subthalamic area, particularly at a white matter region called prelemniscal radiations (Raprl). Recent findings using tractography by magnetic resonance imaging (MRI) demonstrate anatomical relation of the Raprl with cerebellum, pallidum, dorsal brainstem and frontal areas. The aim of this work is to determine if there are specific fibers involved in ablative neurosurgical interventions responsible of producing a reduction in the symptomatology of PD.
Diffusion-weighted images from 10 PD patients were acquired using 120 unique diffusion-gradient directions with a b=2000 s/mm^2 (voxel size of 2x2x2mm^3), in addition to T1 and FLAIR-T2 volumes. MRI was performed before and after the surgery.
One million streamlines were generated for each region of interest (Raprl) and constrained spherical deconvolution (CSD) informed filtering of tractograms was applied to the tractogram. Tracts were virtually dissected according to cortical and subcortical areas according to the Desikan-Killiany Atlas (Freesurfer5.3). Segmentation of the lesion was performed in the postoperative MRI. Patients were evaluated with the UPDRS pre and post surgery. The correlation of the clinical improvement with the weights of the tracts contained in the lesion was performed using Spearman correlation coefficient.
The statistical analysis showed a positive correlation between the percentage of contralateral cerebellar tracts contained in the lesion and the change in the overall UPDRS score ($p=0.021$, $\rho=0.71$), as well as a positive correlation between the percentage of contralateral cerebellar tracts with the improvement of posture and gait ($p=0.021$, $\rho=0.71$). Negative correlations were obtained in the percentage of tracts within the lesion towards prefrontal cortex in the pars opercularis ($p=0.026$, $\rho=-0.7$) and the middle rostral frontal gyrus ($p=0.01$, $\rho=-0.74$) with posture and gait. As well there were negative correlations of tracts towards subcortical structures such as putamen ($p=0.004$, $\rho=-0.82$) and pallidum ($p=0.028$, $\rho=-0.69$) with posture and gait.
Ablative neurosurgery in the Raprl achieves a significant reduction in the motor symptoms of PD. The tracts involved in the symptomatic improvement of the patients are the ones from the cerebellum that are included in the lesion at the height of the Raprl. Recent studies indicate that frontal degeneration of white matter is related to symptoms of PD with a predominance of postural alterations, which is in agreement with the findings of the present study.

Disclosures: **M. Garcia-Gomar:** None. **F. Velasco:** None. **L. Concha:** None.

Poster

211. Parkinson's Disease: Human Therapeutic Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 211.16/M9

Topic: C.03. Parkinson’s Disease

Support: Department of Veterans Affairs Office of Research and Development; Rehabilitation R&D Service Grant 1I01RX000181

Title: Optimizing cognitive neurorehabilitation in parkinson's disease

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Abstract: Neurocognitive training has been shown to be effective in Parkinson’s disease (PD). One important unanswered question is the duration of training that produces the maximum result with the minimum demand on the participant. To identify the optimal duration of training, we analyzed task performance for 30 days of neurocognitive training. 17 PD and 15 control participants trained for 30 days on a computer task in which they were presented with a string of numbers. Participants responded by typing the sequence of numbers (externally cued response). A green dot then appeared to prompt the participant to re-enter the sequence of numbers (internally generated response). The task was adaptive, with an increasing number of digits presented as performance improved. About half (n=10) of the participants with PD showed impaired performance on this task. This impaired group showed significantly greater reduction in completion time (600 ms) than the control or unimpaired PD groups. We calculated optimal training duration using the CUSUM (or cumulative sum control chart) technique, a sequential analysis technique designed for monitoring change detection. While the control group showed peak task performance improvement at 13 days, the impaired PD group continued to improve for 28 days of training. Latency of peak change was correlated with measures of age, processing speed, verbal fluency, and switching, indicating that participants with greater cognitive deficits needed longer training periods. Measures of mobility and manual dexterity were not associated with latency of peak performance.

Disclosures: H.M. Nguyen: None. **K.S. Holly:** None. **A. Aravindakshan:** None. **E.A. Disbrow:** None.

Poster

211. Parkinson's Disease: Human Therapeutic Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 211.17/M10

Topic: C.03. Parkinson’s Disease

Support: The Colonial Foundation

Victorian Government via Operational Infrastructure Support Program

Title: Clinical validation of a novel palm-worn device to quantify rigidity in Parkinson's disease

Authors: *T. PERERA[1,2], N. C. SINCLAIR[1,2], M. JONES[3,1], J. L. TAN[1,2,4], E. L. PROUD[2], W. L. LEE[1], R. F. PEPPARD[3,1], H. J. MCDERMOTT[1,2]
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Abstract: Rigidity is a cardinal symptom of Parkinson's disease (PD) often used to monitor the efficacy of treatments. Rigidity is characterised by subjectively assessing the resistance of joints to passive movement. The results gained from this technique are often categorised into 4 or 5 levels making them insensitive to minor variations in disease severity. Moreover, the assessment must be administered by a trained professional and insufficient inter-rater agreements pose significant challenges to the interpretation of clinical trial outcomes. Here we aim to validate a novel instrument to quantify rigidity against current clinical best practice.
Our apparatus is a lightweight palm-worn device designed to automatically flex the middle finger about the metacarpophalangeal joint. Embedded feedback technology within a miniature motor allows precise positioning of the finger joint and a force transducer located between the finger and the mechanical linkage generates quantifiable data.
Eight participants (44-61 years of age; 6 male) diagnosed with PD and receiving deep brain stimulation (DBS) therapy gave informed written consent. Participants were assessed following overnight withdrawal of dopaminergic medication. Rigidity of both arms was consecutively assessed by our instrument and 3 movement disorder specialists (2 of whom were blinded to the experimental parameters). Following a baseline assessment (on-DBS), we exploited the wash-out characteristics of DBS by turning the therapy off and monitoring the worsening of symptoms at 10-minute intervals over the course of 1 hour. Rigidity was rated using the Movement Disorder Society's Unified Parkinson's Disease Rating Scale (MDS-UPDRS) and subsequently compared to force and torque data obtained from our device. Data from our instrument were used to train a stepwise multiple linear regression model to predict clinical ratings. This model was evaluated using stratified 10-fold cross validation.
Our regression model shows strong congruence with mean clinical ratings (adjusted $R^2 = 0.77$) and cross-validation confirms goodness of fit with a root mean square error 0.78. Notably, data from our device shows gradual worsening of symptoms over time following DBS cessation in agreement with coarse clinical ratings.
Our device was able to quantify rigidity in agreement with clinical observation and also delineate between therapeutic states. Further trials will seek to determine specificity, sensitivity and repeatability of our instrument prior to its routine use in the clinic.

Disclosures: **T. Perera:** None. **N.C. Sinclair:** None. **M. Jones:** None. **J.L. Tan:** None. **E.L. Proud:** None. **W.L. Lee:** None. **R.F. Peppard:** None. **H.J. McDermott:** None.

Poster

211. Parkinson's Disease: Human Therapeutic Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 211.18/N1

Topic: C.03. Parkinson's Disease

Support: NIH

Title: Prefronto-subthalamic modulation of movement inhibition in Parkinson's disease

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Abstract: Introduction Parkinson's disease (PD) is a movement disorder characterized by symptoms such bradykinesia, rigidity, and freezing of gait, which suggest excessive movement inhibition. A hyperdirect pathway between the inferior frontal gyrus (IFG) and the subthalamic nucleus (STN) has been hypothesized to mediate rapid movement inhibition. Previous studies have separately assessed electrophysiological activity in the IFG of patients with epilepsy and in the STN of PD patients. Increases in beta band (13-30 Hz) activity in these structures were associated with stopping. However, high-resolution electrophysiological evidence of stopping-related beta activity in both the IFG and STN in PD does not yet exist, and whether movement inhibition is mediated by the IFG-STN hyperdirect pathway is still unknown. Here, we aim to 1) establish electrophysiological evidence of an IFG-STN hyperdirect pathway in PD patients, and 2) assess circuit activity during stopping. We hypothesize that beta band hypersynchronization in this prefrontal-basal ganglia circuit correlates with deficits in the ability to inhibit movements.
Methods We use intraoperative, multisite, high-resolution electrophysiology to assess IFG-STN connectivity in PD patients. First, we stimulated in the STN and recorded evoked cortical potentials to assess connectivity. We also characterized the circuit's activity while patients performed a stop signal task.
Results We found short-latency potentials in the IFG at ~1ms following STN stimulation, consistent with antidromic hyperdirect activation. We also found stopping-related modulation of beta power and coherence in both structures during the stop signal task.
Conclusions This work provides high spatiotemporal resolution, functional evidence of IFG-STN connectivity in PD patients. It will contribute to our understanding of Parkinsonian pathophysiology to inform therapeutic ways to alter network activity.

Disclosures: W. Chen: None. **C. de Hemptinne:** None. **A. Miller:** None. **P.A. Starr:** None.

Poster

211. Parkinson's Disease: Human Therapeutic Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 211.19/N2

Topic: C.03. Parkinson’s Disease

Support: NIH Grant NS060722

NIH Grant ES019672

NIH Grant NS082151

NIH Grant NS035032

NIH Grant AR048563

NCATS TL1 TR000125

Title: Effects of deep brain stimulation on synergic control of hand and whole-body tasks in Parkinson's patients

Authors: *A. FALAKI[1], J. HANG JIN[2], X. HUANG[3], M. M. LEWIS[3], B. K. O'CONNELL[3], S. DE JESUS[3], M. L. LATASH[1]
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Abstract: A number of previous studies have provided evidence for changes in the synergic control in patients with Parkinson’s disease (PD). These studies showed that in both multi-finger hand tasks and multi-muscle whole-body tasks, PD led to smaller indices of synergies stabilizing salient performance variables (impaired stability) and smaller anticipatory synergy adjustments in preparation to quick action (impaired agility). Indices of both stability and agility improve on dopamine-replacement drugs. We explored the effects of deep brain stimulation (DBS) on the synergic control of both the hand and whole body in a group of ten male PD patients. Patients had DBS implants in the subthalamic nucleus (n = 7) or the internal segment of the globus pallidus (n = 3), and were at Hoehn and Yahr stage II (n = 7), stage III (n = 2), or stage IV (n = 1). The patients performed three tasks: 1) a multi-finger accurate force production task followed by a quick force pulse to a target; 2) a whole-body voluntary sway task; and 3) a self-initiated load-releasing task. Five of the patients were able to perform both tasks satisfactorily. The tasks were performed in the DBS-on and DBS-off states (counter balanced) without changes in oral medications. Synergy indices were quantified within the framework of the uncontrolled manifold hypothesis in the spaces of hypothetical commands, finger modes, and muscle modes,

respectively. DBS led to no significant change in the composition of modes, but increased significantly indices of agility (longer and larger anticipatory synergy adjustments) without comparable effects on indices of stability (synergy index, ΔV, during the steady-state). Analysis across the five subjects who performed both tasks showed correlations between both indices of stability (ΔV) and indices of agility (duration of anticipatory synergy adjustments). Our results suggest that synergy indices reflect systemic neural mechanisms shared across tasks and effectors. The contrasting effects of DBS on indices of stability and agility suggest that these indices and their changes in PD reflect different functional neural subsystems. They also imply that DBS may have little effect on steady-state tasks (e.g., quiet standing) while being beneficial for tasks that require quick actions.

Disclosures: A. Falaki: None. **J. Hang Jin:** None. **X. Huang:** None. **M.M. Lewis:** None. **B.K. O'Connell:** None. **S. De Jesus:** None. **M.L. Latash:** None.

Poster

211. Parkinson's Disease: Human Therapeutic Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 211.20/N3

Topic: C.03. Parkinson’s Disease

Title: Discounting of delayed rewards after deep brain stimulation

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Abstract: Despite deep brain stimulation of the subthalamic nucleus (STN-DBS) is an effective surgical treatment for Parkinson's disease (PD), it may expose patients to non-motor side effects as, for instance, increased impulsivity and changes in decision-making behaviour [1]. Interestingly, studies on rats showed that STN lesions or stimulations increase impulsive actions in stop signal tasks but decrease impulsive choices in delayed discounting tasks. However, the majority of the studies on patients with Parkinson’s disease failed to report a significant effect of STN-DBS on temporal discounting (TD) of monetary rewards [2]. In this study, we investigated inter-temporal choice after STN-DBS, by using both primary and secondary rewards [3]. In particular, PD patients who underwent STN-DBS (in ON medication/ON stimulation), PD patients without STN-DBS (in ON medication) and healthy matched controls (C) performed three temporal discounting tasks with food (primary reward), money and discount vouchers (secondary rewards). All participants performed also a series of neuropsychological tests and questionnaires. Our preliminary results show that overall STN-DBS patients exhibited increased preference for delayed rewards compared with controls. In particular, this difference was significant for food rewards while no group difference emerged for money and discount voucher.

Furthermore, significant correlations were found between TD for food and disease duration, TD for money and discount voucher and DBS duration. In conclusion, this study suggests that STN-DBS may enhance the incentive salience assigned to natural reward, but not artificial rewards, consistently with studies on animals and on patients with PD [2].

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2. Uslaner, J. M., & Robinson, T. E. (2006). Subthalamic nucleus lesions increase impulsive action and decrease impulsive choice− mediation by enhanced incentive motivation?. European Journal of Neuroscience, 24(8), 2345-2354.
3. Schiff, S., Amodio, P., Testa, G., Nardi, M., Montagnese, S., Caregaro, L., ... & Sellitto, M. (2016). Impulsivity toward food reward is related to BMI: evidence from intertemporal choice in obese and normal-weight individuals. Brain and cognition, 110, 112-119.

Disclosures: M. Aiello: None. **D. Terenzi:** None. **R. Eleopra:** None. **A. Piani:** None. **R.I. Rumiati:** None.

Poster

211. Parkinson's Disease: Human Therapeutic Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 211.21/N4

Topic: C.03. Parkinson’s Disease

Support: NIH UH3 NS100544-02

NIH R01 NS090913-01

UC President's Postdoctoral Fellowship

Title: Closed loop deep brain stimulation for dyskinesia control in Parkinson's disease

Authors: *N. C. SWANN[1], C. DE HEMPTINNE[1], M. C. THOMPSON[3], S. MIOCINOVIC[4], A. MILLER[1], R. GILRON[1], J. OSTREM[2], H. J. CHIZECK[3], P. A. STARR[1]
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Abstract: Introduction: Deep brain stimulation (DBS) is an effective treatment for Parkinson’s disease (PD), but has limitations. One shortcoming is that though PD is a dynamic disorder with symptoms that wax and wane, DBS therapy is continuous and constant. This can result in sub-optimal symptom control or stimulation-induced adverse effects. One way to mitigate this limitation is to adjust stimulation based on changing symptoms – creating “closed loop DBS”. Here we used a totally implantable device capable of long-term recording and stimulation (Activa PC+S). We used signals from motor cortex electrocorticography (ECoG) to update DBS

stimulation. Specifically, we adjusted stimulation based on a previously identified narrowband gamma oscillation (~80 Hz) associated with involuntary hyperkinetic movements (dyskinesia). Dyskinesia can occur as a result of stimulation or medication.
Methods: We tested closed loop DBS in 2 PD patients who experience dyskinesia and are implanted with Activa PC+S. Stimulation changes were triggered either via an internal algorithm (both patients) or via streaming to an external computer (in 1 patient). For both patients we adjusted stimulation within a safe voltage range specified by the patient's neurologist. For each patient a threshold for gamma power was set. When gamma power exceeded this value, DBS voltage was reduced. When gamma power dropped below the threshold, voltage was increased. For 1 patient, clinical rating scales were obtained before the closed loop session started and every 20 minutes during the session. Patient symptoms were monitored with video recordings, accelerometry, electromyography, and commercially available wearable sensors.
Results: We implemented closed loop DBS in 2 patients experiencing dyskinesia during short runs of 10 minutes to 1 hour. For both patients we observed multiple instances where the algorithm appropriately adjusted the voltage in response to gamma power. For the longest run which occurred during dyskinesia there was an approximately 39% and 26% reduction in power usage for each patient respectively. For all sessions, there were no adverse effects.
Discussion: We have demonstrated the feasibility of implementing closed loop DBS in PD patients using an ECoG signal related to dyskinesia. In all our patients we had no adverse events and patients did not report any discomfort. We demonstrated a battery use reduction in our short sessions. We are currently testing clinical efficacy based on blinded clinical ratings. Future directions will test closed loop DBS in longer sessions (up to 1 week).
Keywords: Brain Initiative, ECoG, DBS, Parkinson's disease

Disclosures: **N.C. Swann:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); university has filed a preliminary patent related to this work. **C. de Hemptinne:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); university has filed a preliminary patent related to this work. **M.C. Thompson:** None. **S. Miocinovic:** None. **A. Miller:** None. **R. Gilron:** None. **J. Ostrem:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); university has filed a preliminary patent related to this work. **H.J. Chizeck:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); donation from medtronic. **P.A. Starr:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); university has filed a preliminary patent related to this worki.

Poster

211. Parkinson's Disease: Human Therapeutic Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 211.22/N5

Topic: C.03. Parkinson’s Disease

Support: NIH R01NS67371

Title: Information processing improves in Parkinson's disease patients following aerobic exercise

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Abstract: Objective: The aim of this project was to determine the impact of aerobic exercise training on information processing capabilities of Parkinson’s disease (PD) patients.
Background: Declines in information processing are well-documented in PD patients. While there is emerging evidence for the use of aerobic exercise to improve the motor symptoms associated with PD, its impact on non-motor functions, such as information processing are poorly understood. A two-choice reaction time (CRT) paradigm was used to evaluate information processing.
Methods: Sixty-one participants with idiopathic PD (Hoehn and Yahr stage (II-III) on medication) that did not have any medical or musculoskeletal contraindications to exercise completed this trial. Two types of aerobic exercise were completed, one in which cadence was augmented. Aerobic exercise was completed 3x/week for 8 weeks (50 min. sessions) within 60-80% of their heart rate reserve in both groups. A mobile device application was developed to assess CRT under a two-choice compatible paradigm. The interval between presentation of the stimulus and movement initiation was defined as the RT. Additionally, the interval between movement initiation and target acquisition was determined to be movement time (MT). Participants were assessed: 1) baseline, prior to any exercise intervention in the off medication state and 2) at the end of exercise treatment (EOT), also while off medication.
Results: Both median reaction time and median movement time were significantly faster at EOT compared to baseline values (5.2%; p=0.003 and 6.5%; p=0.02, respectively).
Conclusions: Aerobic exercise improved information processing and movement execution. Improved information processing, coupled with reduced bradykinesia, provide evidence that non-motor aspects of PD are amenable to change following the completion of an aerobic exercise intervention.

Disclosures: A. Rosenfeldt: None. **M. Miller Koop:** None. **J.L. Alberts:** None.

Poster

211. Parkinson's Disease: Human Therapeutic Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 211.23/N6

Topic: C.03. Parkinson’s Disease

Support: MnDRIVE Brain Conditions

NIH Grant NINDS 1P50NS098573

Title: The effects of dopamine replacement therapy on response inhibition in Parkinson's disease

Authors: *J. E. AMAN, E. L. TWEDELL, S. E. COOPER
Neurol. Dept., Univ. of Minnesota, Minneapolis, MN

Abstract: Parkinson's disease (PD) patients suffer from a variety of neuropsychiatric symptoms related to impulse control (Weintraub et al 2010) and impaired response inhibition (Gauggel et al 2004). Dopamine agonists have long been shown to improve motor function, yet their effect on inhibitory control has shown varied outcomes, with some reporting improved inhibition control while others show a detrimental effect on impulsiveness.
METHODS: Here, we looked to evaluate the effects of dopamine therapy on a response inhibition task in Parkinson’s disease patients. 7 PD patients in the off-meds state and 10 PD patients in the on-meds state were recruited to perform the task. Participants were presented with four possible targets on a monitor, one in each of the superior, inferior, right and left portions of the screen and a joystick-controlled cursor in the center. One of the four targets was then indicated as the correct target for which they needed to acquire. Following a variable time delay, the participant was given a go signal. Using the joystick, participants were instructed to move the cursor to the indicated target as quickly and accurately as possible. On pseudo-random trials, a stop signal was presented following the go signal, indicating to the participate to abort their movement. Reaction times were calculated as the time between the go signal and initial movement. Stop signal delay for each trial (SSD - time between go signal and stop signal) was determined by an adaptive algorithm based on response correctness of the previous trial. A stop signal reaction time (SSRT) was calculated across all trials as the difference between SSD (adjusted for correct response rate) and median reaction time and was taken as the outcome variable of interest as a measure of response inhibition.
RESULTS: Reaction times were lower in controls compared to PD patients off medication, which improved with medication. Distance traveled by the cursor until target acquisition was lowest in controls, showing a smoother excursion compared to PD patents. SSRT were shortest in controls and longest in the on medication state of PD patients. There was no statistically significant difference in SSRT between on and off medication states in PD patients.
CONCLUSIONS: These data indicate that PD patients were motorically worse and had impaired

response inhibition compared to controls. Dopamine replacement therapy improved PD patients motorically but, on average, showed no change in the response inhibition task, indicating no effect on response inhibition in PD patients on medication compared to off.

Disclosures: J.E. Aman: None. **E.L. Twedell:** None. **S.E. Cooper:** None.

Poster

211. Parkinson's Disease: Human Therapeutic Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 211.24/N7

Topic: C.03. Parkinson's Disease

Support: NIH R01 MH106173

Title: Dissecting the biophysical basis of local field potentials recorded from deep brain stimulation electrodes using patient-specific models

Authors: *N. MALING[1], S. F. LEMPKA[2], Z. BLUMENFELD[3], H. BRONTE-STEWART[3], C. C. MCINTYRE[1]
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Abstract: Clinical deep brain stimulation (DBS) technology is evolving to enable chronic recording of local field potentials (LFPs) which may prove useful as biomarkers of the disease state. However, little is known about the biophysical basis of these LFPs, or how the patient's unique brain anatomy and electrode placement impact these recordings. Therefore, we developed a patient-specific framework to theoretically analyze clinical DBS LFP recordings that was customized to the patient's anatomy, lead location, and physiology. We applied this patient-specific framework to a subject with Parkinson's disease implanted with a Medtronic Activa PC+S DBS system. We virtually reconstructed the subthalamic nucleus (STN) and DBS electrode location using the patient's magnetic resonance imaging data. The model STN was then populated with ~250,000 multi-compartment neuron models, distributed with histologically based densities, and time varying synaptic inputs were applied to each individual neuron. We used a finite element volume conductor model to represent the electrical properties of the DBS electrode and brain tissue medium. Finally, a reciprocity-based solution was used to simulate the LFPs generated by the STN model neurons. This patient-specific DBS LFP model enabled an examination of the role of sub-populations of highly synchronous STN neurons, primarily driven by beta-band inputs, on the recorded power spectrum. We used three bipolar pairs of experimental LFP recordings to combinatorially determine the best fit model parameters. The results show that incorporating patient-specific STN anatomy substantially impacted the simulated LFP compared to an idealized sphere of STN neurons. The primary determinant of

LFP amplitude was the spatial extent and degree of synchrony of the neuronal activity. Our model data best matched the experimental data with a 2.4 mm radius of synchronous neurons located in the dorsolateral region of the STN. Our patient-specific DBS LFP model results agree with previously published indirect electrophysiological estimates and assumptions about potential origins of beta oscillations. However, it also allowed us to dissect the LFP signal at both a network and cellular levels, while directly comparing our model results to experimental recordings. We believe this knowledge will be useful for analyzing and interpreting LFP recordings in clinical DBS applications.

Disclosures: **N. Maling:** None. **S.F. Lempka:** None. **Z. Blumenfeld:** None. **H. Bronte-Stewart:** None. **C.C. McIntyre:** None.

Poster

211. Parkinson's Disease: Human Therapeutic Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 211.25/N8

Topic: C.03. Parkinson’s Disease

Title: Precision deep brain stimulation: Defining the tractographic profile for maximal therapeutic benefit

Authors: W. KINDEL[1], J. ZYLBERBERG[1], *J. A. THOMPSON[2]
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Abstract: Parkinson’s disease (PD), a neurodegenerative condition resulting from the depletion of dopamine release in the striatum, causes devastating motor symptoms. When PD patients with significant motor fluctuations and dyskinesia are unresponsive to pharmacological treatments, deep brain stimulation (DBS) of the subthalamic nucleus (STN) can reduce these motor symptoms and improve function. In clinical practice, effective DBS requires precisely implanting an electrode in the STN and optimizing the stimulation parameters. Thus, finding an optimal DBS target is the crux of clinically effective DBS. Although DBS is targeted to individual basal ganglia nuclei, recent evidence suggests that adjacent white matter structures—activated via indirect stimulation— may also contribute to good therapeutic outcomes. However, it is not understood how modulation of subthalamic white matter fiber tracts contributes to either ameliorating PD motor symptoms or suboptimal suppression of adverse effects. Here, we present progress towards understanding how DBS target modulation impacts therapeutic outcomes by identifying the associations between stimulation parameters and tractographic circuity and their outcomes. Using a combination of diffusion tensor imaging (DTI), post-operative DBS MR analysis and stimulation programming data, we identify brain areas targeted by fiber tracts within tractography seeds based on modeling the volume of activated tissue centered on individual DBS

electrodes. In our initial analyses (n = 5 patients), we observe unique fiber populations that differentiate between stimulation parameters: those that induce sensory side effects (e.g., paresthesias) and those that trigger motor side effects (e.g., contractions). These activated fiber bundles differ in their tractographic profile (i.e., fiber number, fiber density, fractional anisotropy and mean diffusivity) as well as the brain areas in which they terminate. These results represent the first step in developing a tractographic-based model to inform which neural circuits optimally contribute to a good therapeutic outcome and minimize adverse-effect profile, ultimately eliminating the need for multiple trial-and-error sessions to optimize post-operative stimulation parameters. Moreover, we intend to build upon these results to enable surgeons to prospectively plan more precise targets for DBS implantation and stimulation.

Disclosures: W. Kindel: None. **J. Zylberberg:** None. **J.A. Thompson:** None.

Poster

211. Parkinson's Disease: Human Therapeutic Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 211.26/N9

Topic: C.03. Parkinson’s Disease

Support: NIH Grant R01NS67371

Title: Mobility during Timed-Up-and-Go improves following aerobic exercise training in individuals with Parkinson's disease

Authors: *M. MILLER KOOP[1], J. L. ALBERTS[2]
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Abstract: Objective: To determine if Timed-Up-and-Go (TUG) performance, quantified by an inertial measurement unit (IMU) from a mobile device, improved after aerobic exercise training in individuals with Parkinson’s disease (PD).
Background: PD decreases gait and turning stability, which could lead to falls, and reduced quality of life. The TUG was developed to quantify mobility and balance during turning, walking, sitting and standing. Utilization of IMU sensors to quantify movements during the TUG can increase the objectivity of the outcome measures. In this project, IMU data from a mobile device were used to quantify the impact of aerobic exercise training on mobility during the TUG.
Methods: Sixty-one participants with idiopathic PD (Hoehn and Yahr Stage (II-III) on medication) and that did not have any medical or musculoskeletal contraindications to exercise completed this trial. Two types of aerobic exercise were completed, one in which cadence was augmented. Aerobic exercise was completed 3x/week for 8 weeks (50 min. sessions) within 60-80% of their heart rate reserve in both groups. An iPad/iPhone mobile application was developed that utilized the embedded IMU to collect acceleration and rotational data to quantify the center

of mass movement in the medial-lateral (ML) and anterior-posterior (AP) planes and trunk rotation (TR) while the participant performed the TUG. Participants were assessed: 1) baseline, prior to any exercise intervention in the off medication state and 2) at the end of exercise treatment (EOT), also while off medication. A paired t-test or a Wilcoxon signed rank test was used to assess significant difference between performance metrics measured at baseline and EOT.
Results: Total trial time was significantly decreased by 6% (p=0.02), from baseline to EOT. In addition, the RMS of AP acceleration was significantly increased by 20% (p=0.01) during the turning phase of the TUG.
Conclusions: Overall mobility in participants with PD was significantly improved after aerobic exercise training, as evidenced by an average decrease in time to complete the TUG. Furthermore sensors from the mobile device showed mobility during turning was significantly improved after eight weeks of exercise as well. These results indicate that aerobic exercise training improves lower extremity motor function in PD patients. The use of mobile technology provides greater insight into specific effects of exercise on lower extremity function.

Disclosures: M. Miller Koop: None. **J.L. Alberts:** None.

Poster

211. Parkinson's Disease: Human Therapeutic Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 211.27/N10

Topic: C.03. Parkinson’s Disease

Title: Motor cortex plasticity and behavior improvement promoted by treadmill exercise in an initial phase of Parkinson disease rat model

Authors: *C. C. REAL[1], K. H. BINDA[1], P. C. GARCIA[1], C. D. CARNEIRO[2], D. FARIA[2], C. A. BUCHPIGUEL[2], L. R. G. BRITTO[1]
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Abstract: Parkinson's disease (PD) is the second most common eldery neurodegenerative disease, and promote disabilities. Exercise has been described as a good intervention for PD. The objective of this study was analyze if treadmill exercise protocol, a non-pharmacological tool, can promote plasticity in the motor cortex, area that excitability is altered in the PD. Then, rats were subjected to the unilateral PD model induced by striatal 6-hydroxydopamine and a treadmill exercise protocol (3x / week for 40 minutes). The behavioral responses was investigated with cylinder test in two moments of the study, before and 10 days after the induction of the PD model. The changes in structural and synaptic proteins were determined by immunostaining of synaptic proteins (synapsin and synaptophysin) and structural

(neurofilaments and MAP-2) 10 days after induction model of PD. The immunohistochemistry data were correlated with neurofunctional changes in motor cortex assessed by method of positron emission tomography (PET) marked with radiopharmaceuticals Fludesoxiglicose-(^{18}F) ([^{18}F]FDG), which assesses the activity of glucose in the brain of these animals. The data obtained so far in the project reveal that the treadmill exercise protocol is able to promote dopaminergic protection and neuroplasticity in motor cortex even after only 10 days of exercise. Our data showed that that was an improvement in motor behavior with decreased asymmetry in the cylinder test in animals injected with 6-OHDA and trained. In addition, there was a neuroprotective effect on dopaminergic neurons of the substantia nigra. The data from sedentary parkinsonism animals revealed an increased in the expression of MAP-2 in primary and secondary motor cortex, suggesting an excitability cortical increased, being reversed by the exercise protocol. In addition, the [^{18}F]FDG data corroborate the staining data and showed changes in the motor cortex between the groups. Thus, this study suggest that this exercise protocol could be normalize the cortical excitability, and improve the motor behavior that occur in initial phase.

Disclosures: **C.C. Real:** None. **K.H. Binda:** None. **P.C. Garcia:** None. **C.D. Carneiro:** None. **D. Faria:** None. **C.A. Buchpiguel:** None. **L.R.G. Britto:** None.

Poster

211. Parkinson's Disease: Human Therapeutic Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 211.28/N11

Topic: C.03. Parkinson’s Disease

Support: Deutsche Forschungsgemeinschaft (DFG) ME4197/2-1

Title: The inferior colliculus: An alternative structure for deep brain stimulation in Parkinson s disease?

Authors: *L. MELO-THOMAS[1], K.-A. ENGELHARDT[1], R. SCHWARTING[2]
[1]Philipps Univ. Marburg, Marburg, Germany; [2]Rainer Schwarting, Marburg, Germany

Abstract: The inferior colliculus (IC) is widely known as a midbrain auditory relay station. Additionally, IC has also been implicated in processing sensory-motor responses as demonstrated in the animal model of haloperidol-induced catalepsy. High-frequency (830Hz) deep brain stimulation (DBS) of the rat IC reduces haloperidol-induced catalepsy, which models akinesia of Parkinson`s disease, but clinical implication of this DBS type is limited since it is aversive. However, typical DBS stimulation frequencies range between 30-130Hz. We therefore asked whether low-frequency (30Hz) DBS of the IC can improve catalepsy without aversive side effects. Young adult rats were implanted with a stimulation electrode unilaterally into the central

nucleus of the IC. We determined individual escape threshold intensities during 830Hz DBS of the IC and then assessed the effects of 5min sub-chronic 30Hz DBS at individual escape thresholds on haloperidol-induced catalepsy (0.5mg/kg, i.p.) compared to a sham-stimulated control. We further assessed possible aversive side effects of our stimulation protocol in a conditioned place preference (CPP) test, using 4 conditioning trials. Sub-chronic 30Hz DBS of the IC strongly ameliorated haloperidol-induced catalepsy without any evidence of aversive behavior induced by the stimulation. In fact, in the CPP test we found that the preference for the 30Hz DBS-paired side increased after conditioning, indicating that our stimulation protocol was appetitive. The results show that the IC can serve as an alternative target for DBS in Parkinson's disease. DBS targeted at the IC might be even effective in reducing comorbid depression-related symptoms.

Disclosures: L. Melo-Thomas: None. **K. Engelhardt:** None. **R. Schwarting:** None.

Poster

211. Parkinson's Disease: Human Therapeutic Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 211.29/DP03/N12 (Dynamic Poster)

Topic: C.03. Parkinson's Disease

Title: Gait adaptation patterns in subjects with Parkinson's disease - a split belt treadmill study

Authors: E. ARAD[1], S. HASSIN-BAER[3,2], A. GRINBERG[1], *M. PLOTNIK[1]
[1]Ctr. of Advanced Technologies in Rehabil., [2]Movement Disorders Inst. and Sagol Neurosci. Ctr., Sheba Med. Ctr., Ramat Gan, Israel; [3]Fac. of Med., Tel Aviv Univ., Tel Aviv, Israel

Abstract: *Background:* Physiotherapy interventions using split belt treadmills (SBTM) have been proposed in order to improve gait in subjects with neurological disorders, commonly accompanied by profound gait asymmetry (GA; e.g., Parkinson's disease - PD). Comparative effects in conjugated SBTM conditions were not systematically reported. *Objective:* To systematically compare the adaptation effects caused by SBTM walking with respect to the type (increased\decreased speed) and the side of the manipulated belt in PD patients. *Methods:* Eight participants with PD (age: 62.3±9.95 yrs.) were tested. Baseline (BL) speed was individually defined based on over ground comfortable walking. For each participant, based on the severity of the disease's motor symptoms, the 'worst' side (WS) and the 'best' side (BS) were defined. All subjects performed four trials of SBTM walking presented in random order and separated by five min of seated rest periods. Each trial consisted of two minutes tied belt (TB) configuration, followed by five min of SB setting - either WS or BS belt's speed increased or decreased by 50% from BL speed value. Finally, the belts moved in TB configuration for additional three minutes. Carried over after effects between consecutive trials were negligible according to post hoc analysis. *Results:* Motor symptoms had asymmetric presentation, yet, step length values during

BL did not differ significantly between the BS and WS legs. The effect on step length and, in turn, induced GA in the early adaptation period (first 30 sec in the SB settings) was more pronounced in the 'decreasing speed' conditions. The mean values (± SEM) of the percentile change in GA, from BL, were 34.0±21.2% and 11.3±8.5%, when decreasing and increasing belt speed, respectively (nonparametric testing: *p=0.0078*; lumping both 'decrease' trials for comparison with both 'increase' trials). Further calculations showed that GA modification during the early adaptation period can be accounted for in part by the obvious differential leg excursion, and in addition by stance time alterations in the non-manipulated side. *Conclusions:* The present systematic analysis supports the notion that stronger adaptation effects can be obtained by decreasing one side belt's speed, rather than increasing the speed of the opposite belt, since for the first time, all four conditions were compared within subjects with PD, in reference to their natural over ground gait speed. Further research is warranted to study post adaption effects among persons with PD with apparent step length GA, in order to define optimal adaptation schemes to maximize the therapeutic effect of SBTM based interventions.

Disclosures: E. Arad: None. **S. Hassin-Baer:** None. **A. Grinberg:** None. **M. Plotnik:** None.

Poster

212. Molecular Mechanisms of Huntington's Disease

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 212.01/O1

Topic: C.04. Movement Disorders

Support: NIH/NINDS Grant R01NS084298

Hereditary Disease Foundation (HDF) Grant Leslie Gehry Brenner Award

Title: complement c3 deficiency modifies bachd disease phenotypes

Authors: *X. GU[1], D. WILTON[2], A. DAGGETT[1], C. LEE[1], B. A. STEVENS[2], X. YANG[1]
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Abstract: The complement system plays an important role in maintaining neuronal homeostasis including synaptic pruning during development and aging. Under disease conditions, such as in Alzheimer disease (AD), upregulation of the complement pathway leads to excessive synaptic loss and disease exacerbation. Our prior study showed complement activation is associated with synapse loss in multiple AD mouse models. Here we specifically test whether a genetic reduction of complement component 3 (C3) may alter the disease pathogenesis in BACHD, a well characterized human genomic transgenic mouse model of Huntington’s disease (HD). Our

ongoing study showed the genetic deletion of C3 in BACHD mice modifies several behavioral phenotypes and brain atrophy. Detailed analyses of synaptic and molecular phenotypes may further shed light on the possible mechanisms of disease modification by C3 deficiency. In summary, our study may provide further validation that C3 reduction could be a disease modifying mechanism for HD.
Fund: NIH/NINDS (R01NS084298); Leslie Gehry Brenner Award from Hereditary Disease Foundation (HDF)

Disclosures: X. Gu: None. **D. Wilton:** None. **A. Daggett:** None. **C. Lee:** None. **B.A. Stevens:** None. **X. Yang:** None.

Poster

212. Molecular Mechanisms of Huntington's Disease

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 212.02/O2

Topic: C.04. Movement Disorders

Title: Cortico-striatal phase-amplitude coupling in gamma genesis

Authors: *S. NAZE[1], J. HUMBLE[1], P. ZHENG[2], S. BARTON[3], G. V. REBEC[3], J. KOZLOSKI[1]
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Abstract: The increase in striatal local field potential (LFP) Gamma power observed in Huntington's Disease (HD) is an important phenotype in HD mouse models, and is consequently an important target for computational modeling. Gamma oscillations are observed in many brain regions across several functional contexts, and refining a model of Gamma genesis in HD may be necessary to elucidate specific disease mechanisms at the circuit level.
Here we analyze experimental data addressing relationships between simultaneous cortical and striatal oscillations using an algorithm to detect significant transient increases in Gamma power, which we term 'Gamma events'. We find: 1) cortical Delta oscillations are strongly synchronized across electrodes; 2) striatal Gamma events are phase locked to cortical Delta; 3) the distribution of inter-Gamma event intervals can arise from a Poisson-like process; and 4) Gamma event correlations across electrodes in striatum are highly variable.
Together, these findings suggest that segregated amplitude-modulated cortical Delta inputs may trigger striatal Gamma events, and do so more frequently in HD.
To address how interaction of neuronal populations generate such abnormal gamma within striatum, we simulated a network model of striatal fast spiking interneurons (FSIs) with realistic topological constraints and replicate these experimental observations. A critical component of

the model is the presence of gap junctions between FSIs; which are necessary for the emergence of Gamma oscillations within our FSI network. Our findings suggest that Gamma oscillations in HD may be due to abnormal gamma genesis caused by: 1) abnormally strong electrotonic coupling between FSIs, 2) abnormally strong cortical input, and/or 3) abnormally strong cortical-FSI coupling. Alternately, Gamma genesis may be ongoing in WT, but weakly detectable in LFP. In this case, Gamma detection may be increased in HD due to increased synaptic potentials at Gamma generating FSI synapses.

Disclosures: S. Naze: None. **J. Humble:** None. **P. Zheng:** None. **S. Barton:** None. **G.V. Rebec:** None. **J. Kozloski:** None.

Poster

212. Molecular Mechanisms of Huntington's Disease

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 212.03/O3

Topic: C.04. Movement Disorders

Title: Kinome Profiling of Neural Stem cells (NSC) derived from (induce pluripotent stem cells (iPSC) of Huntington's disease patient

Authors: *A. BAHARANI[1], E. SCRUTEN[2], S. NAPPER[3]
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Abstract: Primary cell lines derived from patients with Huntington Disease (HD) can be used to investigate physiologically relevant molecular aberrations in a cellular context. We used primary HD neuronal stem cells (NSCs), that were reprogrammed from induced pluripotent stem cells (iPSCs) isolated from an HD patient, as a model to investigate the signaling aberrations associated with HD pathogenesis. The primary HD cell lines we used were sampled from a 48-year old HD patient and characterized as having 56 polyglutamine (CAG) repeats. We utilized a custom-designed peptide array comprising 300 unique peptides corresponding to functionally annotated phospho-sites of known signaling intermediates. Lysates from primary HD cells and control human cells were applied on our peptide arrays and phosphorylation intensities corresponding to individual peptides quantified. The intra-array peptide replicate phospho-intensities were normalized and data presented as fold-change difference in peptide-specific phosphorylation between the HD cells and control cells. Our analyses led to the identification of various signaling intermediates that were differentially phosphorylated in HD cells compared to control cells. Using quantitative immunoblotting analyses, we validated a subset of the identified targets that included AKT1 Ser 473, LIMK1 Thr 508 and PTEN Thr 382 in HD cells. We confirmed that, in HD cells, the hypophosphorylation of AKT1 at Ser 473 led to increased phosphorylation of the AKT substrate, GSK3b at Ser 9. Further, we also validated the

hyperphosphorylation of PTEN at Thr 382, a phospho-site associated with promoting protein stability. Given that PTEN is a negative-regulator of AKT, our data suggest that the AKT signaling axis is negatively regulated in HD cells, leading to reduced neuronal cell survival. Likewise, we also validated LIMK1 Thr 508 as a hypophosphorylated phospho-site in HD cells. We further found that the hypophosphorylation of LIMK1 at Thr 508 led to hyper phosphorylation of the LIMK1 substrate, Cofilin at Ser 3. The deregulation of LIMK1 and Cofilin represents HD-specific pathway which is linked to disordered cytoskeletal dynamics. Taken together, our data identified key signaling proteins deregulated in HD cells which may be suggestive of a prognostic significance in HD pathogenesis.

Disclosures: A. Baharani: None. **E. Scruten:** None. **S. Napper:** None.

Poster

212. Molecular Mechanisms of Huntington's Disease

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 212.04/O4

Topic: C.04. Movement Disorders

Support: NIH/NINDS Grant 5U01NS082074

Title: NTRK2 as a modifier of frontal gray matter and cognition in prodromal Huntington disease

Authors: J. CIAROCHI[1], J. LIU[3], V. CALHOUN[3], J. BOCKHOLT[4], H. JOHNSON[4], M. MISIURA[1], J. LONG[4], S. PLIS[3], F. ESPINOZA[3], A. CAPRIHAN[3], V. VERGARA[3], *J. A. TURNER[2], J. PAULSEN[4]
[1]Neurosci., [2]Georgia State Univ., Atlanta, GA; [3]Mind Res. Network, Albuquerque, NM; [4]Univ. of Iowa, Iowa City, IA

Abstract: Huntington Disease (HD) is a heritable condition characterized by involuntary movements (chorea) and cognitive symptoms manifesting up to a decade before diagnosis. HD is caused by an expanded cytosine-adenine-guanine (CAG) repeat at an *HTT* exon 1 locus. Higher repeat-numbers confer younger onset and accelerated progression, but variability in age-of-onset is observed and is greater at lower CAG-numbers. Additional genetic factors may promote or suppress HD-conversion, and are likely reflected by differences in **prodromal** (pre-diagnosis) brain structure and clinical functioning.
Brain-derived neurotrophic factor (*BDNF*) co-localizes with HTT in brain regions and is necessary for proper cortico-striatal synaptic activity and the survival of **medium spiny striatal neurons (MSNs)**, the most vulnerable neuronal population in HD**.** BDNF is also a promising prodromal candidate; BDNF deficiency only modestly contributes to early-life MSN survival, but significantly reduces MSNs in later life (consistent with delayed-onset). Asymptomatic HD

transgenic mice have reduced striatal BDNF, and additional reduction lowers onset-age and worsens motor symptoms. Efforts to relate BDNF genotypes (such as Val66Met) to onset-age have produced mixed results; additional variation may be accounted for by other BDNF-signaling related genes.
Using data from the multi-side prodromal PREDICT-HD dataset, prodromal **gray matter concentration** (**GMC**) patterns were tested for correlations with genetic (**single nucleotide polymorphism,** or **SNP**) profiles using **parallel ICA (pICA)** with reference. pICA detected a frontal GMC profile that significantly correlated with a SNP profile highlighting *NTRK2*, the gene encoding BDNF's p75 receptor ($p < 0.001$). In individuals 2-4 standard deviations (SDs) above or below the mean *NTRK2* SNP profile level, the frontal GMC network significantly correlated with all three Stroop measures as well as the Symbol Digit Modalities Test (SDMT).

Disclosures: J. Ciarochi: None. **J. Liu:** None. **V. Calhoun:** None. **J. Bockholt:** None. **H. Johnson:** None. **M. Misiura:** None. **J. Long:** None. **S. Plis:** None. **F. Espinoza:** None. **A. Caprihan:** None. **V. Vergara:** None. **J.A. Turner:** None. **J. Paulsen:** None.

Poster

212. Molecular Mechanisms of Huntington's Disease

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 212.05/O5

Topic: C.04. Movement Disorders

Title: Cannabinoid signaling, modulation and risk in Huntington's disease

Authors: *J. HUMBLE, J. KOZLOSKI
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Abstract: Dysregulated cannabinoid signaling and the loss of cannabinoid receptors are important phenotypes of Huntington's disease (HD). The precise contribution that cannabinoid signaling has at the network level, if any, is unknown. To explore cannabinoid signaling we began by modeling a population of spiking neurons and synapses with cannabinoid signaling present. In the model, we found that cannabinoid signaling can function as a homeostatic control mechanism, permitting the adjustment of pre-synaptic neurotransmitter release such that excess neurotransmitter release is reduced. We termed the amount of excess neurotransmitter "headroom". Furthermore, the size of this headroom, and its dynamics and modulation, are potential risk factors. We therefore next used the model to quantify risk across different neurons in a population under different perturbation conditions in both WT and HD states.

Disclosures: J. Humble: None. **J. Kozloski:** None.

Poster

212. Molecular Mechanisms of Huntington's Disease

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 212.06/O6

Topic: C.04. Movement Disorders

Support: PO1NS092525

Title: TRiC reagents act through enhanced BDNF trafficking and signaling to both prevent and rescue HD phenotypes in BACHD portico-striatal cultures

Authors: X. ZHAO[1], X.-Q. CHEN[2], J. OVERMAN[3], A. LAU[4], W. CHIU[5], L. M. THOMPSON[6], *C. WU[7], W. C. MOBLEY[8]
[1]Dept. of Neurosciences, [2]UCSD, La Jolla, CA; [3]Neurobio. and Behavior, Univ. of California Irvine, Irvine, CA; [4]Univ. of California, Irvine, Irvine, CA; [5]Baylor college of Med., Houston, TX; [6]Psychiatry/Neurobiology and Behavior, Univ. California, Irvine, CA; [7]Neurosciences MC0624, UCSD Sch. of Med., La Jolla, CA; [8]Dept. of Neurosciences, Univ. of California San Diego Dept. of Neurosciences, La Jolla, CA

Abstract: Huntington disease (HD) is a neurodegenerative disorder caused by an expanded CAG repeat in the *huntingtin* (HTT) gene. Mutant Htt (mHTT) plays a central role in HD pathology. Among the many features of pathogenesis are defects in BDNF synthesis, trafficking and signaling. Our previous studies using primary neurons from the BACHD mouse model of HD recapitulated the striatal atrophy and decreased cortico-striatal synaptic connectivity that characterize HD pathology. Using a microfluidic cortico-striatal co-culture system we showed that decreased anterograde BDNF trafficking in the axons of cortical neurons was responsible. In recent studies, we have used the co-culture system to show that degeneration of the cortico-striatal circuit is progressive. Degeneration of striatal neurons begins as early as DIV5 and progresses through DIV21. Both striatal atrophy and reduced synaptic activity increase through DIV21. In ongoing studies, the ability of TRiC-inspired reagents treatment to prevent and rescue degenerative phenotypes is being explored.

Disclosures: **X. Zhao:** None. **X. Chen:** None. **J. Overman:** None. **A. Lau:** None. **W. Chiu:** None. **L.M. Thompson:** None. **C. Wu:** None. **W.C. Mobley:** None.

Poster

212. Molecular Mechanisms of Huntington's Disease

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 212.07/O7

Topic: C.04. Movement Disorders

Support: WW Smith Charitable Trust

University of the Sciences

Title: Prion-like transmission of mutant huntingtin aggregates in *Drosophila* brains

Authors: *K. M. DONNELLY, M. M. P. PEARCE
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Abstract: Huntington's Disease (HD) is an inherited neurodegenerative disorder caused by an autosomal dominant mutation in the gene that encodes the protein huntingtin (Htt). This mutation results in expansion of a polyglutamine (polyQ) region located near the N-terminus of the Htt protein. Expanded polyQ stretches prevent the Htt protein from folding properly and causes it to self-assemble into protein aggregates that are visible as dense, proteinaceous inclusions within neurons and glia in HD patient brains. Mounting evidence supports the hypothesis that mutant Htt aggregates and pathogenic aggregates associated with other neurodegenerative diseases (e.g. Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis) spread between cells in a manner similar to infectious prions. These aggregates can transfer to neighboring cells and there cause nucleated aggregation of native proteins. This "prion-like" transfer is thought to contribute to the progression of pathogenesis in neurodegenerative diseases. We have previously used the model organism *Drosophila melanogaster* to demonstrate prion-like transfer of mutant Htt aggregates from neurons to phagocytic glia in intact brains (Pearce et al., 2015, *Nat Commun*). These experiments use the Gal4-UAS and QF-QUAS binary expression systems to generate transgenic flies that express mutant and wild-type Htt proteins in independent cell populations in the same brain. Our studies also exploit the ability of mutant Htt aggregates to effect prion-like conversion of wild-type Htt expressed in "recipient" cells as a reporter for cytoplasmic entry of aggregates originating in "donor" cells. Applying a similar experimental paradigm, we have recently found that mutant Htt aggregates transfer from pre-synaptic olfactory receptor neurons (ORNs) to post-synaptic projection neurons (PNs) in the *Drosophila* brain. Remarkably, ORN-to-PN transfer of Htt aggregates requires the glial phagocytic receptor, Draper. These results indicate that mutant Htt aggregates can transfer between diverse cell populations in intact brains and suggest that phagocytic glia promote trans-synaptic aggregate transmission. A better understanding of the molecular mechanisms that allow pathogenic aggregates to spread through the brain will lead to the identification of novel therapeutic targets to combat these fatal disorders.

Disclosures: **K.M. Donnelly:** None. **M.M.P. Pearce:** None.

Poster

212. Molecular Mechanisms of Huntington's Disease

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 212.08/O8

Topic: C.04. Movement Disorders

Support: NIH Grant NS036232

NIH Grant NS101701

NIH Grant NS095279

National Natural Science Foundation of China Grant 91332206

Title: CRISPR/Cas9-mediated therapeutic effects in Huntington's disease mice

Authors: *S. YANG, R. CHANG, S. LI, X.-J. LI
Human Genet., Emory Univ., Atlanta, GA

Abstract: Although suppressing the expression of mutant huntingtin (mHTT) has been a therapeutic strategy to treat Huntington disease, considerable efforts have gone into developing allele-specific suppression of mHTT expression due to the fact that loss of Htt in mice can lead to embryonic lethality. It remains unknown whether depletion of HTT in the adult brain regardless of its allele could be a safe therapy. Here we report that permanent suppression of the endogenous expression of mHTT via CRISPR/Cas9 in the striatum of HD140Q knock-in mice can effectively deplete HTT aggregates and early neuropathology. The reduction of HTT expression in striatal neuronal cells in the adult HD140Q KI mice does not affect their viability, but alleviates their motor deficits. Our studies show that CRISPR/Cas9-mediated gene editing in a non-allele-specific manner can be used to efficiently and permanently eliminate polyQ expansion-mediated neuronal toxicity in the adult brain.

Disclosures: **S. Yang:** None. **R. Chang:** None. **S. Li:** None. **X. Li:** None.

Poster

212. Molecular Mechanisms of Huntington's Disease

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 212.09/O9

Topic: C.04. Movement Disorders

Support: Cure Huntington's Disease Initiative

Title: Multiple sources of aberrant calcium signaling in motor cortex pyramidal neurons from the Q175 mouse model of Huntington's disease

Authors: *C. A. BRIGGS, S. CHAKROBORTY, A. R. WEST, G. E. STUTZMANN
Neurosci., Rosalind Franklin Univ. of Med. and Sci., North Chicago, IL

Abstract: Huntington's disease (HD) is a genetic neurodegenerative disorder arising from abnormal expansion in CAG trinucleotide repeats within the *huntingtin* gene. This mutation induces the degeneration of corticostriatal networks via synthesis of mutant huntingtin protein. One consequence of this mutation may be network instability due to abnormal calcium signaling within cortical and striatal neurons. Studies in HD models have demonstrated specific calcium release abnormalities from the endoplasmic reticulum (ER), a large intracellular calcium store important for neuronal signaling and protein handling. This increased ER calcium release is thought to mediate the synaptic loss and defective corticostriatal circuit function which leads to the early-stage cognitive and motor deficits in HD. The current study used whole-cell patch clamp recordings and 2-photon calcium imaging to examine ryanodine receptor (RyR)- and voltage gated calcium channel (VGCC)-mediated calcium signaling in pyramidal neurons from primary motor cortical slices from aged (14-16 months old) wild-type (WT) and Q175 heterozygous knock-in mice. We found that neurons recorded from Q175 mice had greater RyR-calcium release evoked by caffeine (20 mM) exposure than WT control neurons. Similar elevations in calcium influx through VGCC were observed in neurons from Q175 mice following spike trains as compared to WT controls. Approximately 50% of cortical neurons (10 of 20 cells) from Q175 mice exhibited abnormally elevated RyR- calcium release (high responding), whereas the remaining 50% were similar to WT animals. High responding neurons in Q175 mice also exhibited increased frequency of spontaneous EPSPs (sEPSP) upon RyR-activation relative to WT controls. sEPSP amplitude was similar across groups as were passive and active membrane properties. These observations support the presence of widespread calcium mishandling in critical motor circuits in HD, and that drugs designed to normalize ER calcium signaling may be useful therapeutic agents for restoring corticostriatal transmission and alleviating the motor and cognitive symptoms of HD. Indeed, targeting the RyR may be a powerful strategy for restoring intracellular calcium homeostasis and motor network stability in early stage HD.

Disclosures: C.A. Briggs: None. **S. Chakroborty:** None. **A.R. West:** None. **G.E. Stutzmann:** None.

Poster

212. Molecular Mechanisms of Huntington's Disease

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 212.10/O10

Topic: C.04. Movement Disorders

Support: NIH Grant NS 38194

Title: A preliminary study on Rapamycin-regulated miRNA against huntingtin gene

Authors: *W. LIU[1], F. BOREL[2], Q. TANG[2], C. GREER[2], L. KENNINGTON[1], K. CHASE[1], M. DIFIGLIA[3], C. MUELLER[2], N. ARONIN[1]
[1]Med., UMass Med. Sch., Worcester, MA; [2]Gene Therapy Ctr., Univ. of Massachusetts Med. Sch., Worcester, MA; [3]MassGeneral Inst. for Neurodegenerative Dis., Massachusetts Gen. Hosp., Charlestown, MA

Abstract: Huntington's disease (HD) is caused by expansion of CAG trinucleotide repeats in the first exon of the HTT gene. Most HD patients carry one normal allele containing 6 to ~35 CAG triplets and a mutant, disease-causing allele containing >36 CAG triplets. The resulting mutant HTT protein causes selective loss of neurons. Currently, there is no efficient treatment available for HD. Here we present a preliminary study on Rapamycin-regulated artificial mi-RNA expression against HTT gene as a potential therapeutic strategy for HD. An AAV-based vector is designed to express mi-RNA against HTT gene under regulation of rapalogs. Preliminary results of the experiments show that expression of the artificial mi-RNA is very sensitive to the rapalog concentration from 32 nM to 500 nM (final concentration in medium). At 125nM, the expression increased by about 50 fold over the basal expression, and at 500 nM it increased to over 200 fold. It seems the effects did not increase significantly by above 500nM. Both *in vitro* and *in vivo* experiments show that artificial miRNA induced by rapalogs knocked down the target gene expression expectedly.
Keywords: Huntington disease, miRNA, Rapamycin, AAV

Disclosures: W. Liu: None. **F. Borel:** None. **Q. Tang:** None. **C. Greer:** None. **L. Kennington:** None. **K. Chase:** None. **M. DiFiglia:** None. **C. Mueller:** None. **N. Aronin:** None.

Poster

212. Molecular Mechanisms of Huntington's Disease

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 212.11/P1

Topic: C.04. Movement Disorders

Support: CHDI Foundation, Inc.

Title: Genetic reduction of ATM modifies transcriptional network and neuropathology in the zQ175 mouse model of Huntington's disease

Authors: *C. D. LEE, N. WANG, P. LANGFELDER, F. GAO, J. B. RICHMAN, S. HORVATH, G. COPPOLA, X. YANG
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Abstract: Among the myriad molecular pathways implicated in pathogenesis of Huntington's disease (HD), mitochondrial bioenergetics deficits, oxidative stress, and DNA damage have been consistently observed in HD patients as well as in cell and genetic mouse models of HD. However, it remains unclear whether these pathways are essential to aspects of neurodegenerative disease pathogenesis and hence should be pursued as targets for therapy. Ataxia telangiectasia mutated (ATM) is a central regulator of DNA damage response (DDR). Emerging evidence shows that the ATM signaling pathway is indeed dysregulated in neurodegenerative disorders, including AD and HD. Our study provides genetic and pharmacological evidence that reduction of ATM signaling can ameliorate mutant huntingtin (mHTT)-mediated toxicity in HD neurons and a mouse model. However, it remains unknown how mHTT causes aberrantly elevated ATM signaling and ATM inhibition mediates neuroprotection. In the current study, we extended our original observation of genetic reduction of Atm to another HD mouse model, zQ175 heterozygous mice (knock-in mice expressing endogenouse level of full-length mHtt). We observed that significantly elevated pATM and mono-ubiquitinated γH2AX in the brains of zQ175 mice compared to WT controls were robustly reduced in zQ175/$Atm^{+/-}$. Interestingly, we saw an unexpected increase, but not decrease of striatal mHtt aggregation in zQ175/$Atm^{+/-}$ compared to Q175 mice. However, this increased in mHtt aggregation did not translate to worsened Darpp-32 pathology. We took advantage of the well-established Htt CAG length-dependent networks from our previous study (Langfielder, 2016), which reported dysregulation of preserved gene coexpression network in zQ175 mice and HD patients, and demonstrated that reducing of Atm genomic dosage in zQ175 mice modestly but significantly rescue the transcriptomic deficit in 6m and 10m cortex. WGCNA analyses reveal one interesting module, which showed opposite transcriptional signals in zQ175/$Atm^{+/-}$ vs zQ175 alone. This module is enriched in presynaptic proteins, Wnt signaling and axon guidance molecules, and upstream regulator such as Mecp2, Fezf2, Satb2, Tgfbr1, and Calmodulin. This

module could be further explored to investigate the Atm heterozygosity effects on striatal transcriptional signals in Q175 mice. While further studies using independent methods are needed to validate these findings, our study shares molecular insights for ATM signaling in HD pathogenesis and substantiates that reducing ATM signaling may be a potential therapeutic target of HD.

Disclosures: C.D. Lee: None. **N. Wang:** None. **P. Langfelder:** None. **F. Gao:** None. **J.B. Richman:** None. **S. Horvath:** None. **G. Coppola:** None. **X. Yang:** None.

Poster

213. Ataxia

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 213.01/P2

Topic: C.04. Movement Disorders

Support: NIH Grant NS04496

NIH Grant NS069688

Title: Ankyrin-R is required for cerebellar Purkinje cell survival

Authors: *S. R. STEVENS, M. N. RASBAND
Neurosci., Baylor Col. of Med., Houston, TX

Abstract: Ankyrin (Ank) proteins, are found throughout the body and act as the primary link between the spectrin-based cytoskeleton and the cytoplasmic domain of many membrane-associated proteins. 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 AnkR can compensate for a loss of AnkG and cluster Na^+ channels at nodes of Ranvier. Additionally, multiple studies have indicated various neurological disturbances have disruptions in AnkR, 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 subsets of neurons, including cerebellar Purkinje cells. To elucidate the role of AnkR in these cells, we examined AnkR knockout mice ($AnkR^{pale/pale}$). We found $AnkR^{pale/pale}$ mice have progressive Purkinje cell degeneration marked by abnormal accumulation of beta-amyloid precursor protein (beta-APP) and calbindin-D, resulting in cell loss in aged mice. Additionally, gait analyses show ataxia in null animals. Interestingly, mutations of beta-III spectrin underlie spinocerebellar ataxia type 5 (SCA5), characterized by disrupted gait and progressive Purkinje cell degeneration, phenotypically similar to $AnkR^{pale/pale}$ mice. Although the precise molecular mechanisms underlying these changes remain unknown, our data confirms AnkR and beta-III spectrin interact

in the brain. Taken together, these data suggest AnkR plays an important role in stabilizing the spectrin cytoskeleton in Purkinje cells. Future studies using AnkR conditional knockout mice will further elucidate the role of AnkR in the nervous system.

Disclosures: S.R. Stevens: None. **M.N. Rasband:** None.

Poster

213. Ataxia

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 213.02/P3

Topic: C.04. Movement Disorders

Support: NIH Grant NS058901

Title: Altered excitability of the motor cortex in a mouse model of spinocerebellar ataxia type 8

Authors: *R. CARTER[1], G. CHEN[1], M. GRAY[1], J. D. CLEARY[2], T. S. REID[2], L. P. W. RANUM[2], T. J. EBNER[1]
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Abstract: Spinocerebellar ataxia type 8 (SCA8) is a progressive neurodegenerative disease resulting in marked cerebellar atrophy accompanied by progressive deterioration of numerous coordinated muscle movements, from gait to eye motion. In addition to ataxia, patients also display cognitive deficits associated with pathological changes in the cerebrum. Previous results have shown that there is a decreased inhibitory response to cortical stimulation of the cerebellar cortex in a mouse model of SCA8. Here, we wanted to investigate if this decreased inhibition is also present throughout the cerebral cortex, to potentially give a mechanism for the non-cerebellar deficits seen in SCA8 patients. To test this, we performed *in vivo* flavoprotein autofluorescence imaging, a surrogate for neuronal activation, in SCA8+ and littermate control mice. Mice were anesthetized with urethane, and we examined the fluorescence response in the motor cortex to either a single pulse stimulation or a 10Hz train stimulation. Flavoprotein responses to both stimulation paradigms were greatly increased and prolonged in SCA8+ mice compared to littermate control mice. Additionally, when we blocked GABAA receptors, the flavoprotein responses were increased for the littermate controls, but not in SCA8+ mice. This effect was also seen in peripheral electrical hindpaw stimulation, with a greater flavoprotein response observed in SCA8+ mice. We also performed viral vector injection of the calcium indicator, GCaMP6f, into the motor cortex of both SCA8+ and littermate control mice. Using two-photon microscopy, we observed a greater number of cells having spontaneous calcium transients in SCA8+ mice. Taken together, these results suggest an overall decrease of inhibition in the cerebral cortex of SCA8+ mice, mirroring the previous results in the cerebellum. Further

studies will be needed to assess if this is strictly due to decreased inhibition, or if there are other mechanism involved. Understanding how this contributes to the behavioral phenotype in these mice may lead to newer therapeutic strategies that can be developed to help treat SCA8.

Disclosures: R. Carter: None. **G. Chen:** None. **M. Gray:** None. **J.D. Cleary:** None. **T.S. Reid:** None. **L.P.W. Ranum:** None. **T.J. Ebner:** None.

Poster

213. Ataxia

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 213.03/P4

Topic: C.04. Movement Disorders

Support: National Ataxia Foundation

ABCD Charitable Trust

NIH Grant NS093287

Title: Bidirectional transcription at the PPP2R2B gene locus in spinocerebellar ataxia type 12

Authors: *P. P. LI, H. KHALED, D. D. RUDNICKI, R. L. MARGOLIS
Psychiatry, Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: Spinocerebellar ataxia type 12 (SCA12) is a neurodegenerative disease caused by a CAG repeat expansion in the gene *protein phosphatase 2 regulatory subunit Bbeta* (*PPP2R2B*). We tested the possibility that the repeat region of the *PPP2R2B* gene locus is bidirectionally transcribed. By strand-specific reverse transcription PCR (SS-RT-PCR) with linkered (LK) primers flanking the repeat in *PPP2R2B* exon 7, we detected expression of both a *PPP2R2B* transcript containing a CAG repeat and a *PPP2R2B* antisense (*PPP2R2B-AS*) transcript with a CUG repeat from the repeat locus. Using a similar protocol with RNA extracted from iPSCs derived from SCA12 patients, we detected expression of normal and expanded alleles from both sense and antisense transcripts. We conclude that sense and antisense *PPP2R2B* transcripts containing expanded repeats may have a role in SCA12 pathogenesis. Which of these transcripts is the predominant faction in neurotoxicity, and whether the effect is at the RNA or the protein level, remains to be determined.

Disclosures: P.P. Li: None. **H. Khaled:** None. **D.D. Rudnicki:** None. **R.L. Margolis:** None.

Poster

213. Ataxia

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 213.04/P5

Topic: C.04. Movement Disorders

Support: NIH F31

Title: Activation of alpha1 adrenergic receptors and mGluR1 receptors is required for attacks of motor dysfunction in a mouse model of episodic ataxia type 2

Authors: *A. VITENZON[1], E. TARA[2], H. SNELL[3], C. CHEN[3], K. KHODAKHAH[3]
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Abstract: Episodic ataxia type 2 (EA2) is a channelopathy that arises from mutations in the *CACNA1A* gene encoding for the α1 pore forming subunit of P/Q-type voltage-gated calcium channels. Patients with this disorder exhibit motor attacks in the form of ataxia, dyskinesia and dystonia, which are brought about by physical or emotional stress, or consumption of caffeine or alcohol. We used a well-established mouse model of EA2, *tottering*, to explore the mechanisms by which stressors trigger attacks. Because cerebellar Purkinje cells (PCs) are required for the expression of attacks in *tottering* mice, we recorded their activity in awake head restrained mice when they had attacks. We found that PCs exhibited high frequency burst firing during attacks independent of the stressor used. This finding suggested that the triggers might share a common mechanism to induce attacks. Previous work in *tottering* mice has shown that α1 adrenergic receptors play a role in stress-induced attacks. Thus, we explored whether stress, caffeine, and ethanol trigger attacks via activation of the noradrenergic system. Using a pharmacological approach we found that activation of α1 adrenergic receptors in the cerebellum by itself was sufficient to induce attacks. Moreover, we found that activation of α1 adrenergic receptors in the cerebellum was required for stress-induced attacks, but it was not implicated in caffeine or ethanol-induced attacks. We found however, that caffeine-induced attacks were blocked by mGluR1 receptor antagonists.
To delineate how activation of α1 adrenergic receptors and/or mGluR1 receptors in PCs could lead them to burst fire, we recorded spontaneous PC activity in acutely prepared slices. We found that bath application of the specific α1 agonist cirazoline increased PCs irregularity but didn't drive them to burst fire. Similarly, we found that increasing the affinity of mGluR1 receptors to glutamate using the positive allosteric modulator RO-674853 also increased PC irregularity but didn't cause them to burst. Interestingly however, we found that co-application of cirazoline and RO-674853 induced high frequency burst firing in *tottering* PCs. Taken together, our findings suggest that stress requires both activation of α1 adrenergic receptors and mGluR1

activity to
induce attacks, whereas caffeine requires the activation of mGluR1 receptors on PCs to induce attacks.

Disclosures: **A. Vitenzon:** None. **E. Tara:** None. **H. Snell:** None. **C. Chen:** None. **K. Khodakhah:** None.

Poster

213. Ataxia

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 213.05/P6

Topic: C.04. Movement Disorders

Support: NIH NINDS 2R37NS033123-14A1

NIH NINDS 5R21NS079852

Utah Neuroscience Initiative Collaborative Pilot Project Award

National Ataxia Foundation Post-doc Fellowship Award

Title: Deep cerebellar stimulation to treat degenerative cerebellar ataxias

Authors: *C. ANDERSON[1], A. D. DORVAL[2], S. M. PULST[3]
[2]Dept. of Bioengineering, [1]Univ. of Utah, Salt Lake City, UT; [3]Univ. of Utah Clin. Neurosciences Ctr., Salt Lake City, UT

Abstract: Background: Degenerative cerebellar ataxias, both Mendelian and sporadic in form, affect as many as 1 in 5,000 people worldwide, leading to motor symptoms including incoordination, tremor, and falls. Despite more than twenty years since the first ataxia-causing genes were found, treatment strategies are limited. Notwithstanding a large amount of etiologic variation, the various forms of degenerative cerebellar ataxia commonly share the loss of cerebellar Purkinje cells, a major source of input to the deep cerebellar nuclei. Thus, we have worked to develop an electrical stimulation-based approach based in the dorsal dentate nucleus, the major motor output from the cerebellum, to treat the motor symptoms of degenerative cerebellar ataxias.
Methods: We tested this therapeutic strategy in the Wistar Furth *shaker* rat, which first presents with a full-body cerebellar tremor, eventually progressing to a shaking ataxia, with frequent falling. We developed a methodology to directly quantify each of the above-mentioned primary symptoms in an operator-independent manner, enabling easy validation of symptom relief and comparison of stimulation parameters. We have bilaterally, stereotactically implanted a cohort of shaker rats with stimulating electrodes to test the hypothesis that electrical stimulation of the

dorsal dentate nucleus can reduce each of these motor symptoms, and we have quantified each symptom in comparison to wild type rats.
Results: We tracked the motor performance of cohorts of shaker and wild type Wistar Furth rats from 7 weeks, prior to the onset of symptoms, to 35 weeks, at which point Purkinje cells are almost totally lost and symptoms have stopped progressing, quantifying the progression of symptoms in comparison to unaffected animals. We tested a number of stimulation parameters in a cohort of young (~15 week) affected animals. We found that electrical stimulation at approximately 30 Hz most effectively reduced the then-primary symptoms tremor and falls, with a significant, but reduced effect with higher frequency stimulation. We further tested similar stimulation parameters in a cohort of aged (~30 week) affected animals, and we similarly found 30 Hz stimulation to be most effective in treating the then-primary symptoms of incoordination and falls.
Conclusions: Electrical stimulation of the dorsal dentate nucleus may provide a novel method for treating the motor symptoms of degenerative cerebellar ataxias.

Disclosures: C. Anderson: A. Employment/Salary (full or part-time):; University of Utah. **A.D. Dorval:** A. Employment/Salary (full or part-time):; University of Utah. **S.M. Pulst:** A. Employment/Salary (full or part-time):; University of Utah.

Poster

213. Ataxia

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 213.06/P7

Topic: C.04. Movement Disorders

Support: NIH Grant R01 DC015803 (DAM)

NIH Grant R01 NS083706 (JL)

Acoustical Society of America Stetson Scholarship for Phonetics and Speech Science (GAC)

Title: Disrupted vocalization production in a mouse model of spinocerebellar ataxia type 1

Authors: *G. A. CASTELLUCCI[1], D. A. MCCORMICK[2], J. LIM[3]
[1]Neuroscience, Linguistics, [2]Neurosci., [3]Genet., Yale Univ., New Haven, CT

Abstract: Spinocerebellar ataxias (SCAs) are a genetically heterogeneous but clinically similar group of disorders which share many neurological and pathological features, including ataxia and cerebellar Purkinje cell degeneration. Dysarthria and oral motor abnormalities affecting speech production are also common symptoms observed in patients with SCAs. Interestingly, knock-in mice expressing a mutant *Atxn1* gene with an expanded CAG trinucleotide tract -

similar to the gene variants which cause SCA type 1 in humans - also display stark abnormalities in the production of their ultrasonic vocalizations (USVs). Specifically, a majority of the knock-in mice fail to produce USVs altogether, despite a lack of gross motor defects. Additionally, knock-in mice that vocalize show a reduction in call duration and call sequence duration similar to what has been reported for heterozygous *Foxp2* knockout mice (Castellucci *et al., Sci Rep*, 2016), implicating a shared cerebellar mechanism for the observed vocal defects. Finally, knock-in mice were also found to exhibit an abnormally high degree of variability in the normally stable coordination between phonation onset and the onset of exhalation during USV production, demonstrating that vocal motor coordination is disrupted by mutant *Atxn1* expression. Further investigations of the cellular and molecular basis of the disrupted vocal motor coordination in *Atxn1* knock-in mice is underway, but our preliminary findings suggest that these mice may provide a useful model in which to study the mechanisms of disrupted speech motor coordination in patients with SCA1, as well as the role of the cerebellum in speech and general mammalian vocalization production.

Disclosures: G.A. Castellucci: None. **D.A. McCormick:** None. **J. Lim:** None.

Poster

213. Ataxia

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 213.07/P8

Topic: C.04. Movement Disorders

Support: JSPS KAKENHI

Title: Evaluation of microstructural alterations in spinocerebellar ataxia type 6 by neurite orientation dispersion < density imaging

Authors: *A. YOSHIDA[1], K. SHIMOJI[2], A. UEMATSU[3], I. YABE[4], H. SASAKI[4], M. TANAKA[3]
[1]RIKEN, Kobe, Japan; [2]Radiology, Tokyo Metropolitan Geriatic Hosp., Tokyo, Japan; [3]Physiol., [4]Neurol., Hokkaido Univ. Sch. Med., Sapporo, Japan

Abstract: Spinocerebellar ataxia type 6 (SCA6) is one of the autosomal dominant spinocerebellar ataxia, and is characterized by selective degeneration and loss of Purkinje cells in the cerebellum. Although SCA6 can be definitely diagnosed by genetic testing, MR imaging can narrow down the candidate and might become a biomarker. Neurite orientation dispersion and density imaging (NODDI) is one of the non-Gaussian diffusion images and proposed model that a tissue for each voxel is consist of intra-cellular, extra-cellular, and cerebrospinal fluid (CSF) compartments, and considered to be detect the microstructural changes more specifically. One of its characteristics is to permit the characterization of microstructural integrity gray matter (GM).

However, there are few sensitive techniques to detect changes in GM selectively. The purpose of this work was to develop a new technique for analyzing GM (GM-based spatial statistics (GBSS)) like Tract-based spatial statistics (TBSS) and to examine the possibility of it to detect the microstructural alteration in SCA6.
We acquired MR images of the brain in 12 SCA6 patients and 12 age- and sex-matched healthy controls with a 3T MRI scanner. 3D T1 images were acquired. Diffusion images were obtained with b-values of 0, 1000, and 2000 s/mm2 (32 MPG). NODDI images, intra-cellular volume fraction (Vic), isotropic volume fraction (Viso), and orientation dispersion index (ODI), were calculated by matlab toolbox. The following steps were performed by tools in FSL 5.0.9. We used 3DT1WI to create a mean GM skeleton, a GM skeleton mask, and a distance map. FAST (automated segmentation tool) was run on 3DT1WI to segment into different tissues (GM, WM, and CSF). Applywarp was performed using the output from FNIRT to apply the registration matrix to the segmented 3DT1WI in the MNI152 space. The mean of all applywarped GM images was created, and it was then fed into to generate a mean GM skeleton and a GM skeleton mask. A distance map was created from the skeleton mask and used in the projection of parameters onto the skeleton. Values on parameter images were projected onto the skeleton. Voxel-wise statistics across subjects on the skeleton space was performed using a permutation test for group differences between patient and control groups (5000 permutations) using threshold-free cluster enhancement (TFCE) ($P < 0.05$), corrected for multiple comparisons. NODDI detected significant increase of ODI and Viso only in SCA6 cerebellar GM. It also decreased significantly of Vic.
Our results show NODDI can detect the alteration in the cerebellar GM in SCA6. This suggests that NODDI with GBSS is useful for evaluating microstructural changes in SCA6.

Disclosures: **A. Yoshida:** None. **K. Shimoji:** None. **A. Uematsu:** None. **I. Yabe:** None. **H. Sasaki:** None. **M. Tanaka:** None.

Poster

213. Ataxia

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 213.08/P9

Topic: C.04. Movement Disorders

Support: A-T Children's Project

Action for A-T

Title: Modeling the Neurological Phenotype of Ataxia-telangiectasia

Authors: *A. TEWARI, K. KHODAKHAH
Dominick P. Purpura Dept. of Neurosci., Albert Einstein Col. of Med., Bronx, NY

Abstract: Ataxia-telangiectasia (A-T) is a multisystem disorder caused by an autosomal recessive mutation in the *Atm* gene. ATM plays a prominent role in DNA repair and loss of this protein has devastating consequences in patients. Even though the gene implicated in this disorder has been known for over two decades, the mechanisms underlying the dysfunction of ATM that causes A-T remains unknown. This has been hampered by lack of an animal model that recapitulates the major neurological symptom exhibited by A-T patients, ataxia. A common feature in all the genetic mouse models is the targeted disruption of ATM during early embryonic development. We hypothesized that due to a crucial requirement of ATM during development; there may be compensatory proteins and/or mechanisms in place to replace ATM in the event of dysfunction. To address this, we used short-hairpin RNAs (shRNAs) and Crispr-Cas9 to acutely knock down ATM in the cerebellum of adult mice to avoid developmental compensatory mechanisms. Our results demonstrate that ATM knockdown in the adult rodent cerebellum is sufficient to recapitulate the two neurological hallmarks of A-T, ataxia and cerebellar atrophy. To understand alterations in cerebellar circuitry that contribute to the ataxia seen in A-T, we recorded from the cerebellum of awake head-restrained mice and found that there is a significant increase in the irregularity of firing of Purkinje cells (PCs) and cells in the deep cerebellar nuclei (DCN). Furthermore, our results demonstrate that ataxia was associated with irregular cerebellar output caused by changes in the intrinsic activity of Purkinje cells (PC). This animal model will allow further studies to determine how loss of ATM leads to degeneration of PCs and ataxia.

Disclosures: A. Tewari: None. **K. Khodakhah:** None.

Poster

213. Ataxia

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 213.09/P10

Topic: C.04. Movement Disorders

Title: Programming Mathematica and Python to quantify cerebellar Purkinje dendritic length and soma count

Authors: D. E. NGUYEN[1], E. F. BURR[1], T. PHILLIPS[2], *S. LAGALWAR[3]
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Abstract: Spinocerebellar Ataxia type 1 (SCA1), caused by expansion of the polyglutamine-repeat tract in ataxin-1 (ATXN1), results in neurodegeneration of cerebellar Purkinje cells (PCs) prior to progression into the brain stem, cranial nerves and spinal cord. Initial symptomology features deficits in motor coordination and balance. The transgenic mouse line B05 models the PC component of SCA1 through PC-selective overexpression of polyglutamine-expanded

ATXN1. Typical assessment of neurodegeneration in the B05 line include PC soma counts and molecular layer thickness, a measure of dendritic arbor extension. Both measures can be visualized with calbindin staining. Alternatively, ATXN1 serves as a marker of PC nuclei, allowing for easy discrimination of individual PCs. Dendritic length and soma counts from obtained confocal z-stack images are currently scored manually, potentially introducing variability in measurements between images, subjects and scorers. To minimize this potential error, we have recently written programs in Python and Mathematica to compute PC dendritic length and soma numbers. Machine learning capabilities will be applied to advance the program's ability to accurately analyze images. Additionally, we have written a Mathematica program to identify and quantify polyglutamine expanded ATXN1 protein aggregates that accumulate in cultured cells following over-expression. This program is valuable for applications involving identification and/or tracking of different species of aggregates based on size or conformation (oligomeric vs fibrillar, for example). We will be presenting our programming work at the meeting and welcome discussion with others who have written similar programs. We plan to ultimately make our programs available for public use, which is why we have chosen to write in Python and Mathematica.

Disclosures: D.E. Nguyen: None. **E.F. Burr:** None. **T. Phillips:** None. **S. Lagalwar:** None.

Poster

213. Ataxia

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 213.10/Q1

Topic: C.04. Movement Disorders

Title: Motor behavior decline and cerebellar pathology in mouse model of spinocerebellar ataxia type 1

Authors: *C. G. JANUS, G. GIRALDO, S. ARMINANA, R. MANEK, A. COOMES, E. RODRIGUEZ-LEBRON
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Abstract: Spinocerebellar ataxia type 1 (SCA1) is a disorder characterized by progressive movement impairment. SCA1 patients suffer from poor motor coordination and imbalance, but progression of the disease often leads to muscle atrophy, speech difficulties, and cognitive impairment. The disorder is caused by a mutation in the *ATXN1* gene that involves replication of a DNA segment containing CAG (Cytosine, Adenine, Guanine) trinucleotide. In SCA1, this segment is repeated 40 to 80 times, in contrast to up to 40 repeats in normal, healthy individuals. In our study we characterized the motor phenotype of a knock-in (KI) mouse model of SCA1 maintained on C57BL/6 background. In this KI model an additional 154 CAG repeats were inserted into the locus of the endogenous mouse *ATXN1* gene. Preliminary studies revealed

phenotypes that replicated some pathological facets of SCA1 disorder in humans. In our study, we characterized the motor phenotype of the model. The mice were subjected to a battery of tests evaluating the motivation and fluidity of spontaneous motor behavior (beam traversing test), and were challenged in forced motor balance test (Rota-Rod test). The tests were administered at the early and late stages of pathology development in order to identify the age-related changes in motor behavior decline. The analysis of brain pathology at the stage of severe motor impairment revealed abnormal intra-neuronal inclusions, increased vGLUT2 activity in the granule cell layer of the cerebellum, and increased pro-inflammatory activation of SCA1-KI mice as compared to their wild type control littermates. Our results also revealed that impairments in challenging Rota-Rod test presented more reliable predictors of progressing brain pathology in the model.

Disclosures: C.G. Janus: None. **G. Giraldo:** None. **S. Arminana:** None. **R. Manek:** None. **A. Coomes:** None. **E. Rodriguez-Lebron:** None.

Poster

213. Ataxia

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 213.11/Q2

Topic: C.04. Movement Disorders

Support: JSPS KAKENHI 16J40095

JSPS KAKENHI 26242085

Title: A mutation of the spinocerebellar ataxia gene CACNA1G induces cerebellar Purkinje cell death and ataxia in mice

Authors: *Y. MATSUDA[1,2], H. MORINO[1], T. KURASHIGE[3], T. MATSUOKA[4], Y. SOTOMARU[5], K. HASHIMOTO[4], H. KAWAKAMI[1]
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Abstract: Spinocerebellar ataxia type 42 (SCA42) exhibits progressive ataxia and cerebellar atrophy. SCA42 is an autosomal dominant neurodegenerative disorder caused by a mutation in the *CACNA1G* gene, which encodes the calcium channel, $Ca_V3.1$. We have reported that we performed linkage analysis and exome sequencing of Japanese families with autosomal dominant SCA and identified *CACNA1G* as a causative gene. The most patients exhibited a pure form of cerebellar ataxia, and the other two of them further showed prominent resting tremor. The purpose of this study is to evaluate the induction of pathology by the *CACNA1G* mutation.

$Ca_V3.1$ is classified as a low-threshold voltage-dependent calcium channel (T-type) and is expressed in central nervous system, especially in cerebellum and thalamus. The identified mutation p.Arg1715His was located at segment 4 of repeat IV, the voltage sensor of the $Ca_V3.1$. Similar to the wild type, the mutant $Ca_V3.1$ transfected into HEK293T cells showed normal distribution to the plasma membrane. Electrophysiological analyses revealed that the membrane potential dependency of activation and inactivation shifted toward a positive potential in the mutant $Ca_V3.1$. We successfully developed knock-in mice harboring the same mutation. Motor performances were initially normal, but the mice began to show time latencies in rotor-rod tests and beam-walking tests around one year after birth. Morphological analysis revealed signs of the cerebellar Purkinje cell (PC) degeneration. This knock-in mouse could be a much-needed SCA animal model, which enables us to explore the roles of Ca^{2+} signaling pathway in the death of PCs in SCA.

Disclosures: Y. Matsuda: None. **H. Morino:** None. **T. Kurashige:** None. **T. Matsuoka:** None. **Y. Sotomaru:** None. **K. Hashimoto:** None. **H. Kawakami:** None.

Poster

213. Ataxia

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 213.12/Q3

Topic: C.04. Movement Disorders

Support: NINDS NS085054

Title: Addressing both aberrant spiking and increased dendritic excitability is necessary for sustained improvement in motor dysfunction in spinocerebellar ataxia type 1

Authors: *D. BUSHART[1], R. CHOPRA[2], V. SINGH[5], G. G. MURPHY[3], H. WULFF[6], V. G. SHAKKOTTAI[4]
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Abstract: The intersection between neuronal dysfunction, motor impairment, and neurodegeneration remains poorly understood. This is evident in spinocerebellar ataxias, a group of neurodegenerative disorders affecting the cerebellum and its associated pathways. Recent studies illustrate that aberrant neuronal excitability contributes to motor impairment and may drive neurodegeneration in cerebellar ataxias. However, it is unclear whether changes in somatic and dendritic membrane excitability contribute independently to motor impairment and dendritic atrophy. Previously, we have illustrated that cerebellar Purkinje neuron membrane excitability is altered in ATXN1[82Q] mice, a well-established mouse model of spinocerebellar ataxia type 1

(SCA1). In ATXN1[82Q] Purkinje neurons, reduced expression and function of large conductance calcium-activated (BK) and G-protein coupled inwardly-rectifying (GIRK1) potassium channels results in loss of repetitive spiking and abnormal depolarization of the membrane. Additionally, loss of these channels results in increased dendritic excitability. In order to de-lineate how these changes in somatic and dendritic membrane excitability contribute to motor impairment and dendritic degeneration, we first identified ion-channel modulators which target aberrant ATXN1[82Q] Purkinje neuron excitability. When applied together, activators of small conductance calcium-activated potassium (SK) channels and baclofen (indirect GIRK1 activator through $GABA_B$) restore spontaneous spiking to depolarized ATXN1[82Q] Purkinje neurons. These compounds also improve motor function in ATXN1[82Q] mice in the short-term. However, long-term motor impairment and dendritic degeneration persist when somatic spiking alone is targeted through these compounds. We illustrate that compounds which improve not only somatic spiking but also reduce dendritic hyperexcitability provide sustained improvements in motor dysfunction in ATXN1[82Q] mice. Surprisingly, the same compounds act on different targets in the dendrite and cell body to improve alterations in membrane excitability. These results highlight the importance of considering compartment-specific changes in membrane excitability when designing therapies to treat neurodegenerative disorders.

Disclosures: D. Bushart: None. **R. Chopra:** None. **V. Singh:** None. **G.G. Murphy:** None. **H. Wulff:** None. **V.G. Shakkottai:** None.

Poster

213. Ataxia

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 213.13/Q4

Topic: C.04. Movement Disorders

Title: Impact of altered expression of excitatory amino acid transporter on intrinsic spontaneous activity of cerebellar Purkinje cells - Possible contribution to the pathophysiology of Niemann-Pick disease type C1?

Authors: *M. RABENSTEIN, A. ROLFS, M. J. FRECH
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Abstract: Niemann-Pick disease Type C1 (NPC1) is a rare progressive neurodegenerative disease caused by mutations in the NPC1 gene. Mutations lead to an impaired lipid transport resulting in an accumulation of cholesterol and gangliosides in late endosomes and lysosomes. The pathogenic mechanisms ultimately leading to neurological manifestations caused by neuronal dysfunction and cell death are not exactly understood. Of special interest is the

degeneration of the cerebellar Purkinje cells (PCs) leading to ataxia. An altered intrinsic activity of the PCs could precede the degeneration, resulting in ataxia. Alterations in the pattern distribution of intrinsically generated action potentials were described for groups of other hereditary ataxia, namely spinocerebellar ataxia and episodic ataxia. The generation of the intrinsic pace maker activity of PCs is modulated by synaptic input from neurons, as well as feedback from glia cells. In regards of synaptic transmission, the impact of excitatory amino acid transporters (EAATs) is of especial interest. Reduced cerebellar EAAT protein levels were described in NPC1 and spinocerebellar ataxia, possibly contributing to PC degeneration.
To date only a few electrophysiological studies where done to determine intrinsic or synaptic alterations of PCs in NPC1 and no data are available in regards of alterations in the pattern distribution of the intrinsic activity and the impact of EAATs on PCs.
Therefore we checked if the cerebellar protein levels of EAAT1, EAAT2 and EAAT4 and found reduced levels of these in NPC1 deficient mice.
Based on this we recorded the intrinsic activity of PCs in NPC1 deficient and control mice, by means of patch clamp recordings, and checked the influence of EAAT inhibition on the activity patterns. We found three types of activity pattern: tonic firing, burst firing and inactive. Significantly more PCs were active in a tonic manner in NPC1 deficient mice and more PCs in the control group showed burst firing pattern or were inactive. The tonically firing PCs in NPC1 deficient mice showed a significantly reduced firing frequency and a significantly higher spike regularity. Inhibition of the EAATs showed different effects on the activity pattern between NPC1 deficient and control mice, supporting the idea that a hampered EAAT function contributes to the altered PC activity in NPC1 deficient mice.
In conclusion, reduced EAAT expression in NPC1 could affect the intrinsic spike generation of PCs due to a reduced removal of glutamate possibly leading to ataxia and later to PC death due to excitotoxicity. This marks the EAATs as interesting targets for pharmacological intervention.

Disclosures: **M. Rabenstein:** None. **A. Rolfs:** None. **M.J. Frech:** None.

Poster

213. Ataxia

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 213.14/Q5

Topic: C.04. Movement Disorders

Support: FARA Center of Excellence Grant (DL)

FARA New Investigator Grant (JM)

CHOP Foerderer Grant for Excellence (HL)

Title: Frataxin deficiency impairs IP3R-coupled ER-mitochondrial signaling in cerebellum of Friedreich ataxia mouse models

Authors: H. LIN[1], S. H. HALAWANI[1], D. M. MALIK[2], A. RATTELLE[1], E. M. CLARK[2], Y. DONG[1], J. MAGRANE[3], *D. R. LYNCH[2]
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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 deficiency of frataxin and mitochondrial dysfunction in patients. RNA-sequencing analysis in FRDA patient fibroblasts identify abnormal upregulation of type III IP3R, a calcium release channel from the endoplasmic reticulum (ER) coupled with mitochondrial calcium signaling, as a potential biomarker for FRDA patients (Butler, Napierala, Lynch, unpublished observation). IP3Rs and ER-mitochondria contact have been implicated in spinocerebellar ataxia and neurodegeneration, but their association with FRDA cerebellar pathology remains unknown. Using both the frataxin knock-in/knockout (KIKO) and the inducible frataxin shRNA knockdown (siKD) FRDA mouse models, we examined if IP3R-coupled ER-mitochondria signaling pathways are altered in cerebellum of FRDA mice using immunohistochemistry, Western blot and co-immunoprecipitation assays. Immunohistochemical studies show high abundance and predominant expression of type I and III IP3R (IP3R1 and IP3R3) in the soma and dendrites of cerebellar Purkinje neurons in normal mice. Co-immunoprecipitation assays show that IP3R1 and IP3R3 interact with the mitochondrial chaperone protein GRP75 and the outer membrane protein VDAC1, demonstrating IP3Rs/GRP75/VDAC1 signaling pathways in mouse cerebellum. Western blotting and immunohistochemical studies show reduction of IP3R1 and IP3R3 in cerebellar homogenates and in the soma and dendrites of cerebellar Purkinje neurons in KIKO FRDA mice compared with age-matched controls. Co-IP assays further show interactions between IP3Rs and GRP75 are markedly decreased, whereas their interactions with VDAC1 are increased in cerebellar homogenates of KIKO mice, suggesting that dysregulated IP3R-coupled ER-mitochondrial calcium signaling in cerebellar Purkinje neurons may contribute to cerebellar dysfunction and ataxia in FRDA. Dysregulation of IP3R1 and its signaling with GRP75 and VDAC1 in cerebellum of siKD mice further supports impairment of IP3R-coupled ER-mitochondrial signaling in FRDA mouse cerebellum. Our findings thus suggest that frataxin deficiency impairs IP3R-coupled ER-mitochondrial signaling in cerebellar Purkinje neurons, which may contribute to cerebellar dysfunction and ataxia in FRDA patients.

Disclosures: H. Lin: None. **S.H. Halawani:** None. **D.M. Malik:** None. **A. Rattelle:** None. **E.M. Clark:** None. **Y. Dong:** None. **J. Magrane:** None. **D.R. Lynch:** None.

Poster

213. Ataxia

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 213.15/Q6

Topic: C.04. Movement Disorders

Support: NAF Post-Doctoral Research Grant

Title: Increased dendritic excitability drives Purkinje neuron dendrite degeneration in cerebellar ataxia

Authors: *R. CHOPRA[1], D. D. BUSHART[2], S. M. PULST[3], A. H. WASSERMAN[2], C. I. DE ZEEUW[4], V. G. SHAKKOTTAI[2]
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Abstract: Degenerative cerebellar ataxias are a heterogeneous group of progressive conditions which present with motor incoordination linked to neurodegeneration in the cerebellum and associated pathways. In degenerative cerebellar ataxias, Purkinje neurons undergo progressive simplification and degeneration of the dendritic arbor prior to cell loss. Although dendritic degeneration strongly correlates with motor impairment in many models of cerebellar ataxia, the mechanisms behind this pathologic dendritic remodeling are not well understood.
In a mouse model of the inherited ataxia spinocerebellar ataxia type 1 (SCA1), we investigated the hypothesis that Purkinje neuron dendritic degeneration is a result of alterations in dendritic membrane excitability. Whole-cell patch clamp recordings in the soma and dendrite suggest that SCA1 Purkinje neuron dendrites are more excitable throughout the course of dendrite degeneration. This dysfunction of dendritic membrane excitability is observed in association with reduced expression of several potassium channels, and a treatment strategy targeting these channels normalizes dendritic excitability, acutely improves motor performance, and prevents dendrite degeneration. These data suggest that dysfunctional dendritic excitability is a driver of pathologic dendritic remodeling.
In our efforts to identify a downstream effector which might link altered intrinsic dendritic excitability to pathologic remodeling, we identified a progressive increase in protein kinase C (PKC) activity. Increased PKC activity in SCA1 Purkinje neurons was dependent on calcium entry, suggesting that the observed increase in PKC activity might be downstream of altered dendritic membrane excitability. SCA1 mice were crossed to mice expressing a PKC inhibitor peptide in Purkinje neurons (PKCi mice), and surprisingly SCA1xPKCi mice showed accelerated dendritic degeneration. Importantly, SCA1xPKCi mice showed impaired dendritic electrical shunting relative to SCA1 littermate controls, further supporting the observed link between

increased intrinsic dendritic excitability and pathologic dendritic remodeling. These results suggest that reducing dendritic membrane excitability may be an important therapeutic target in SCA1 and potentially other degenerative ataxias. These results also provide compelling evidence for dendritic ion channel activity being a critical determinant of dendritic structural remodeling in disease, which adds to the literature that has suggested that dendritic ion channels may be a critical therapeutic target across a range of neurodegenerative diseases.

Disclosures: R. Chopra: None. **D.D. Bushart:** None. **S.M. Pulst:** None. **A.H. Wasserman:** None. **C.I. De Zeeuw:** None. **V.G. Shakkottai:** None.

Poster

213. Ataxia

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 213.16/Q7

Topic: C.04. Movement Disorders

Support: NIH Grant NS083706

Title: Investigation of the contribution of ATXN1 phosphorylation on cerebellar pathology in SCA1

Authors: *J. LEE[1], T. M. DRIESSEN[2], H. T. ORR[3], J. LIM[2]
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Abstract: Spinocerebellar ataxia type 1 (SCA1) is a progressive neurodegenerative disease caused by an expanded polyglutamine repeat in Ataxin-1 (ATXN1), and results in progressive ataxia, cognitive impairment, dysarthria, and respiratory failure. Degeneration of neurons, specifically in the cerebellum and brain stem, is a hallmark of SCA1, though the underlying mechanisms of degeneration remain unknown. In a previous study, we examined the role of Nemo-like kinase (NLK), a serine/threonine kinase, on SCA1 disease pathogenesis. Constitutive heterozygous *Nlk* mice crossed with a Sca1 knock-in mouse model displayed suppressed cerebellar neuropathological phenotypes, indicating that loss of *Nlk* may partially rescue SCA1 disease phenotypes. This partial rescue may be mediated by decreased phosphorylation of ATXN1. ATXN1 is known to be phosphorylated at several sites *in vivo*, including serine 239. When serine 239 was mutated to alanine (S239A), the NLK-mediated pathogenic effects on SCA1 were significantly reduced in our cell culture system. To further examine these effects *in vivo*, we developed the S239A transgenic mouse model, which expresses polyglutamine expanded ATXN1 specifically in Purkinje cells. We examined the effect of the S239A mutation on cerebellar neuropathology by measuring changes in the molecular layer thickness and quantification of Purkinje cell numbers. We also analyzed molecular phenotypes in this mouse model. Collectively, these data will help determine how elimination of phosphorylation at serine

239 can functionally affect the role of mutant ATXN1 in SCA1 pathogenesis, and whether this offers a potential site of therapeutic intervention in the future.

Disclosures: **J. Lee:** None. **T.M. Driessen:** None. **H.T. Orr:** None. **J. Lim:** None.

Poster

213. Ataxia

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 213.17/Q8

Topic: C.04. Movement Disorders

Support: National Ataxia Foundation

Baden-Württemberg Stiftung

Title: Characterizing the physiological and pathophysiological functions of ataxin-3 and its isoforms

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Abstract: Spinocerebellar ataxia type 3 (SCA3) or Machado-Joseph disease (MJD) is caused by an expansion of a CAG repeat in the *ATXN3* gene resulting in an expanded polyglutamine repeat in the encoded ataxin-3 protein. SCA3/MJD is the most common form of spinocerebellar ataxias worldwide and belongs to the group of polyglutamine diseases comprising of nine neurodegenerative diseases including Huntington's disease. In addition to the polymorphic CAG repeat, the affected *ATXN3* gene contains three nonsynonymous single nucleotide polymorphisms (SNP) that cause amino acid changes and a premature stop. Moreover, *ATXN3* is alternatively spliced and two full-length isoforms of ataxin-3 (ataxin-3a and ataxin-3c) can be detected on protein level. Both isoforms differ in their C-terminus and thereby in their number of ubiquitin interacting motifs (UIM). Here we examined the effect of the variances of ataxin-3 and its isoforms and the effect of the premature stop polymorphism on major physiological functions of ataxin-3 as well as their influence on main pathomechamisms in SCA3/MJD. In order to exclude the effect of endogenous ataxin-3, we performed these experiments in an *ATXN3* knockout background. We observed that both the alternative splicing and the premature stop impact the stability of ataxin-3. Ataxin-3 isoforms further differ in their enzymatic deubiquitination activity, their subcellular distribution and their interaction with other proteins.

On the pathological level we demonstrate that the expansion of the polyglutamine repeat stabilizes the isoforms and that they differ in their aggregation properties on multiple levels. Interestingly, we further demonstrate for the first time a crosstalk between the normal and the expanded ataxin-3 allele: The interaction of ataxin-3 variants modifies physiological as well as pathophysiological properties of ataxin-3. Taken together, our data provide novel insight into the pathogenic mechanisms in SCA3/MJD patients. Alternative splicing and polymorphic variances of ataxin-3 as well as the second, normal ataxin-3 allele contribute differently to the pathophysiology of SCA3/MJD. We anticipate that our results will lead to the identification of mechanisms that can be used as novel targets for innovative treatment strategies of this fatal disease.

Disclosures: **T. Schmidt:** None. **D. Weishaeupl:** None. **J. Schneider:** None. **B. Peixoto Pinheiro:** None. **F. von Zweydorf:** None. **C. Gloeckner:** None. **O. Riess:** None.

Poster

213. Ataxia

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 213.18/Q9

Topic: C.04. Movement Disorders

Support: Estonian Research Council (IUT2-5)

European Union's Horizon 2020 Research and Innovation Programme under grant agreement 692202

Title: Wolframin (WFS1) deficiency is associated with trigeminal atrophy

Authors: *M. A. HICKEY, V. VDOVENKOVA, K. TULVA, M. MANDEL, A. VAARMANN, A. KAASIK
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Abstract: Loss-of-function mutations in the *WFS1* gene give rise to psychiatric disorders, increased vulnerability to cisplatin-induced ototoxicity, Mendelian forms of deafness and Wolfram syndrome (WS). Using an accurate mouse model of WS (*Wfs1* knockout[1]), we have examined brain atrophy in detail, to shed light on important manifestations of loss of Wfs1. We now report a progressive loss in volume of the trigeminus in Wfs1 KO mice. The trigeminus is the largest of the cranial nerves, but it is little studied in neurodegenerative disease. The sensory component receives input from the entire face and transmits this information to the trigeminal sensory nucleus (TSN) in pons. The motor component emerges from the trigeminal motor nucleus (TMN) in pons to control mastication and swallowing. Patients with WS frequently complain of a trigeminal neuralgia-type pain, and by late stage disease, show impaired

swallowing. However, this aspect of the disease is not understood and has never been examined in detail.
Here, we show that at the time of the earliest volume loss (8 months of age) of trigeminus, detected using ex vivo MRI, Wfs1 KO mice showed reduced sensory trigeminal function (von Frey hair test and sensorimotor function) compared with WT littermates; however, they also showed reduced climbing and rearing motor activity. We thus examined cryosections from much younger mice (P22), where no behavioural deficits have thus far been detected. Even at this age, the area of the spinal trigeminal tract was reduced in Wfs1 KO mice compared with WT littermates. Stereological analysis of these sections revealed no loss in TMN neuron or TSN neuron density in the P22 KO mice.
We have recently shown impaired calcium homeostasis in primary rat cortical neurons deficient in Wfs1, which leads to increased mitophagy (mitochondrial turnover) and reduced mitochondrial trafficking and fusion. Ultimately, ATP levels decline and neuronal development is inhibited[2]. Further study of the Wfs1 KO mouse will shed light on how loss of Wfs1 impairs trigeminal function and induces trigeminal atrophy. These data will also shed light on other diseases in which mitochondrial dynamics are impaired and where disorders of mastication and swallowing are present.
[1]Behavioural Brain Research, 2009, 198(2), 334- 345. [2]PLoS Biology, 2016, 14(7), e1002511

Disclosures: M.A. Hickey: None. **V. Vdovenkova:** None. **K. Tulva:** None. **M. Mandel:** None. **A. Vaarmann:** None. **A. Kaasik:** None.

Poster

213. Ataxia

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 213.19/Q10

Topic: C.04. Movement Disorders

Title: Characterization of vestibular and optokinetic reflexes and adaptation in a mouse model of spinocerebellar ataxia type 6

Authors: *H. V. CHANG[1,2], S. JAYABAL[3], A. J. WATT[4], K. E. CULLEN[2]
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Abstract: Spinocerebellar Ataxia Type 6 (SCA6) is a mid-life onset neurodegenerative disease that affects motor coordination. Patients with SCA6 experience progressive ataxia, dysarthria, and nystagmus. This autosomal dominant disease is caused by the expansion of a CAG repeat tract in a CACNA1A gene that encodes the α1A subunit of the P/Q type voltage-gated Ca^{2+} channel. A hyper-expanded polyglutamine (84Q) mouse model of SCA6 ($SCA6^{84Q/84Q}$), is characterized by impaired locomotive function. Using both *in vitro* and *in vivo* recordings, we

have recently shown that, in this same mouse model, the firing precision of cerebellar Purkinje cells in lobule 3, areas of the cerebellum generally associated with locomotion, is significantly reduced (Jayabal et al., 2016). A recent study has further demonstrated an impairment in eyeblink conditioning in a different, Purkinje-cell specific SCA6 mouse model, likely due to alteration in the cerebellar circuitry (Mark et al., 2015). Accordingly, we hypothesized that $SCA6^{84Q/84Q}$ mice would likely show deficits in other cerebellar-dependent behaviors. To test this hypothesis and to understand the pathophysiology of SCA6 mice in more detail, we characterized their vestibular-ocular reflex (VOR), optokinetic reflex (OKR) and VOR adaptation by quantifying their eye movements. VOR was evoked by delivering horizontal rotations to a head-restrained mouse at frequencies (0.2-3 Hz) similar to those in natural behaviors. VOR eye movement responses were measured in both dark and light conditions for both 8 and 16 deg/s stimulation. OKR was evoked by rotation of visual stimulus at the same frequencies and velocities. VOR adaptation was studied by subjecting mice to a 30-min training session of sinusoidal in phase rotation (2 Hz at 16 deg/s). We found that SCA6 mice exhibited significantly lower VOR gain and approximately 35% reduction in their OKR gain compared to litter-matched control WT mice. In addition, analysis of the relationship between peak quick-phase velocity versus amplitude (i.e., main sequence) revealed that SCA6 mice generate slower saccades. Finally, our preliminary data further suggest VOR adaptation is also impaired in SCA6 mice. Together, these findings are consistent with our hypothesis that changes in neuronal responses due to the disease may not be limited in cerebellar lobules that are associated with locomotion, but suggest a more widespread pathophysiology of SCA6 mice.

Disclosures: **H.V. Chang:** None. **S. Jayabal:** None. **A.J. Watt:** None. **K.E. Cullen:** None.

Poster

213. Ataxia

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 213.20/Q11

Topic: C.04. Movement Disorders

Support: Gordon and Marilyn Macklin Foundation

Title: Emotion dysfunction and its correlates in cerebellar ataxia

Authors: *C. L. MARVEL[1,2], S. I. KRONEMER[3], J. R. PIETROWSKI[1], L. I. ROSENTHAL[1], C. U. ONYIKE[2]
[1]Dept. of Neurol., [2]Psychiatry, Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [3]Neurol., Yale Univ., New Haven, CT

Abstract: The cerebellum has long been associated with emotion control. In fact, pioneering research in the 1970s used chronic subdural cerebellar stimulation as a “brain pacemaker” to

normalize behaviors of intractable patients with violent outbursts (Heath, 1977). More recently, cerebellar cognitive affective syndrome (CCAS) has been described in association with cerebellar disorders (Schmahmann, 1998). However, the association between the cerebellum and emotion has not been considered in mainstream science. To examine the relation between the cerebellum and emotion, we assessed psychiatric symptoms in patients with neurodegenerative cerebellar ataxia. We interviewed 20 patients and their spouse/close friend ("informant") regarding changes in the patient's mood since the onset of ataxia. Consensus ratings were conducted on all interviews by assessing symptom severity of the 12 psychiatric symptoms of the Neuropsychiatric Inventory Questionnaire (NPI-Q). Even though 7 (35%) patients were on anti-depressants, depression and anxiety were reported in 70% and 80% of patients, respectively, endorsed by patients and informants. However, informants were more likely than patients to endorse "agitation/aggression" and "irritability/lability" in the patients (paired samples t-tests, $p = .02$ and .09, respectively). The severity of symptoms associated with agitation/aggression inversely correlated with impairments in real-world fine motor skills (writing with a pen, using utensils, tying shoes, $p = .001$), gross motor skills (standing from a chair, climbing stairs, driving, $p = .04$) and speech (from ICARS, $p = .003$). Relationships were not observed between motor function and other emotion categories depression, anxiety, irritability. These data indicate that: 1) emotion control is affected by cerebellar degeneration, 2) depression and anxiety are highly prevalent in cerebellar ataxia, 3) family members are more likely than patients to perceive certain mood changes, and 4) motor impairments track with "agitation/aggression" severity. These findings highlight the association between emotion control and the cerebellum and bear implications for clinical treatment and prognosis in cerebellar ataxia.

Disclosures: C.L. Marvel: None. **S.I. Kronemer:** None. **J.R. Pietrowski:** None. **L.I. Rosenthal:** None. **C.U. Onyike:** None.

Poster

213. Ataxia

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 213.21/Q12

Topic: C.04. Movement Disorders

Support: Gordon and Marilyn Macklin Foundation

Title: Visuospatial processing and strategy formation in cerebellar ataxia

Authors: *M. SLAPIK[1], S. I. KRONEMER[2], J. A. MANDEL[1], R. D. BLOES[1], J. A. CREIGHTON[1], S. D. LIEBERMAN[1], L. I. ROSENTHAL[1], C. L. MARVEL[1]
[1]Dept. of Neurol., Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [2]Neurol., Yale Univ., New Haven, CT

Abstract: Background: Progressive degeneration of the cerebellum leads to severe motor disabilities, including poor balance and coordination. Cerebellar ataxia is also associated with cognitive impairments, including visuospatial deficits, which can lead to an increased risk of falls, caregiver burden and an overall worse quality of life. It is unclear, however, whether visuospatial deficits in these patients come primarily from impairments of visual perception and encoding (input) or visuomotor response (output). Given the cerebellum's role in motor coordination, we hypothesized that the observed deficits were actually more closely tied to motor-based output strategies than to visuospatial processing.Methods: To compare visual input and motor output strategies, we measured the performance of cerebellar ataxia patients and healthy controls on three visuospatial tests.
Rey-Osterrieth Complex Figure (ROCF): Participants copied a complex figure and then drew it from memory 30 minutes later on a computerized tablet. Drawings were scored for accuracy and strategy organization based on previously developed criteria (Osterrieth, 1944) which contrasted holistic vs. piecemeal approaches to figure drawing (N= 37 ataxia; 41 controls).
Block Design: Participants reproduced visual patterns that varied in gestalt properties using blocks from the WAIS. Accuracy scores were normalized by the number of blocks completed in 2 minutes (N= 17 ataxia; 12 controls).
Optical Illusions: Participants viewed four images that could be perceived in two ways, and were asked to report both perceptions. Reaction times and accuracy were recorded for each image (N=11 ataxia; 4 controls).
Results: ROCF: Ataxia patients used less organized strategies for figure drawing than did controls. They also attained lower accuracy scores than did controls during figure copy but not during 30-minute recall. Organized strategies predicted higher 30-minute recall accuracy in controls, but not in ataxia.
Block Design: Ataxia patients made significantly more orientation errors (blocks rotated incorrectly) on the block design than did controls.
Optical Illusions: Ataxia patients and controls were equally fast at identifying one of the two perceptions within each image, but ataxia patients took longer to strategize and shift to the second perception.
Conclusions: Taken together, these preliminary results suggest that reports of visuospatial deficits associated with cerebellar damage may be better explained by impairments in the formation and implementation of motor-based output strategies than to impairments of visuospatial perception.

Disclosures: M. Slapik: None. **S.I. Kronemer:** None. **J.A. Mandel:** None. **R.D. Bloes:** None. **J.A. Creighton:** None. **S.D. Lieberman:** None. **L.I. Rosenthal:** None. **C.L. Marvel:** None.

Poster

213. Ataxia

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 213.22/R1

Topic: C.04. Movement Disorders

Support: Gordon and Marilyn Macklin Foundation

Title: Selective working memory deficits in cerebellar ataxia

Authors: *R. BLOES[1], S. I. KRONEMER[2], J. OTERO-MILLAN[1], J. PETERBURS[3,1], C. MARVEL[1]
[1]Dept. of Neurol., Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [2]Yale Univ., New Haven, CT; [3]Med. Psychology & Systems Neurosci., Univ. of Muenster, Muenster, Germany

Abstract: Background: Neurodegenerative cerebellar ataxia involves progressive neuronal loss within the cerebellum, leading to poor motor control and coordination, and abnormal eye movements (hypermetria). The cerebellum has also been associated with language functions, including phonological rehearsal during working memory (WM). We tested WM in cerebellar ataxia by comparing verbal WM, which included a phonological rehearsal component, to non-verbal WM, which relied on non-phonological rehearsal strategies. We used eye tracking in conjunction with WM testing to confirm any relationship between eye movements during visual stimulus encoding and WM performance. We hypothesized that WM deficits would be specific to the verbal domain and independent of eye movement abnormalities. Methods: The WM task consisted of two stimulus types: verbal (6 letters) and non-verbal (1 Chinese character—participants could not read or speak Chinese). Each trial consisted of three phases: 1) encoding: stimulus presentation (verbal or non-verbal stimuli), 2) rehearsal: silent rehearsal of the stimuli, and 3) retrieval: probe presented and participants decided whether it matched the stimuli. Trials consisted of three conditions: match (50%), non-match similar (25%) and non-match dissimilar (25%). In non-match similar trials, the probe item was phonologically similar to the stimuli (e.g., probe “g” and a stimulus that included “d”) or visually similar (one of two Chinese radicals in the probe matched the stimuli). For non-match “dissimilar” trials, the probe item was not phonologically or visually like the stimuli. Eye tracking data were recorded during encoding, prior to probe presentation. Eye fixation durations and percent “dwell” time were computed for each stimulus type. (Ataxia N=26; Controls N=20). Results: Difficulty was equated between verbal and non-verbal stimulus types. Participants were most accurate on the non-match dissimilar trials. A group x stimulus x condition interaction revealed that the ataxia group was impaired only on verbal match trials. Longer dwell and fixation durations during encoding correlated with accuracy in the verbal match condition, but only in the ataxia group. For both groups, there was no relationship between eye movements and any other conditions across

stimuli. Interpretations: Deficits of WM in cerebellar ataxia were observed in association with verbal stimuli, and specifically in the match condition. Verbal WM deficits implicate a role for impaired phonological rehearsal strategies. Despite these WM deficits, the better a patient's ability to fixate on letters while encoding, the better their WM performance.

Disclosures: R. Bloes: None. **S.I. Kronemer:** None. **J. Otero-Millan:** None. **J. Peterburs:** None. **C. Marvel:** None.

Poster

213. Ataxia

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 213.23/R2

Topic: C.04. Movement Disorders

Support: Scholarship CAPES (Coordination for the Improvement of Higher Education Personnel)

Title: The influence of visual feedback on aiming movements' performance and learning in individuals with cerebellar dysfunction

Authors: *V. F. GIANGIARDI[1,3], S. M. S. F. FREITAS[2], S. R. ALOUCHE[2]
[1]Physiotherapy, [2]Master's and Doctoral Program in Physical Therapy, Univ. Cidade De São Paulo, São Paulo, Brazil; [3]Master's Program in Physical Therapy, Univ. Cidade de São Paulo, Sâo Paulo, Brazil

Abstract: Introduction: The cerebellum plays a role in the planning and execution of voluntary movements, improving performance and stabilizing motor learning through sensorial integration. The consequences of cerebellar dysfunction on aiming movements' performance and learning as well as the role of augmented visual feedback (AVF) have been minimally explored. **Objectives:** To analyze the influence of AVF on the motor performance and learning of upper limbs' aiming movements in individuals with cerebellar dysfunction. **Methods:** Twenty-eight right-handed individuals, 14 with degenerative cerebellar disorder (cerebellar group: CBG) and 14 age- and gender-matched heathy individuals (control group: CTG), participated in the study. The CBG had been diagnosed on average 8 years prior and was assessed by the Scale for the Assessment and Rating of Ataxia (SARA score 9 — 25/40 points), digital and handgrip strength, and motor dexterity (Box and Block Test). Participants were asked to perform upper limb aiming movements on a digitizing tablet. The CBG used the most affected limb and the CTG the paired limb. Two experiments were conducted. Experiment 1 compared the aiming movements' performance between groups and when the movement trajectory (AVF) was presented during movement execution. Experiment 2 analyzed the influence of the AVF in learning aiming movements. Temporal (reaction and movement time, peak velocity, and relation between time to

peak velocity and movement time) and spatial (initial direction error, smoothness, and final position error) variables were analyzed. **Results:** The CBG showed worse performance in all analyzed variables. The use of AVF produced increased movement duration and slower and less smooth movements for both groups. Additionally, the practice with visual feedback generated similar duration, initial direction error, and smoothness between the CBG and the CTG. When practice was done without AVF, the CBG showed worse performance than CTG in these variables. No interaction between factors was found. **Conclusion:** Cerebellar dysfunction causes temporal and spatial impairment of upper limb' aiming movements, independently of the use of AVF. However, the use of AVF for practice improves aiming movement in individuals with cerebellar dysfunction, making their performance similar to the healthy individuals. It is suggested that the use of AVF during practice can facilitate motor learning, improving aiming movement's performance.

Disclosures: V.F. Giangiardi: None. **S.M.S.F. Freitas:** None. **S.R. Alouche:** None.

Poster

214. Cell Biology of Ischemia

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 214.01/R3

Topic: C.07. Ischemia

Support: NSF Grant 81671229

AHA Grant 09SDG2310180

Title: Alpha-chimaerin suppresses axonal connections in peri-infarct cortex of a mouse model after ischemic stroke

Authors: *S. LI[1], J. JIN[1], Y. JIN[1], A. J. BRUMM[2], M. MACHNICKI[2], H. ZHANG[3], J. XIAO[3], G. LIANG[3], S. T. CARMICHAEL[4], X. LI[5]
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Abstract: Stroke is the leading cause of long-term disability in adult. Axonal sprouting in peri-infarct cortex is associated with functional recovery after stroke. With high-throughput gene expression analysis of single sprouting neurons, upregulation of α-chimaerin, a Rho GTPase-activating protein, has been identified during the initiation of axonal sprouting in somatosensory cortex after stroke of aged animals. To define the functional roles of α-chimaerin in axonal sprouting, gain- and loss-of-function strategies were employed in the current experiments. We

first examined the effect of α-chimaerin in axonal outgrowth of the mouse postnatal day 3 primary cortical neurons. Quantitative analysis indicated that α-chimaerin siRNA duplex significantly enhanced axonal outgrowth, while α-chimaerin-GFP (lentiviral constructs carrying a whole sequence of the α-chimaerin gene linked to the GFP) notably suppressed axonal outgrowth of the neurons *in vitro* compared to the controls, respectively. We further tested the role of α-chimaerin in axonal sprouting *in vivo* in the peri-infarct somatosensory cortex using a mouse photothrombotic cortical stroke model. The duplex of α-chimaerin/control siRNA or the lentiviral α-chimaerin/control-GFP was respectively injected into a region of motor cortex that mediates recovery after stroke (Li et al., *Nat Neurosci* 2015) at 1 week following focal cortical stroke. Animals were sacrificed 3 weeks after the siRNA or lentiviral transfection and the tissue processed in tangential cortical sections to visualize the mouse somatosensory cortical map. There was no significant difference in axonal sprouting between α-chimaerin siRNA and scrambled non-stroke mice. However, stroke animals administrated with α-chimaerin siRNA duplex shown a significant increase of axonal connections in peri-infarct cortex in comparing with the scrambled-treated stroke mice. In contrast, axonal sprouting in the lentiviral α-chimaerin-GFP treated group was significantly inhibited in peri-infarct cortex when compared to the lentiviral GFP control, reducing new patterns of connections in premotor and motor cortex and in first and second somatosensory areas. The behavioral study of α-chimaerin is currently under analysis. This data identifies the important and differential functional roles of α-chimaerin, as to those of growth-associated genes *Atrx, Igf-1* and *Gdf10,* in the axonal sprouting post-stroke and suggests alternative therapeutic strategies in the development of neural repair drugs.

Disclosures: S. Li: None. **J. Jin:** None. **Y. Jin:** None. **A.J. Brumm:** None. **M. Machnicki:** None. **H. Zhang:** None. **J. Xiao:** None. **G. Liang:** None. **S.T. Carmichael:** None. **X. Li:** None.

Poster

214. Cell Biology of Ischemia

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 214.02/R4

Topic: C.07. Ischemia

Support: KU Research Sector Grant MY 04/16

Title: Oxygen glucose deprivation causes a short-lasting, transient contraction of rat brain pericytes in primary culture

Authors: *Z. REDZIC[1], L. ABDULLAH[1], A. HENKEL[1], J. CRAIG[2]
[1]Physiol., [2]Biochem., Fac. of Med., Safat, Kuwait

Abstract: Neural repair that follows recanalization of the occluded cerebral artery is often impeded by the no-reflow phenomenon, which occurs when no blood flow is restored to the

capillary bed [1]. *In* vivo studies produced conflicting data on whether or not the no-reflow is due to the rapid death and subsequent prolonged contraction (*rigor mortis*) of brain pericytes after the onset of ischemia, which obstructs capillary lumen [2, 3]. To overcome limitations in monitoring these cells *in vivo*, contractility of brain pericytes has been estimated by measuring electrical impedance of the growth surface *in vitro*, but this approach revealed several limitations [4]. In this study video imaging and image analysis was used in order to establish whether or not oxygen glucose deprivation (OGD) protocols cause a rapid death and prolonged contractions of rat brain pericytes (RBPs) in primary culture. RBPs were cultured as described earlier [5]. Stacks of images (1/5min for 15h) of 11-22 single RBPs from different flasks were taken before and after 20mins-6h OGD protocols and analysed by a software that estimated the following parameters: single cell membrane mobility (SCMM), area/perimeter (A/P) ratio and fractal dimension (Df). Significance of differences before and after OGD protocols was estimated by the Student's t-tests. Cell viability was estimated by Annexin/7-AAD staining after 2-24h exposure of primary cultures to OGD or to control conditions. This approach enabled clear detection of RBPs contractions after application of vasodilators adenosine (0.01mM) and nimodipine (0.03mM) and a vasoconstrictor endothelin-1 (50 nM). Twenty minutes and 1h OGD protocols caused a significant reduction in SCMM ($p<0.05$ and $p<0.01$, respectively *vs.* before OGD), which was accompanied by a significant increase in A/P ratios ($p<0.01$), indicating contractions of RBPs. However, no significant differences in SCMM were revealed after 3h and 6h OGD protocols ($p>0.05$ *vs.* before OGD), which was accompanied by a significantly decreased A/P ratio ($p<0.05$) and a significantly increased Df ($p<0.01$) after OGD protocols, which indicated elongation of cellular processes. Two to 6h OGD protocols caused a marginal reduction in cell viability, which was followed by a sharp decline in viability after 12 and 24h OGD protocols. In conclusion, we could not find evidence that deprivation from oxygen and glucose *in vitro* causes rapid cell death and prolonged contractions of brain pericytes.

1. Nour M et al. (2013) Interv Neurol 1: 185-199.
2. Hall C et al. (2014) Nature 508, 55-60.
3. Hill R et al. (2015) Neuron, 87, 95-110.
4. Neuhaus A et al. (2016) J Cereb Blood Flow Metab (*in press*).
5. Redzic Z et al. (2015) Int J Stroke 10:407-14.

Disclosures: Z. Redzic: None. **L. Abdullah:** None. **A. Henkel:** None. **J. Craig:** None.

Poster

214. Cell Biology of Ischemia

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 214.03/R5

Topic: C.07. Ischemia

Support: NIH Grant NS065008

NIH Grant NS076620

NIH Grant NS100245

Title: Role of microglia and Interferon-B in establishing ischemic preconditioning

Authors: *A. MCDONOUGH, T. LE, J. R. WEINSTEIN
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Abstract: Ischemic preconditioning (IPC) is a brief period of ischemia that confers robust neuroprotection against subsequent ischemic events. Microglia, the resident immune cells in the CNS, play a significant role in the neuroinflammatory response to ischemia. Although microglial activation has typically been considered a pro-inflammatory process in stroke, a growing body of research suggests that microglia could play a protective role in IPC. Recent studies, including from our group, have implicated innate immune pathways, including Toll-like receptors (TLRs) and type 1 interferon (IFN) signaling in IPC-mediated protection. We have shown that intact interferon signaling in microglia is critical for protection in white matter models of ischemia. In this study, we aim to further characterize the importance of microglia and interferon signaling in IPC-mediated neuroprotection in a mouse model of focal ischemia. We show that after IPC, microglia initiate a robust interferon-stimulated gene (ISG) response that is dependent on IFNAR1. We also show that IFNβ administration induces a similar ISG response and confers IPC-like neuroprotection against stroke. Based on these findings, we intend to characterize the potent IPC-like neuroprotective effects of IFNβ administration prior to stroke using a variety of methods, including transgenic mice with either systemic IFNAR1 knockout or microglial-specific IFNAR1 knockdown. These studies will help us better understand the role of type 1 IFN signaling in IPC with a focus on microglia specifically, which we hypothesize are the primary mediators of IPC-mediated neuroprotection. Our results suggest that type 1 IFN signaling is a critical component of IPC, and IPC-like neuroprotective effects can be achieved using interferons.

Disclosures: **A. McDonough:** None. **T. Le:** None. **J.R. Weinstein:** None.

Poster

214. Cell Biology of Ischemia

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 214.04/R6

Topic: C.07. Ischemia

Support: AHA (16SDG31170008)

NIH (P20 GM109098)

NIH (P01 AG027956)

NIH (U54 GM104942)

Title: miR-34a opens blood-brain barrier and exacerbates stroke

Authors: *X. REN, ***X. REN**, H. HU, S. N. S. SARKAR, I. FAROOQI, K. GRASMICK, J. W. SIMPKINS
Ctr. for Basic and Translational Stroke Research, Physiol. & Pharmacol. PO, West Virginia Univesity Robert C. Byrd Healthe Sci. Ctr., Morgantown, WV

Abstract: Background and Objective: Stroke is the second leading cause of death and the leading cause of disability worldwide. The blood-brain barrier (BBB), a highly specialized vascular interface that maintains homeostasis in brain, is disrupted in acute ischemic stroke, and blood solutes penetrate into the central nervous system CNS parenchymal extracellular space then cause cerebral edema. We have recently demonstrated that mitochondria play a critical role in maintaining BBB integrity. Bioinformatics analysis suggests miR-34a targets several mitochondria-associated genes. The aim of the study is to investigate whether miR-34a plays a role in BBB openings and stroke outcomes. **Methods:** Cerebrovascular endothelial cells (CECs) culture; mitochondrial function evaluation; ATP evaluation; flow cytometry; real-time PCR; transient middle cerebral artery occlusion (tMCAO) stroke model in mice. **Results:** *In vitro,* miR-34a triggered the breakdown of BBB in the monolayer of CECs paralleled by reduction of mitochondrial oxidative phosphorylation and ATP production, and decreased cytochrome c levels. *In vivo,* using tMCAO stroke model, we demonstrated that miR-34a was upregulated in the brain and serum of post-stroke mice. Furthermore, we demonstrated that knockout of miR-34a reduced stroke infarction compared to wild type control mice following 60 minutes tMCAO and 24 hours reperfusion. **Discussion and Conclusions:** We have found that a novel mechanism underlying BBB integrity: miR-34a mediates regulation of BBB through a mitochondrial mechanism. The data suggest that miR-34a opens BBB and worsens acute ischemic stroke outcomes. Therefore, targeting of miR-34a might have application as a novel therapy for this devastating neurologic condition.

Disclosures: X. Ren: None. **H. Hu:** None. **S.N.S. Sarkar:** None. **I. Farooqi:** None. **K. Grasmick:** None. **J.W. Simpkins:** None.

Poster

214. Cell Biology of Ischemia

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 214.05/R7

Topic: C.07. Ischemia

Support: NIH NS95192

AHA 15IRG23050015

Title: The role of Tet enzymes and DNA hydroxymethylation in neuroprotection following experimental stroke

Authors: *K. MORRIS-BLANCO, T. KIM, M. J. BERTOGLIAT, R. VEMUGANTI
Univ. of Wisconsin-Madison, Madison, WI

Abstract: Advancements in epigenetics have revolutionized our understanding into the mechanisms involved in neurological disorders including stroke-induced brain damage. The recent discovery of the mammalian ten-eleven translocases (TET1-3), hydroxylases that convert DNA methyl groups to hydroxymethylcytosine (5hmC), has revealed a role for the 5hmC epigenetic modification in transcriptional regulation and neuronal function. Emerging evidence indicates that the TET enzymes promote neuronal survival by enhancing 5hmC and expression of protective genes under adverse conditions. In the current study, we aimed to assess the role of TET activity and 5hmC in secondary brain damage after transient focal ischemia. Adult C57BL/6J male mice subjected to middle cerebral artery occlusion showed increased 5hmC and TET activity at early and late reperfusion time points (5 min to 24h of reperfusion) in cortical penumbral tissue. Furthermore, TET3, but not TET1 and TET2 mRNA levels showed a sustained increase from 6h to 24h of reperfusion. Immunohistochemical evaluation showed increased TET3 expression preferentially in the penumbral neurons at 24h of reperfusion following focal ischemia. Knockdown of TET3 by intracerebral injection of TET3 siRNA blocked the post-ischemic increase in 5hmC levels, and exacerbated cortical infarction and mortality. TET3 knockdown also increased the expression of several pro-inflammatory and pro-apoptotic genes and concurrently decreased the antioxidant and DNA repair genes after focal ischemia. These results indicate that TET3 is the major regulator of DNA hydroxymethylation and provides endogenous neuroprotection after stroke. Further understanding the neuroprotective role of TET3 may reveal a novel stroke therapeutic target. Funded by AHA and NIH.

Disclosures: K. Morris-Blanco: None. **T. Kim:** None. **M.J. Bertogliat:** None. **R. Vemuganti:** None.

Poster

214. Cell Biology of Ischemia

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 214.06/R8

Topic: C.07. Ischemia

Support: NIH Grant 5U54NS083924-03

Title: Effect of a nicotinic receptor blocker in murine astrocyte primary culture after an ischemia model

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Abstract: Astrocytes are key players in the multicellular response to brain injury such as ischemic stroke. After a stroke, astrocytes around the affected area change to a reactive state, proliferate, and form a barrier around the affected infarct area called the glial scar. Scar formation can ultimately lead to inhibition of neurite outgrowth. This study aims to determine if modulation (reduction) of astrocytic reactivity through nicotinic signaling is neuroprotective upon stroke-like conditions.
The 4R cembranoid is a small molecule that has been shown to decrease astrocyte reactivity *in vivo* upon neurotoxic insults and has neuroprotective effects against ischemic stroke. Evidence suggests that this neuroprotective effect is mediated by nicotinic acetylcholine receptors (nAChRs). The goal of this study is to determine whether 4R exerts an astrocyte-specific neuroprotective effect by analyzing reactivity after direct drug exposure to isolated astrocytes. We hypothesize that 4R induces a neuroprotective effect in the central nervous system (CNS) by reducing reactive astrogliosis. In this investigation, we examine astrocyte proliferation and reactivity after an induced astrogliosis, using an *in vitro* model for cerebral ischemia-like conditions in the presence and absence of 4R.
To determine if 4R can exert an astrocyte-specific effect, primary astrocytes were isolated from mouse cortices and grown to confluency. They were then exposed to oxygen-glucose deprivation (OGD) for 6 hours. After this insult, cells were treated for 24 hours with 4R or vehicle. Glial fibrillary acidic protein (GFAP) and proliferating cell nuclear antigen (PCNA) expression were used as astrocyte markers for reactivity and proliferation, respectively, and detected by immunofluorescence. The immunocytochemical analysis suggests that treatment with 4R significantly reduces the ratio of GFAP and PCNA expressing cells by 26.7% and 3.5% respectively, which indicates a decrease in astrogliosis. These results show that 4R induces a

direct effect on astrocytes after OGD.
This study aims to add valuable information to the current understanding of astrocyte biology and their nAChRs under normal and ischemic stroke-like conditions. Most importantly, it will help us elucidate the mechanisms of action of a novel compound, one that may become a new small molecule candidate to afford neuroprotection upon the devastating effects of ischemic stroke.

Disclosures: G.E. Sanchez: None. **L.G. Rivera García:** None. **W. Castro:** None. **A.H. Martins:** None. **N. Sabeva:** None. **P.A. Ferchmin:** None. **V.A. Eterovic:** None. **Y. Ferrer Acosta:** None.

Poster

214. Cell Biology of Ischemia

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 214.07/R9

Topic: C.07. Ischemia

Support: NIDCR Intramural Research Program

Title: Perlecan is essential for the maintenance and repair of the blood-brain barrier against ischemic stroke through interacting with and activating pericytes

Authors: *K. NAKAMURA[1,3], T. IKEUCHI[1], P. ZHANG[1], C. RHODES[1], Y. CHIBA[1], T. AGO[3], Y.-S. MUKOUYAMA[2], Y. YAMADA[1]
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Abstract: Ischemic stroke with severe symptoms is the leading cause of disability in the U.S. However, there is no effective treatment that promotes functional recovery after acute phase treatment. Disruption of the blood-brain barrier (BBB), a brain-specific selective permeability barrier, occurs when the integrity of BBB components is lost under ischemic conditions. In the process of repairing BBB functions, pericytes are activated through the upregulation of platelet-derived growth factor receptor β (PDGFRβ).
Perlecan, a major heparan sulfate proteoglycan of basement membranes, is expressed by endothelial cells (ECs) and is adjacent to pericytes, suggesting supportive functions in the BBB. However, the role of perlecan in the BBB remains unclear. We hypothesized that perlecan may play a protective role in BBB maintenance, and it may act on pericytes during the repair of the BBB disruption caused by ischemic stroke.
We induced a 60-minute middle cerebral artery occlusion (MCAO) in adult conditional *perlecan*-deficient (*Perlecan*$^{-/-}$-Tg) mice, which express the perlecan transgene only in cartilage,

but not in brain, to rescue the perinatal lethality of *Perlecan*$^{-/-}$ mice.
In wild-type mice, MCAO induced increased expression levels of perlecan in the infarct lesion. *Perlecan*$^{-/-}$-Tg mice demonstrated larger infarct volumes and more BBB leakage than the control mice on post-surgery day (PSD) 2 after MCAO. Although the control mice showed increased numbers of PDGFRβ-positive pericytes around the ischemic lesion on PSD 3, this upregulation was inhibited in *Perlecan*$^{-/-}$-Tg mice, suggesting that perlecan may contribute to pericyte activation.
Cultured pericytes and brain endothelial cells (ECs) predominantly expressed integrin α5β1, a potential receptor for perlecan. In wild-type mice, integrin α5 expression was upregulated both in pericytes and in ECs in the ischemic lesion. In addition, we found that pericytes attached to recombinant perlecan domain V (DV) through integrin α5β1 and that DV enhanced the PDGF-BB-induced phosphorylation of PDGFRβ, as well as that of SHP-2 and FAK, which were downstream molecules of both PDGFRβ and integrin signaling. Moreover, DV promoted the migration of pericytes induced by PDGF-BB.
These results revealed that perlecan is necessary to activate pericytes through the cooperative function of PDGFRβ and integrin α5β1, and may contribute to the repair process of the BBB after ischemic stroke. Perlecan DV may be useful as a potential therapeutic agent that promotes repair of BBB function in ischemic stroke.

Disclosures: K. Nakamura: None. **T. Ikeuchi:** None. **P. Zhang:** None. **C. Rhodes:** None. **Y. Chiba:** None. **T. Ago:** None. **Y. Mukouyama:** None. **Y. Yamada:** None.

Poster

214. Cell Biology of Ischemia

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 214.08/R10

Topic: C.07. Ischemia

Support: R01NS056839-11

NS078791

Title: Targeted photothrombotic stroke to mouse motor cortex instigates sustained increases in dendritic spine turnover that continue after impairments improve

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Abstract: Stroke remains one of the leading causes of long-term disability and impairments in upper extremity function are particularly common. Ischemic damage to the motor cortex (M1) in

mice instigates reorganization of motor maps in remaining M1 that are influenced by post-stroke behavioral experience and support functional behavioral improvements. The underlying structural cellular events that give rise to reorganization of motor maps have been unclear. Several studies have addressed the effects of ischemia on dendritic structure *in vivo*, and reported ongoing dendritic structural plasticity and elevated spine turnover. However, no study has yet addressed how these changes in dendritic structure coincide with behavioral recovery. We combined *in vivo* two-photon microscopy with a mouse model of chronic upper-limb impairments to examine the temporal relationship between cortical neuronal structural plasticity and behavioral recovery. Male and female transgenic mice expressing GFP in a subset of layer 5 pyramidal neurons were implanted with cranial windows over M1 opposite their preferred reaching forelimb. Mice were then trained on the single seed retrieval task (SSR), for 2 weeks prior to targeted photothrombosis or sham procedures. For photothombososis, green laser light (532 nm) was illuminated over single arteriole branches of the middle cerebral artery draining into M1 for 4 minutes after rose bengal administration. Multi-exposure speckle imaging was performed prior to as well as 2 days after photothrombosis to determine cerebral blood flow disruption and estimate the size of the ischemic core. *In vivo* 2P imaging was performed prior to and each week following ischemia for up to 9 weeks, and changes in dendritic spine turnover, new spine stabilization and dendritic volume in the peri-infarct zone were assessed. Mice were also tested weekly on behavioral performance on the SSR task. We found that targeted photothrombosis instigated time-dependent increases in dendritic spine turnover. Initial surges in spine elimination in the first week after stroke were met by delayed increases in spine formation during the second week. For the remaining 6 weeks, spine formation and elimination remained elevated. Initial decreases in dendritic volume measurements returned to baseline levels by the end of 8 weeks. However, some areas still showed marked decreases in overall spine density. Although mice showed initial behavioral impairments in skilled forelimb use, mice returned to pre-injury reaching performance levels by 2 weeks suggesting that dendritic structural plasticity in the peri-infarct zone persists long after improvements in behavioral performance.

Disclosures: **T. Clark:** None. **C. Sullender:** None. **A. Dunn:** None. **T. Jones:** None.

Poster

214. Cell Biology of Ischemia

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 214.09/S1

Topic: C.07. Ischemia

Support: NIH Grant RO1NS083858.

Title: Impact of global ischemia-induced spreading depolarization on dendrites and dendritic spines in the murine neocortex examined by two-photon imaging and quantitative serial section electron microscopy

Authors: I. V. FOMITCHEVA, J. SWORD, *S. A. KIROV
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Abstract: Spreading depolarization (SD) causes rapid neuronal swelling and dendritic beading with spine loss representing acute damage to synaptic circuitry. Yet, very little is known about the immediate impact of SD on synaptic circuits at the ultrastructural level. Urethane-anesthetized mice of the B6.Cg-Tg(Thy1-EGFP)MJrs/J strain expressing EGFP in a fraction of pyramidal neurons underwent a craniotomy over the sensorimotor cortex and *in vivo* 2-photon microscopy was used to assess dendritic integrity. Transient global cerebral ischemia was induced on the microscope stage by bilateral common carotid artery occlusion (BCCAO) achieved by tensioning sutures looped around each CCA. Controlled reperfusion was accomplished by relieving the tension of the sutures as soon as the SD was recorded with a glass microelectrode at the site of imaged dendrites. Ischemia during BCCAO and the return of blood flow during reperfusion were verified by laser speckle imaging. Somatosensory stimulus evoked intrinsic optical signal imaging (IOS) was employed to monitor loss and recovery of cortical circuit function during ischemia and reperfusion. As expected, BCCAO-induced SD invariably beaded dendrites, but dendrites recovered after reperfusion accompanied by the return of IOS maps. After confirmation of the intact dendritic structure in sham-operated mice (n=3), or SD-induced dendritic beading after BCCAO (n=3), and dendritic recovery after reperfusion (n=3), mice were perfusion-fixed through the heart with mixed aldehydes, and the brain was processed for serial section electron microscopy. Three-dimensional reconstructions from sham-operated mice revealed intact dendrites with spines and healthy synapses. Dendritic cytoplasm contained intact microtubules, tubular mitochondria, and smooth endoplasmic reticulum (SER). Dendrites disrupted by SD in mice subjected to BCCAO were beaded and swollen with watery cytoplasm and disordered microtubules. Mitochondria had blebby appearance with swollen segments interconnected by thin segments indicating the beginning of fragmentation. Several dendritic beads contained swollen cisterns of SER. Most spines were collapsed on beaded dendrites but still attached to the presynaptic axonal boutons. The cytoplasm of recuperated dendrites after reperfusion contained arrays of microtubules, tubular mitochondria, and recovered cisterns of SER. All spines on recuperated dendrites had synapses. Our findings indicate that even in tissue with severe energy deficits as during global ischemia, SD-inflicted dendritic injury is reversible if blood flow can be rapidly restored immediately after SD onset.

Disclosures: I.V. Fomitcheva: None. **J. Sword:** None. **S.A. Kirov:** None.

Poster

214. Cell Biology of Ischemia

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 214.10/S2

Topic: C.07. Ischemia

Support: NHMRC Scholarship APP1076290

Title: Tau mediates excitotoxic brain injury in middle cerebral artery occlusion model of stroke

Authors: *M. BI[1], A. GLADBACH[1], J. VAN EERSEL[1], A. ITTNER[1], M. PRZYBYLA[1], Y. D. KE[1], L. M. ITTNER[1,2]
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Abstract: AIM: Stroke is a leading cause of death, second only to cardiovascular conditions. The majority are ischemic strokes, resulting in focal anoxic injury followed by secondary excitotoxic injury in the penumbra region. Neuronal excitotoxicity induced by aberrant excitation of glutamatergic receptors contributes to neuronal injury during ischemia in stroke. We have previously shown that tau-deficient mice are protected from Aβ-induced toxicity in an APP23 model of Alzheimer's disease. We hypothesize that tau-depletion will likewise ameliorate excitotoxicity and injury in stroke.
METHOD & RESULTS: We induced ischemic stroke using an established middle cerebral artery occlusion (MCAO) with reperfusion model in tau-deficient ($tau^{-/-}$) and wildtype ($tau^{+/+}$) mice. Mice were subject to functional testing for two weeks. We showed that $tau^{-/-}$ mice are profoundly protected from ischemic injury and functional deficits following MCAO stroke. Mechanistically, we also show that this protection is due to site-specific inhibition of excitotoxicity by glutamatergic and Ras/ERK-mediated pathways. Consequently, perturbation of this pathway by an AAV-shRNA vector restores the susceptibility of $tau^{-/-}$ animals to ischemic injury.
CONCLUSION: We show that $tau^{-/-}$ mice are protected from ischemia-reperfusion injury in a MCAO-reperfusion model of stroke. In our study, we focused on tau-dependent excitotoxicity and found that the absence of tau reduced excitotoxic Ras/ERK activation down-stream of NMDA-receptors. Our findings introduce a new role for tau in this context, making tau-dependent processes relevant beyond progressive age-related neurodegenerative disorders such as Alzheimer's disease.

Disclosures: **M. Bi:** None. **A. Gladbach:** None. **J. van Eersel:** None. **A. Ittner:** None. **M. Przybyla:** None. **Y.D. Ke:** None. **L.M. Ittner:** None.

Poster

214. Cell Biology of Ischemia

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 214.11/S3

Topic: C.07. Ischemia

Support: NIH Grant NS 101960 01

VA 101 BX002985

Title: miRNA miR-7a-5p ameliorates ischemic brain damage by targeting α-synuclein

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Abstract: Accumulation and aggregation of α-synuclein (α-Syn) is implicated in the pathogenesis of chronic neurodegenerative diseases. We recently showed that α-Syn also contributes to neuronal death after an ischemic stroke. However, effective ways of regulating post-ischemic α-Syn levels remain to be investigated. The microRNA-7a (miR-7a) is highly abundant in neurons and targets α-Syn mRNA. We currently evaluated the role of miR-7a in the post-ischemic regulation of α-Syn and secondary brain damage in young/adult (~3 months old) and middle-aged (~12 months old) rats. Transient focal ischemia induced by middle cerebral artery occlusion rapidly down-regulated cerebral miR-7a. Intracerebral administration of miR-7a mimic prevented post-ischemic α-Syn protein expression, decreased the infarct volume and promoted better recovery of motor and sensory functions evaluated up to 7 days of reperfusion by rotarod test and adhesive removal test following focal ischemia in both sexes and both ages of rats. Interestingly, the neuroprotective efficacy of miR-7a mimic was more pronounced in middle-aged rats compared to young/adult rats. Furthermore, intravenous injection of miR-7a mimic at 2h of reperfusion following focal ischemia in young male mice also decreased cerebral infarction without notable peripheral toxicity. These studies indicate that silencing of miR-7a derepresses α-Syn that mediates ischemic brain damage following a stroke. Furthermore, replenishing miR-7a is a potential therapy for preventing post-stroke α-Syn-mediated brain damage in both sexes at young/adult and aged subjects. Funded by NIH and VA.

Disclosures: **T. Kim:** None. **S.L. Mehta:** None. **H. Kim:** None. **C. Kim:** None. **R. Vemuganti:** None.

Poster

215. Ischemia and Hemorrhage

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 215.01/S4

Topic: C.07. Ischemia

Support: Intramural Research Program of the NIH, NINDS

Title: Generation of Notch3 mutations in marmoset embryos using CRISPR/Cas9 system

Authors: *J. PARK, X. ZHANG, J. CHOI, A. C. SILVA
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Abstract: Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a monogenetic cerebral small vessel disease caused by mutations in the notch homolog protein 3 (NOTCH3). The molecular mechanisms underlying CADASIL are incompletely understood and studies in animal models of CADASIL will shed light on potential disease mechanisms. The common marmoset (Callithrix jacchus) is an important nonhuman primate model for studying human disease. Recent advances of targeted genetic modification in marmoset has brought greater interest in this species. The adaptation of RNA-guided clustered regularly interspaced short palindromic repeat (CRISPR)-associated Cas9 nuclease for genome editing has facilitated the interrogation of causal genetic variants and the development of disease models. The object of this study was to obtain the Notch3 mutated marmoset embryos using CRISPR/Cas9 system to model CADASIL in marmosets. Specific CRISPR gRNAs for marmoset notch3 exon 8 regions were designed and gRNA/Cas9 protein complexes were microinjected into single cell stage marmoset embryos. The microinjected embryos were cultured in Sequential Cleav culture medium for 3 days and noninvasively transferred to the surrogate mothers. Microinjected embryos were analyzed for the presence of gene modifications and mutations in the Notch3 gene were confirmed by both T7E1 assay and sanger sequencing of PCR amplicons spanning the targeted exon. In total, 58 embryos were transferred to 21 surrogate mothers and 7 recipients (33.3%) were confirmed to be pregnant at early stages of pregnancy by ultrasonography. Two stillborn fetuses were spontaneously miscarried after 77 and 85 days of gestation, from which mutations in notch3 gene were detected by T7E1 assay. These results are important steps in development of a marmoset model of CADASIL, a monogenic archetype of cerebral ischemic small vessel disease. We are confident these animals which will constitute a useful model system for understanding the pathogenesis of CADASIL, and for developing novel and effective therapies.

Disclosures: J. Park: None. **X. Zhang:** None. **J. Choi:** None. **A.C. Silva:** None.

Poster

215. Ischemia and Hemorrhage

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 215.02/T1

Topic: C.07. Ischemia

Title: Resveratrol regulates SUR1 expression in cerebral ischemia

Authors: *I. M. ALQUISIRAS BURGOS[1], ***I. M. ALQUISIRAS BURGOS**[1], A. ORTIZ PLATA[2], P. AGUILERA HERNANDEZ[3], A. MILLAN VEGA[4]
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Abstract: Introduction. Cerebral vascular endothelial cells (CVEC) regulate the flow of ions and molecules between the bloodstream and the brain tissue, maintaining homeostasis in the parenchyma. During cerebral ischemia, the function of CVEC is impaired, causing that microvessels lose their structural integrity giving rise to cerebral edema formation. In the initial phase of edema formation, SUR1-NCCa ion channel increases its *de novo* expression favoring the massive internalization of Na^{2}+ and water to the cell. Expression of the *Abcc8* gene encoding SUR1 depends on the transcriptional factors Sp which are sensitive to oxidative stress. Therefore, its activity might be blocked by antioxidants such as resveratrol, which have a protective effect on ischemia. **Objective.** We evaluated whether resveratrol prevents edema formation through regulation of SUR1-NaCC *de novo* expression in cerebral ischemia. **Material and methods**. Wistar rats were submitted to occlusion of the middle cerebral artery (MCAO) for 2 h followed by 24 h of reperfusion. Resveratrol was given (1 mg/kg, in 50 % ethanol; *i. v.*) at the onset of reperfusion. **Results.** MCAO increased binding activity of Sp transcriptional factors, as well as expression of SUR1. These changes were associated to cerebral edema formation and brain tissue damage. Administration of resveratrol significantly reduced the brain water content and tissue damage; thus, improving on the neurological status of animals and an increasing survival was observed. In addition, we found that resveratrol reduces both, the activity of the transcriptional factors Sp and the expression of SUR1 protein, reaching baseline levels. **Conclusions**. This finding represents an advance in the description of the molecular mechanisms of action of resveratrol that exhorts its subsequent application in clinical studies.

Disclosures: I.M. Alquisiras Burgos: None. **A. Ortiz Plata:** None. **P. Aguilera Hernandez:** None. **A. Millan Vega:** None.

Poster

215. Ischemia and Hemorrhage

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 215.03/T2

Topic: C.07. Ischemia

Title: Rab7 regulates endothelial tight junction protein trafficking and paracellular permeability of the blood-brain barrier after ischemic stroke

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Abstract: Brain endothelial cells form a paracellular and transcellular barrier to blood-borne solutes via tight junctions (TJs) and scarce endocytotic vesicles. The blood-brain barrier (BBB) plays a pivotal role in the healthy and diseased CNS. BBB damage after ischemic stroke contributes to increased mortality; yet the roles of paracellular versus transcellular mechanisms in this process are not well-understood. We have previously shown by intravital two-photon microscopy, using a transgenic strain in which endothelial TJs are labeled with eGFP, that stepwise impairment of transcellular followed by paracellular barrier mechanisms accounts for BBB deficits in stroke. Moreover, Caveolin-1 deficient mice, which have reduced endothelial transcellular permeability, display a normal increase in paracellular permeability after transient MCAO, suggesting that these two mechanisms are independent. Here, we address the role of TJ remodeling in regulation of endothelial paracellular permeability following stroke. The small GTPase Rab7 plays an essential role in regulation of trafficking inside the cell as proteins move from the late endosome to the lysosome for degradation. We have generated mice deficient for Rab7 in endothelial cells (Rab7EChet) and have examined changes in BBB permeability, neuronal survival and neurological deficits at 48h after t-MCAO. We find that Rab7EC-deficient mice have reduced paracellular permeability following stroke, as assessed by leakage of biocytin-TMR tracer. This correlates with preservation of TJ structural integrity and reduced degradation of TJ protein at 48h after t-MCAO in Rab7EChet mice as compared to wild-type littermates. Conversely, leakage of serum IgG via receptor-mediated transcytosis occurs normally in these mutants. Moreover, Rab7EC-deficient mice have a reduced neuronal death in both the sensory and motor cortex and have a moderate protection against stroke as assessed by several neurological tasks. These findings suggest that Rab7 regulates TJ protein trafficking and degradation at the late phase of stroke, which is responsible for the enhancement of paracellular

permeability of the barrier. Moreover, inhibition of Rab7 activation in endothelial cells may protect CNS damage after ischemic stroke.

Disclosures: A. Cottarelli: None. **M. Hsu:** None. **A. Arac:** None. **D. Knowland:** None. **A. Edinger:** None. **D. Agalliu:** None.

Poster

215. Ischemia and Hemorrhage

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 215.04/T3

Topic: C.07. Ischemia

Title: Ependymal motile cilia injury in a novel pre-clinical model of post-hemorrhagic hydrocephalus of prematurity

Authors: *F. S. CONTEH[1], A. OPPONG[1], T. R. YELLOWHAIR[3], J. MAXWELL[4], L. L. JANTZIE[5], S. ROBINSON[2]
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Abstract: Post-hemorrhagic hydrocephalus (PHH) from intraventricular hemorrhage (IVH) in very preterm infants (<32 weeks gestation) remains a serious problem worldwide. Surgical cerebrospinal fluid (CSF) diversion for PHH often fails, or surgery is not available. CSF flow to prevent PHH is dependent on ependymal motile cilia to propel CSF. To seek more effective, safe treatment options, we developed a more translational preclinical model. Most infants born very preterm are exposed prenatally to varying degrees of chorioamnionitis (CAM) and hypoxia-ischemia, which alters the CNS microenvironment during the first 2 weeks postnatally, the period of Ecil maturation. We hypothesized that a prenatal injury that mimics the inflamed CNS at birth, plus early postnatal intraventricular lysed red blood cell (ivRBC) injection would better mimic symptomatic hydrocephalus. On embryonic day 18, pregnant rats underwent laparotomy with transient systemic hypoxia-ischemia plus intra-amniotic lipopolysaccharide injection, an established CAM model. On P1, ivRBC or vehicle (PBS) was injected. We measured Intra-aural distance (IAD) as a surrogate for head circumference, performed MRI, tested for ependymal cytokines with electrochemiluminescence, and quantified ependymal α-tubulin post-translational modifications (PTMs). T test or two-way ANOVA with Bonferroni correction was used to test significance. At P21, IAD was larger for CAM-ivRBC rats compared to sham-veh, sham-ivRBC, or CAM-veh(n=5-19,p=0.01), showing macrocephaly. T2 MRI showed ventriculomegaly (VM) after CAM-ivRBC, but not the other 3 groups, and diffusion tensor imaging showed loss of microstructural integrity. Ependyma analysis 3 days after ivRBC showed elevation of TNFα

($p<0.001$) and chemokine CXCL1 ($p<0.01$) compared to vehicle (n=3-5, t test). Ecil maturation with PTMs proceeds in a caudal to rostral direction. Using Western blots we quantified this change in sham ependyma α-tubulin acetylation ($p<0.001$) and detyrosination ($p<0.01$)(n=5-7, t test), and we will use regional comparison of α-tubulin PTMs as a measure of Ecil maturation and a potential biomarker of Ecil function. This novel model of PHH mimics the prenatal CNS injury of infants born very preterm, plus early postnatal IVH, and will allow intervention testing.

Disclosures: F.S. Conteh: None. **A. Oppong:** None. **T.R. Yellowhair:** None. **J. Maxwell:** None. **L.L. Jantzie:** None. **S. Robinson:** None.

Poster

215. Ischemia and Hemorrhage

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 215.05/T4

Topic: C.07. Ischemia

Support: FRQS Grant # 30633

NSERC Grant # RGPIN- 2015-05084

CFI Grant # 34204

Diabetes Québec

Eye Disease Foundation

Title: Nogo-A-targeting immunotherapy improves blood vessel regeneration and visual recovery in a mouse model of proliferative retinopathy

Authors: *L. RODRIGUEZ[1], S. M. JOLY[1], A. DEJDA[2], P. SAPIEHA[2], V. E. PERNET[1]
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Abstract: Nogo-A is a potent inhibitor of axonal regeneration produced by glia in the injured CNS. Neutralizing Nogo-A with function-blocking antibodies such as 11C7 was shown to be efficient at promoting axonal growth and neurological recovery after trauma and stroke in animal models. In addition, our previous data showed that Nogo-A was as negative regulator of developmental angiogenesis. In the present study, we hypothesized that the presence of Nogo-A in gliovascular contacts may impair reparative angiogenesis after retinal ischemia. To address this possibility, we investigated the effects of 11C7 on pathological angiogenesis and retinal function by using the classical model of oxygen-induced retinopathy (OIR) in C57BL/6J mice. Our results revealed a marked upregulation of *sphingosine 1-phosphate receptor 2* (S1PR2), a

Nogo-A receptor, in blood vessels following OIR-induced ischemia, while Nogo-A was abundantly expressed in surrounding glial cells. Single injection of 11C7 (1 μg) was sufficient to dramatically enhance blood vessel recovery and prevent abnormal retinal blood vessel growth towards the vitreous. Moreover, the number of tip cell filopodia was increased in retinae treated with 11C7 compared with control antibody. Electroretinographic recordings allowed to observe strong retinal function improvement after the administration of 11C7 in OIR mice. ERG a-wave and b-wave amplitudes were twice as high in 11C7-injected eyes as in mice receiving control antibody. On histological sections, OIR-induced ischemia led to retinal thinning within a perimeter of ~1 mm from the optic nerve. The thickness of inner retinal layers was better preserved with 11C7 than after control antibody injection. This study suggests that anti-Nogo-A antibody can protect neuronal cells from ischemic damage by facilitating blood vessel repair in the CNS. Targeting Nogo-A by immunotherapy could be effective in restoring blood circulation after vascular injuries such as stroke and ischemic retinopathies.

Disclosures: L. Rodriguez: None. **S.M. Joly:** None. **A. Dejda:** None. **P. Sapieha:** None. **V.E. Pernet:** None.

Poster

215. Ischemia and Hemorrhage

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 215.06/T5

Topic: C.07. Ischemia

Support: AHA Grant 17GRNT33450010

NIH Grant 1R21NS095166

Title: Unique role of CD163 and Haptoglobin in transient middle cerebral artery occlusion ischemic stroke

Authors: *R. PATEL[1], J. L. LECLERC[2], P. K. KAMAT[2], S. JEAN[1], I. SATYAVARAPU[1], S. DORÉ[3]
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Abstract: Ischemic stroke is a devastating neurological deficit that accounts for 87% of all stroke cases in the US. Post ischemic stroke, tissues are faced with oxygen deprivation and inadequate removal of metabolic waste resulting in a high rate of mortality and morbidity. Oxidative stress leads to a production of reactive oxygen species (ROS), which cause considerable tissue damage. Inflammation plays an important role in ischemic stroke brain injury by activating resident cells, such as microglia and producing proinflammatory mediators.

Haptoglobin (Hp), an acute-phase plasma glycoprotein, and CD163, a scavenger receptor, alleviate post ischemic damages resulting from toxic oxidative reactions and inflammation. Ischemic stroke was induced in wildtype mice (WT), CD163 knockout mice (CD163-/-), haptoglobin knockout mice (Hp-/-) and haptoglobin-CD163 double knockout mice (Hp-/-/CD163-/-) along with assessments of various functional and anatomical outcomes. The Hp-/- had 45.2% smaller lesion volume (p=0.0049) and 66.1% reduced hemispheric enlargement (p=0.0174) compared to WT. The Hp-/-/CD163-/- mice had 55.0% smaller lesion volume (0.0210) and 64.5% reduced hemispheric enlargement (p=0.0037) compared to CD163-/-. Together these findings suggest that there is a significant decrease in neuronal damage post ischemic stroke following the genetic deletion of Hp and CD163 can cause anatomical and behavioral differences from the WT.

Disclosures: R. Patel: None. **J.L. Leclerc:** None. **P.K. Kamat:** None. **S. Jean:** None. **I. Satyavarapu:** None. **S. Doré:** None.

Poster

215. Ischemia and Hemorrhage

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 215.07/T6

Topic: C.07. Ischemia

Title: Effect of delayed treatment with ADAMTS13 on cerebral ischemic injury compared with tPA

Authors: *T. NAKANO[1], K. IRIE[1], Y. YAMASHITA[1], T. MYOSE[1], K. SANO[1], Y. NAKAMURA[2], T. SATHO[1], M. KAI[1], K. TOMINAGA[1], H. KAMIMURA[1], K. MISHIMA[1], T. EGAWA[1]
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Abstract: Tissue plasminogen activator (tPA) is effective if administered within 3 - 4.5 hours after the onset of stroke. However, its use is limited in patients with ischemic stroke because of the narrow therapeutic time window available for safe and effective therapy, beyond which tPA may increase the incidence of intracerebral hemorrhage and further brain injury. ADAMTS13 is known to cleave von willebrand factor (VWF) on the surface of platelet thrombi in a shear force-dependent manner, which limits thrombus growth. Thus, ADAMTS13 dissolves only pathological thrombi and not VWF-platelet primary hemostatic thrombi, and may therefore have a low risk of inducing intracerebral hemorrhage following dissolution of thrombi in ischemic stroke. In this study, we examined whether ADAMTS13 has a longer therapeutic time window in ischemic stroke than tPA in mice subjected to middle cerebral artery occlusion (MCAO). ADAMTS13 (0.1 mg/kg) or tPA (10 mg/kg) was administered i.v., immediately after reperfusion

of after 2-h or 4-h MCAO for comparison of the therapeutic time windows in ischemic stroke. Infarct volume, hemorrhagic volume, and cerebral blood flow (CBF) were measured 24 hours after MCAO. Both ADAMTS13 and tPA improved the infarct volume without hemorrhagic complications in 2-h MCAO mice. On the other hand, ADAMTS13 reduced the infarct volume, and improved CBF without hemorrhagic complications in 4-h MCAO mice, but tPA was not effective and these animals showed massive intracerebral hemorrhage. These results indicated that ADAMTS13 has a longer therapeutic time window in ischemic stroke than tPA, and ADAMTS13 may be useful as a new therapeutic agent for ischemic stroke.[1] 1) Nakano et al. *Brain Res*. 22;1624:330-5 (2015).

Disclosures: **T. Nakano:** None. **K. Irie:** None. **Y. Yamashita:** None. **T. Myose:** None. **K. Sano:** None. **Y. Nakamura:** None. **T. Satho:** None. **M. Kai:** None. **K. Tominaga:** None. **H. Kamimura:** None. **K. Mishima:** None. **T. Egawa:** None.

Poster

215. Ischemia and Hemorrhage

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 215.08/T7

Topic: C.07. Ischemia

Support: NIH Grant AG051556

Title: Functional characterization of diabetic mice with and without stroke

Authors: L. BUITRAGO[1], J. LI[2], J. PERK[2], D. CEPEDA[1], A. BRICKMAN[3], J. LUCHSINGER[3], F. BARONE[2], *H. W. MORENO[4]
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Abstract: Numerous studies report an association of type 2 diabetes (diabetes) with dementia, including late onset Alzheimer's disease and/or vascular dementia. Diabetes contributes to cerebrovascular disease that is responsible for vascular cognitive impairment. We modeled these human conditions in mice by comparing hippocampal physiology, behavior, and histopathology in leptin knockout (db/db, diabetes) and normoglicemic db/heterozygous mice with and without transient middle cerebral artery occlusion (tMCAo) at 4 months of age and one-month post-stroke. To induce tMCAo, under isoflurane anesthesia, a monofilament suture 6-0 is inserted through the proximal external carotid artery, advanced into the internal carotid artery and positioned to occlude the origin of middle cerebral artery for 30 to 60 mins. Behavioral analysis of these mice was conducted using hippocampal dependent task- active place avoidance (APA) and novel object recognition (NOR). The conflict variant of APA assay assesses cognitive flexibility (APA conflict; mouse is challenged to learn the location of a new shock zone that is

opposite to the initial location). APA conflict, evaluates prefrontal cortex-ventral hippocampus functional integrity. Preliminary data indicates that diabetic mice at baseline have normal APA and NOR but still exhibit deficits in APA conflict. All APA functional measures are abnormal post-stroke. Ventral horizontal hippocampal brain slices were obtained from male and female mice. Slices were recorded using aCSF at 34°C. Schaffer collaterals to CA1 evoked field excitatory postsynaptic potential (fEPSPs) were recorded. Stable baseline was recorded for 15 mins, followed by induction of LTP with (100Hz, 1s). Spontaneous excitatory-field potentials (sEFPs) were measured from the same type of slices, but with aCSF containing 5mM KCl, in different regions of the EC-HC circuit. Electrophysiological data demonstrated that both control and diabetic mice develop hyperexcitability (significantly increased in {sEFP} duration) mainly in the subiculum, in both the stroked and contralateral hemisphere. Both diabetic and db/heterozygous stroke groups developed abnormal CA3-CA1 synaptic long term potentiation, compared with non-stroke controls, but these effects were greater in diabetic mice. Additionally, IHC analyses of neuronal integrity, glia activation, the endothelium and amyloid angiopathy, p-tau, beta-amyloid pathologies will be presented. These initial findings suggest that diabetic mice have more severe cognitive deficits and less recovery after stroke and that at baseline have a significant level of amyloid angiopathy.

Disclosures: L. Buitrago: None. **J. Li:** None. **J. Perk:** None. **D. Cepeda:** None. **A. Brickman:** None. **J. Luchsinger:** None. **F. Barone:** None. **H.W. Moreno:** None.

Poster

215. Ischemia and Hemorrhage

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 215.09/T8

Topic: C.07. Ischemia

Support: NRF-2014R1A2A1A11052042

NRF-2015M3A9B4067068

HI16C1012

Title: The effect of environmental enrichment on presynaptic plasticity in an animal model of chronic hypoxic-ischemic brain injury

Authors: *S.-Y. SONG[1], J. YU[1], J.-W. PARK[2], S. PYO[1], J. CHOI[3], S.-R. CHO[1,4]
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Abstract: This study aimed to investigate the effects of enriched environment (EE) on promoting synaptic plasticity and neurobehavioral function in an animal model of chronic hypoxic-ischemic (HI) brain injury. HI brain damage was induced in seven day-old CD-1® mice by unilateral carotid artery ligation and exposure to hypoxia (8% O2 for 90 min). At six weeks of age, the mice were randomly assigned to either EE or standard cages (SC) for two months. Rotarod, and grip strength tests were performed to evaluate neurobehavioral function. In order to identify synaptic plasticity-regulating genes regulated by EE, a qPCR and western blotting were used to measure the expression in frontal cortex, basal ganglia and hippocampus.
Among the synaptic plasticity-regulating genes, the expression of presynaptic active zone scaffold proteins, synaptic vesicle fusion proteins, SNARE complex proteins and Endocytosis proteins was also confirmed using qPCR and western blotting. The level of synaptic plasticity-regulating genes was significantly higher in the frontal cortex, basal ganglia and hippocampus of EE mice at 8 weeks. This suggests that EE plays a role in increasing presynaptic scaffold proteins such as Piccolo, Rabphilin-3A, RIM and Liprin and activating SNARE complex proteins such as Synaptotagmin2 and Synataxin-1A and stimulating synaptic vesicle fusion protein such as Munc18. By activating overall synaptic protein interaction, it was expected that the activation of functional proteins, synaptic vesicle fusion, and Ca^{2+} ion channel would occur and induce synaptic plasticity. As a result, mice exposed to EE showed significant improvements in rotarod and ladder walking performances compared to SC mice. In conclusion, EE enhances neurobehavioral functions and presynaptic plasticity via the upregulation of synaptic plasticity-regulating genes in chronic hypoxic-ischemic brain injury.
Acknowledgments:
This study was supported by grants from the National Research Foundation (NRF-2014R1A2A1A11052042; 2015M3A9B4067068) and the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (HI16C1012).

Disclosures: S. Song: None. **J. Yu:** None. **J. Park:** None. **S. Pyo:** None. **J. Choi:** None. **S. Cho:** None.

Poster

215. Ischemia and Hemorrhage

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 215.10/T9

Topic: C.07. Ischemia

Title: The cell assay of regenerative associated cells may show the dysfunction of mononuclear cells with moyamoya disease

Authors: *T. NAKAYAMA[1], E. NAGATA[2], H. MASUDA[3], S. KOHARA[2], H. YUZAWA[2], N. FUJII[2], T. OSADA[4], T. SORIMACHI[4], M. MATSUMAE[4], T. ASAHARA[3], S. TAKIZAWA[2]
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Abstract: Background: The researchers reported RNF 213 variants and other genetic factors may lead to moyamoya disease (MMD). Some believed that additional environmental factors such as autoimmune and/or inflammation ignite the cascade of vascular stenosis and aberrant angiogenesis. The etiology of moyamoya disease is still unknown. Using the assay of regenerative associated cells (RACs), which we originated, we found out the differentiation of mononuclear cells in moyamoya disease. Materials and methods: The adult MMD patients without vascular bypass operation (n=12) and healthy age matched adult volunteers (n=16) were registered into our study. We isolated mononuclear cells (MNCs) and serum of peripheral blood form each person. We added the 5 factors (VEGF•SCF•Flt-3 ligand•TPO•IL-6) to MNCs and incubated for 7 days to differentiate into RACs. We searched the cell distributions with FACS for each person's MNCs and RACs. The cell assay applied to MNCs and RACs with 5 factors (bFGF•EGF•IGF-I•VEGF•SCF). We compared between the immature and mature cells' colonies, which were called small and large colonies, at 20±1 days after incubation, also we measured the cytokines of the supernatant, which was incubated for 24 hours with MNCs or RACs. Results: In cell assay, the number of large colony with MMD was significantly lower than that with healthy control ($P<0.05$). The distribution of CD206, CD133, CD34, which were M2 macrophage and hematopoietic progenitor cells' markers, didn't differ between MMD and healthy control. Some cytokines with MMD, such as MMP9, IL-1α, Fas, differed from those with healthy control. Conclusions: Those result indicated the dysfunction of RACs, but not the number and distribution of RACs in MMD, compared to the control.

Disclosures: T. Nakayama: None. **E. Nagata:** None. **H. Masuda:** None. **S. Kohara:** None. **H. Yuzawa:** None. **N. Fujii:** None. **T. Osada:** None. **T. Sorimachi:** None. **M. Matsumae:** None. **T. Asahara:** None. **S. Takizawa:** None.

Poster

215. Ischemia and Hemorrhage

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 215.11/T10

Topic: C.07. Ischemia

Title: Development of a zebrafish (Danio rerio) model of cerebral ischemia

Authors: E. R. SILVA, *J. A. WINDELBORN
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Abstract: Rodent and primate models have dominated the area of *in vivo* cerebral hypoxia/ischemia research for decades. Innumerable advances in our understanding of mechanisms of neuronal damage have arisen from these models. In recent years, widespread use of gene targeting technologies such as CRISPR/Cas9 has allowed for rapid assessment of gene product function in hypoxic/ischemic neuronal damage and recovery. However, lack of access to appropriate facilities and husbandry expertise can be an impediment to the use of these traditional models at small, undergraduate-driven, institutions. To address this impediment, we have built upon previous work with zebrafish (*Danio rerio*) to develop a model that tests the effects of mild-to-moderate hypoxia on molecular, cellular, and behavioral variables. This model is relatively inexpensive and can be quickly learned by undergraduate-level students whose projects are typically short-term. Additionally, exposure of zygotes to gene-targeting agents is simplified by the organism's external fertilization system. Our initial findings indicate that exposure to 10-minute hypoxia (dissolved oxygen < 1.2mg/L) is sufficient to elicit significant damage to the optic tectum of the zebrafish with minimal mortality. Damage is reported as decreased absorbance of 2,3,5-Triphenyltetrazolium Chloride (TTC) in optic tectum homogenate with 48 hours of recovery from hypoxia. The treatment also results in quantifiable behavioral changes. Behavioral measurements in a novel tank included velocity, distance traveled, duration of mobility, turn angle, and meandering (turn angle divided by total distance traveled). The results of this study lay the foundation for further work examining the role of catabolic enzymes in neuronal damage caused by cerebral hypoxia/ischemia.

Disclosures: E.R. Silva: None. **J.A. Windelborn:** None.

Poster

216. Traumatic Brain Injury: Human Studies I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 216.01/T11

Topic: C.09. Brain Injury and Trauma

Title: Submaximal aerobic exertion to detect cognitive deficits in adolescent hockey players with a history of concussions

Authors: *J.-C. LORTIE[1], V. SICARD[1,2], R. MOORE[3], D. ELLEMBERG[1,2]
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Abstract: Concussions are caused by an external force from a direct contact to the head or to the body. It induces different symptoms that normally resolve within 2 weeks (McCrory & al. 2013). Deficits in executive functions can persist at least six months after a first concussion (Ellemberg & al. 2007). The outcomes of a concussion during adolescence are different from college athletes or adults, which are more documented in the literature. Adolescents seem to be more vulnerable

to concussions, likely because of the rapid development of frontal lobe structures (Baillargeon & al. 2012). A recent study observed that a sub-group of asymptomatic college athletes exhibited cognitive deficits after exertion (McGrath & al. 2013). Deficits in executive functions might still be present after the resolution of other clinical symptoms. The objective of our study was to examine if exertion may exacerbate cognitive dysfunctions in adolescents with a history of concussions (HOC). Our hypothesis was that exertion will allow us to detect subtle deficits in executive functions that were not perceptible at rest. Cognitive tasks assessing mental flexibility and inhibition, like the switch-task paradigm, appear to be sensitive enough to detect deficits in executive functions in college athletes with HOC (Mayr & al. 2014). Forty-one adolescent hockey players (22 HOC, 19 controls) completed a colour-shape version of the switch-task at rest and after exertion. The exertion consisted of a 20-minute submaximal effort (60-70% of maximal heart rate) on an ergocycle. Participants were asymptomatic at the time of the testing. Participants with a HOC suffered 1 to 3 concussions and were 6 to 36 months from their last concussion. Both groups had similar demographics ($p \geq 0.328$), in terms of age, education, body mass index, years practising hockey and years playing with body checking. Participants with a HOC took significantly longer to complete the task than controls ($p = 0.007$). There was no main effect of accuracy and no interaction between HOC and exertion. Participants with a HOC exhibit similar deficits at rest and after exertion. Therefore, exertion does not seem to exacerbate deficits in executive functions for adolescent participants. These results suggest that asymptomatic adolescents with HOC have persistent deficits in executive functions.

Disclosures: J. Lortie: None. **V. Sicard:** None. **R. Moore:** None. **D. Ellemberg:** None.

Poster

216. Traumatic Brain Injury: Human Studies I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 216.02/T12

Topic: C.09. Brain Injury and Trauma

Title: Baseline neurocognitive performance and symptoms in those with attention deficit disorders and a history of concussions with a loss of consciousness

Authors: S. KAYE[1], M. H. SUNDMAN[2], *E. E. HALL[3], K. PATEL[4], C. J. KETCHAM[5]
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Abstract: Research has shown that certain pre-existing conditions or individual characteristics may put an individual at risk for concussions and prolonged recovery. One individual factor that has been linked to increased risk and prolonged recovery is Attention Deficit Hyperactivity Disorder (ADHD). There is evidence that axonal integrity is compromised and may be one of the potential mechanisms that leads to this increased risk. Additionally, there is recent evidence that

the axonal integrity of white matter is compromised in individuals with blast injuries with loss of consciousness (LOC) compared to those without LOC. The purpose of this study was to assess if baseline neurocognitive performance and symptom scores was influenced by a diagnosis of ADHD, a history of concussions, and a history of LOC with concussions. 1565 participants (621 Division I collegiate student-athletes; 869 club collegiate student-athletes; 33 collegiate dancers and 42 others) completed a neurocognitive test (Immediate Post-Concussion Assessment and Cognitive Testing) which included 4 composite scores (verbal memory, visual memory, visual motor speed, reaction time), symptom scores (severity of 22 symptom items), and self-reported demographic information. Symptoms were classified into 4 categories (cognitive, emotional, physical, sleep). 182 participants (11.6%) had a diagnosis of ADHD, 433 (27.2%) had a history of concussion, and 122 of those concussed (28.2% of concussed) resulted in a LOC. Results showed that concussion history, history of LOC and ADHD all resulted in higher total symptom scores at baseline compared to no history of concussions or ADHD. Categories of symptoms were affected differently depending on history of concussion, LOC and ADHD. Similarly, neurocognitive performance was influenced by ADHD, history of concussion and history of LOC although not always in what could be considered a negative direction. These results suggest that history of concussion, history of concussion with LOC and ADHD all influence baseline symptoms and neurocognitive performance and may be important pre-existing factors to consider in concussion management and potential long-term effects of concussions. Further research should consider the role of ADHD and LOC and the underlying mechanisms that may lead to disparities in concussion risk and recovery.

Disclosures: S. Kaye: None. **M.H. Sundman:** None. **E.E. Hall:** None. **K. Patel:** None. **C.J. Ketcham:** None.

Poster

216. Traumatic Brain Injury: Human Studies I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 216.03/U1

Topic: C.09. Brain Injury and Trauma

Support: VISN 17 Center of Excellence Pilot Funds

Title: EEG neurofeedback enhances default mode network integration and segregation in patients with a history of traumatic brain injury

Authors: *G. J. MAY[1,2], E. M. GORDON[1,2], R. ATHEY[3], K. GEORGE[3], J. SRIKANTH[3], R. SWEIDAN[1], B. GARY[1], A. MCGINNIS[1], S. M. NELSON[1,2,3]
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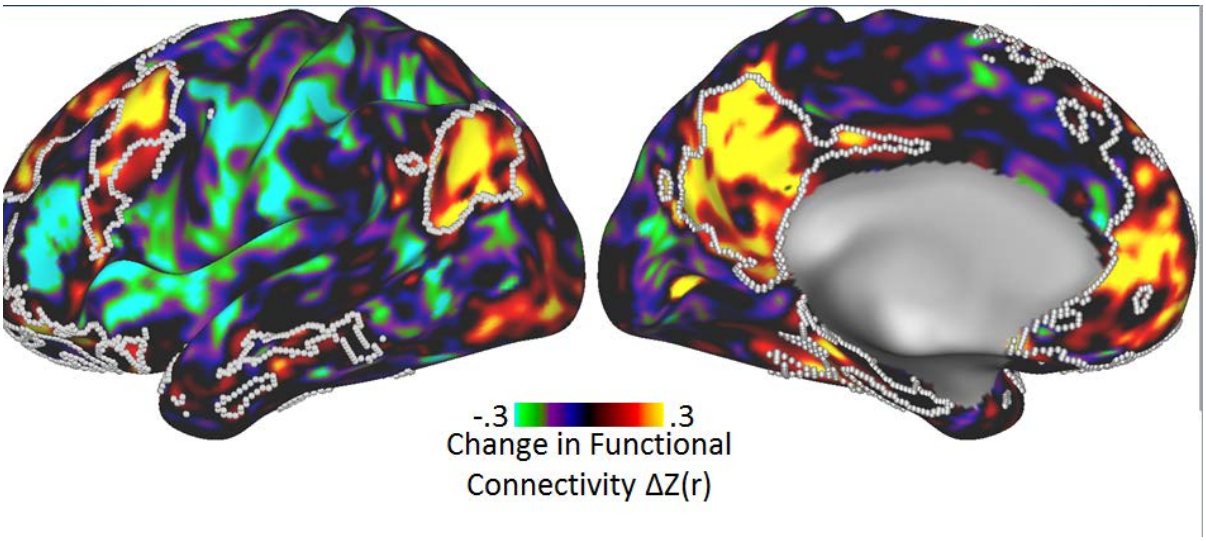
Abstract: EEG neurofeedback is an operant conditioning paradigm by which patients learn to change aspects of the brain's electrophysiology. It may be an effective treatment for TBI sequelae by making plastic changes to network connectivity. However, selection of training goals remains a difficult process, as the effects of a given set of EEG changes on other measures of brain physiology, such as network connectivity, remain poorly understood. We enrolled 8 patients in a double-blind, sham-controlled trial of live Z-score neurofeedback. Training goals were set to minimize Z scores (i.e. differences from a distribution of values from a healthy control population) of relative power and coherence for 5 separate frequency bands at each of 19 electrodes. Patients completed up to 20 sessions of training, each lasting 30 minutes. We also collected over two hours of resting-state functional connectivity (RSFC) MRI data from each patient both before and after treatment. We examined the pre- and post-treatment network connectivity of the well-known default mode network (DMN) by examining correlations in activity between the posterior cingulate cortex (PCC) and each other region of the brain. Two patients demonstrated an ability to change Z scores over time, along with improved cognitive and symptom measures. These patients also demonstrated dramatic changes in DMN connectivity, such that the PCC's integration with other DMN regions coincided with segregation from many non-DMN regions. In post-hoc analysis, we examine EEG correlates of these findings.



Disclosures: **G.J. May:** None. **E.M. Gordon:** None. **R. Athey:** None. **K. George:** None. **J. Srikanth:** None. **R. Sweidan:** None. **B. Gary:** None. **A. McGinnis:** None. **S.M. Nelson:** None.

Poster

216. Traumatic Brain Injury: Human Studies I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 216.04/U2

Topic: C.09. Brain Injury and Trauma

Support: Office of Academic Affiliations, Advanced Fellowship Program in Mental Illness Research and Treatment, Department of Veterans Affairs

VISN 17 Center of Excellence Pilot Funds

Title: EEG coherence changes correlate with changes in cognition after neurofeedback treatment in veterans with TBI

Authors: *L. ZAMBRANO-VAZQUEZ[1], G. J. MAY[1,2], K. GEORGE[3], J. SRIKANTH[3], R. ATHEY[3], A. MCGINNIS[1], S. M. NELSON[1,2,3]
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Abstract: Quantitative EEG has been shown to be related to measures of intelligence and cognitive functioning. For instance, lower EEG coherence scores have been associated with higher intelligence. This relationship between EEG coherence and intelligence has been interpreted as increased spatial differentiation and brain complexity resulting in increased speed and efficiency of information processing. Nonetheless, it has not yet been established whether learning to change one's own coherence leads to improvements in cognitive ability. EEG neurofeedback is a form of biofeedback that uses real-time EEG activity to teach self-regulation of brain function, including EEG coherence. Thus EEG neurofeedback can help elucidate whether learning to change EEG coherence could result in a meaningful change in cognitive ability, particularly in a sample of individuals who have experienced a degree of cognitive impairment as a result of a traumatic brain injury (TBI). As such, the purpose of this study was to test the potential effectiveness of neurofeedback as treatment for TBI. Ten to twenty sessions of EEG visual neurofeedback were delivered to a sample of Veterans with a history of TBI. A battery of neuropsychological testing was administered before and after treatment to assess changes in cognitive functioning across different domains. Changes from pre- to post-treatment in EEG coherence across different frequency bands were correlated with pre-to-post treatment changes in measures of cognitive functioning. Gains in visual processing speed and verbal fluency were correlated with widespread decreases in cross-hemisphere parietal delta, theta, and beta coherence, while verbal fluency improvements also correlated with an increase in parietal coherence changes in the delta and theta bands. These findings have the potential to inform the use of neurofeedback as a treatment modality for Veterans suffering from TBI.

Disclosures: L. Zambrano-Vazquez: None. **G.J. May:** None. **K. George:** None. **J. Srikanth:** None. **R. Athey:** None. **A. McGinnis:** None. **S.M. Nelson:** None.

Poster

216. Traumatic Brain Injury: Human Studies I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 216.05/U3

Topic: C.09. Brain Injury and Trauma

Support: VISN17 Center of Excellence pilot funds

Title: Elucidating relationships between traumatic brain injury, white matter integrity, functional network communication, and post-traumatic stress disorder in veterans precisely characterized with high-data MRI

Authors: *E. M. GORDON[1,2], L. ZAMBRANO-VAZQUEZ[1], M. JIA-RICHARDS[3], B. S. GARY[1], R. SWEIDAN[1], R. ATHEY[3], J. L. REID[3], S. M. NELSON[1,2,3]
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Abstract: Symptoms of post-traumatic stress disorder (PTSD) are common among post-deployment military Veterans who have suffered traumatic brain injuries (TBIs). Such symptoms are believed to be related to the presence of diffuse axonal injury resulting from shearing forces. In theory, this axonal damage reduces the integrity of white matter tracts and thus impairs normal communication between distant brain regions, effectively disrupting the function of brain networks critical for cognitive function. However, previous work has not elucidated direct relationships between TBI, white matter integrity, functional communication within brain networks, and PTSD symptoms.
Recent work by Laumann et al. (2015) has demonstrated that the brain networks of individual humans can be characterized with high fidelity if many hours of MRI data are collected in each individual. Here, we apply a similar high-data MRI approach to study TBI-related effects on brain networks. We collected 1-5 hours of diffusion tensor imaging (DTI) and resting-state functional connectivity (RSFC) MRI data from 23 US Military Veterans with and without a history of TBI (assessed via self-report), and we examined whether DTI and RSFC measures were 1) related to the presence of TBI, 2) predicted PTSD symptom severity, and 3) mediated the relationship between TBI and PTSD.
We found that the presence of TBI predicted increased PTSD symptom severity, as well as reduced strength of RSFC connectivity within and between known networks. However, TBI did not predict white matter integrity (fractional anisotropy; FA) in the DTI data. Further, RSFC strength was found to mediate the TBI-PTSD relationship. Interestingly, FA also independently predicted PTSD symptoms, but did not mediate relationships between TBI/RSFC and PTSD. These findings suggest that, contrary to current conceptualizations of how TBI affects brain structure and function, DTI measures of white matter integrity and RSFC measures of functional

network communication are independent from each other, with both explaining a separate portion of the variance in PTSD symptoms. However, only RSFC was strongly predicted by a history of TBI. We speculate that alterations in FA, and their subsequent effects on PTSD, may be driven by some separate source of injury or degeneration that is not captured by TBI self-report measures.

Disclosures: E.M. Gordon: None. **L. Zambrano-Vazquez:** None. **M. Jia-Richards:** None. **B.S. Gary:** None. **R. Sweidan:** None. **R. Athey:** None. **J.L. Reid:** None. **S.M. Nelson:** None.

Poster

216. Traumatic Brain Injury: Human Studies I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 216.06/U4

Topic: C.09. Brain Injury and Trauma

Title: Ventricular volume changes as a result of severe TBI in pediatric patients

Authors: *M. B. UNSON[1], M. BROWN[1], J. J. WISCO[1,3], E. BIGLER[2], N. MUNCY[2]
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Abstract: Introduction
Traumatic brain injury (TBI) has significant impacts on the psychological and physical health of patients. With many different changes and disruptions occurring in the brain because of TBI, we used the Social Outcomes of Brain Injury in Kids (SOBIK) data collected by Dr. Erin Bigler and associates to investigate changes in brain structure volume in TBI patients. The purpose of this research is to determine if a correlation exist in TBI patients between changes in ventricular volumes and mental function, as measured using the WAISIQ test.
Methods
We obtained MRI images of 124 subjects from the SOBIK data, which included 82 children aged 4-13 who had sustained a TBI, and 42 children ages 5-13 who had sustained an orthopedic injury, and no TBI. The TBI group was split into three subgroups based on Glasgow Coma Scale (GCS) at the time of injury: severe (GCS ≥8), moderate (GCS of 9-12), and mild complicated (GCS >12 and the presence of secondary complications). Of these subjects, we used ANTS brain segmentation software on 90 viable datasets to calculate volumes of 103 cortical, subcortical and ventricular volumes and differences between the right and left hemisphere. In this BYU IRB approved study, we used a MANOVA statistical model to determine volume differences as a result of TBI injury severity. Structure volumes were normalized to total brain volume to correct for head size differences. We reduced the number of structures analyzed by first performing a

Pearson correlation of structure volumes to WASI-IQ scores and selecting only those that were significant at $p<0.05$, leaving eight structures.
Results
Only the overall MANOVA statistical model for TBI category was significant [$F(24,206)=1.587$, $p=0.046$; Wilk's Lambda=0.612]. Bonferroni corrected between-subjects effects revealed significant volume increases for the left lateral ventricle between severe and mild ($p=0.025$), severe and control ($p=0.044$); and for the third ventricle between severe and control ($p=0.011$); but not cortical or subcortical structures.
Conclusions
We found that TBI severity was associated with ventricular volume increases, but no significant changes in cortical or subcortical volumes. We did not analyze white matter volume changes, but a decrease in subcortical white matter volume would explain the ventricular volume increases, particularly since we analyzed total brain normalized volumes. This suggests that severe TBI in pediatric patients affects white matter volume, but not gray matter volume. Future studies will examine white matter integrity using Diffusion Tensor Imaging to determine if particular white matter tracts have a predilection toward traumatic injury.

Disclosures: **M.B. Unson:** None. **M. Brown:** None. **J.J. Wisco:** None. **E. Bigler:** None. **N. Muncy:** None.

Poster

216. Traumatic Brain Injury: Human Studies I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 216.07/U5

Topic: C.09. Brain Injury and Trauma

Support: Lions Foundation

Title: Binocular horizontal saccade velocity abnormalities in mTBI

Authors: *J. H. ANDERSON[1,2]
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Abstract: Traumatic brain injury (TBI) is increasingly being recognized as a significant cause for problems affecting movement, balance, and spatial orientation (Hoffer et al., 2007; Hoffer et al., 2010), and vergence eye movements (Magone et al., 2014; Suhr et al., 2015). There can be problems with eye movements, eye-head-coordination, and visual-motor transformations underlying goal-directed movements. In some cases this can be the result of a single event causing a mild TBI. Also, there is evidence that symptoms can manifest years after the original trauma and become progressively worse over time. Effects of the natural aging processes

probably interact with and compound the effects of the TBI. The present study is part of an effort to evaluate saccadic eye movements during binocular viewing in mTBI. The general aim is to characterize the coordinated movement of the two eyes during horizontal saccades, to compare the eye velocity of the abducting eye with that for the adducting eye, and to relate the velocity trajectories of the two eyes to vergence dysfunction in mTBI. For this initial work, the position and velocity of the left eye versus the right eye is being analyzed. Saccade targets are presented from 5 to 25 degrees to the left and right of center. For large saccade amplitudes there are different velocities for the adducting eye versus the abducting eye in mTBI subjects who have convergence insufficiency or convergence excess. Furthermore, there can be an asymmetry for rightward versus leftward saccades. These results suggest that the velocity profiles of one eye can be different from that of the other during horizontal saccades in mTBI and might be correlated with vergence dysfunction. This would provide further insight into some of the underlying pathophysiology affecting the control of gaze in mTBI.

Disclosures: J.H. Anderson: None.

Poster

216. Traumatic Brain Injury: Human Studies I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 216.08/U6

Topic: C.09. Brain Injury and Trauma

Support: Canadian Institutes of Health Research Fellowship

Alberta Innovates Health Solutions Clinician Fellowship

Own the Podium Operating Grant

MITACS Accelerate Post-doctoral Fellowship

Canadian Academy of Sport and Exercise Medicine Research Grant

Canadian Sport Institute Calgary

Jim Smith, Calgary

Title: Assessment of sensory, motor and cognitive function following sport-related concussion using the KINARM robot: A prospective validation study

Authors: *C. S. MANG[1], T. A. WHITTEN[1], M. S. COSH[2], C. T. DEBERT[1], S. H. SCOTT[3], B. W. BENSON[1], S. P. DUKELOW[1]
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Abstract: Background: There is a critical need for improved tools to objectively assess neurological function after sport-related concussion (SRC). Our group has found that the KINARM robot is reliable for assessment of sensory, motor and cognitive function in stroke, traumatic brain injury, and healthy athletes. The purpose of the current study was to use the KINARM robot to quantify sensory, motor and cognitive function in athletes post-SRC and when clinically asymptomatic (CA). Methods: Baseline robotic assessments were conducted during the pre-season on 1,051 elite athletes participating in contact/collision/high-risk sports between 2011 and 2016. Eighty-seven athletes (mean age±SD, 17.5±3.4 years, 23F) were re-assessed post-SRC (≤10 days), and 68 (17.4±3.5 years, 17F) assessed again when CA. Five robotic tasks were employed (Visually Guided Reaching, VGR; Position Matching, PM; Object Hit, OH; Object Hit and Avoid, OHA; Trail Making B, TMB), from which 44 parameters that characterize sensory, motor and cognitive function were measured and used to determine overall task scores. To characterize abnormal performance on an individual basis, reliable change indices (RCIs, 80% confidence interval) were determined from test-retest reliability in 105 healthy control (CTL) athletes (20.1±4.6 years, 23F) for each parameter and task score. Relationships between post-SRC task scores and symptom severity (Sport Concussion Assessment Tool, v3) were evaluated with Pearson's correlation coefficients (significance considered $p<0.01$). Results: On individual parameters, the percentage of participants identified as abnormal ranged from 6.7-14.3% for CTL, 4.6-28.7% post-SRC and 1.5-29.0% when CA. The percentage of individuals identified as abnormal on at least 1 parameter in each task were (CTL/post-SRC/CA): VGR (46.7%/65.5%/47.1%), PM (24.8%/29.1%/38.2%), OH (65.7%/88.5%/75.4%), OHA (61.9%/79.1%/77.9%), and TMB (18.3%/34.9%/20.6%). The percentage of individuals identified as abnormal on overall task scores were (CTL/post-SRC/CA): VGR (8.6%/9.2%/8.8%), PM (4.8%/18.6%/16.2%), OH (6.7%/6.9%/10.1%), OHA (7.6%/13.1%/2.9%), TMB (5.8%/19.8%/11.8%). There was a weak-to-moderate correlation between decreased post-SRC VGR task score and symptom severity ($r=0.31$, $p=0.008$). Correlations for other task scores were non-significant ($p>0.01$).Conclusions: The KINARM robot detected abnormal sensory, motor and cognitive function at a higher rate in individuals post-SRC than in healthy controls. Results suggest that it can detect abnormalities not captured by standard symptom reporting and that abnormalities may persist beyond symptom resolution.

Disclosures: C.S. Mang: None. **T.A. Whitten:** None. **M.S. Cosh:** None. **C.T. Debert:** None. **S.H. Scott:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Co-founder and Chief Scientific Officer of BKIN Technologies Ltd. (maker of the KINARM robot). **B.W. Benson:** None. **S.P. Dukelow:** None.

Poster

216. Traumatic Brain Injury: Human Studies I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 216.09/U7

Topic: C.09. Brain Injury and Trauma

Title: Affective network in acute mild traumatic brain injury

Authors: *M. SHPANER[1], A. THOMAS[2], K. FREEMAN[3], M. R. NAYLOR[1]
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Abstract: Estimates of long-term emotional complications following mild Traumatic Brain Injury (mTBI) range from 10% to 77%. TBI patients with moderate to severe injuries have deficits in social cognition that may stem in part from their impaired ability to recognize social cues, such as affective facial expressions. To our knowledge, social deficits have not been studied in mTBI. Faces, particularly fearful faces, are a powerful social cue because they can communicate impending danger and are associated with reliable activations within limbic circuits in healthy volunteers. In order to better understand functional changes in emotional networks during the acute stage of recovery from mTBI, we performed functional neuroimaging in patients with mTBI (n=24) and a control group (n=18, mixed healthy and orthopedic injury) within 72 hours post-injury and approximately seven days later. Participants completed an emotional elicitation probe task and a resting state scan. Blocks of emotion-provoking faces (expressing either fear or anger) were interleaved with blocks of simple shapes. To optimize activations of the amygdala, participants were asked to either label gender or match shapes with two buttons. We performed region of interest (ROI) analysis in the left amygdala for the emotional elicitation task. There was a significant group X time interaction ($p = 0.03$) between first and second assessments (<72 hours vs. 1-week) in the mTBI group compared to the control group. Consistent with our prediction, basolateral amygdala activation in the control group decreased over time, whereas amygdala activation in the mild TBI group remained the same. To examine changes within corticolimbic circuits, we analyzed resting state functional connectivity between the amygdala ROI and the 3 prefrontal ROI's (dorsolateral, ventrolateral, & medial). While the group X time interaction over the first two time points did not reach significance for any region, there was a significant group X time interaction ($p = 0.033$) when the mild TBI group was subdivided into patients who recovered over the course of the first week (n=8) compared to those who had residual cognitive symptoms (n=9). Functional connectivity between amygdala and dorsolateral prefrontal cortex increased over the course of the first week post-injury in symptomatic patients, and decreased in patients with symptomatic improvement. Importantly, functional connectivity in the control group also decreased. Functional hyperconnectivity between regions has previously been reported in chronic, more severe TBI. These results document persistent functional alterations in coricolimbic circuits in the acute stage of mTBI.

Disclosures: **M. Shpaner:** None. **A. Thomas:** None. **K. Freeman:** None. **M.R. Naylor:** None.

Poster

216. Traumatic Brain Injury: Human Studies I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 216.10/U8

Topic: C.09. Brain Injury and Trauma

Title: Effects of cognitive reserve on post-deployment neurodegeneration and symptomatology

Authors: J. T. GULLICKSON, *N. D. DAVENPORT
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Abstract: There is emerging evidence from recent military veterans raising the possibility of post-deployment neurodegeneration, potentially due to exposure to explosive blasts and/or mild traumatic brain injury events. However, MRI measures of the brain do not associate well with reports of blast exposure or mTBI. We test the possibility that differences in cognitive reserve (CR) underlie differences in reporting of blast injury experiences within a sample of OIF/OEF veterans studied at two post-deployment time points (average delay 4 years). Change in ventricle-brain ratio (VBR) calculated from volumetric MRI data was used as a measure of neurodegeneration, premorbid IQ based on WTAR and years of education were used as measures of CR, and measures of mental health symptoms and post-concussive symptoms were collected by self-report. Higher change in VBR was associated with higher post-concussive and post-traumatic symptoms. Measures of cognitive reserve correlated negatively with both amount and rate of VBR change, as well as with post-concussive and post-traumatic symptoms. Change in VBR was not associated with mild traumatic brain injury in our sample, and thus while the cause of increased VBR in this sample remains to be clarified (aging and PTSD are possible contributing factors), large change in VBR is associated with higher symptomology, and it appears that cognitive reserve may act as a protective factor both against neurodegeneration and troubling post-deployment symptoms.

Disclosures: **J.T. Gullickson:** None. **N.D. Davenport:** None.

Poster

216. Traumatic Brain Injury: Human Studies I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 216.11/U9

Topic: C.09. Brain Injury and Trauma

Support: MOST 104-2314-B-038-031

TMU102-AE1-B27

TMU105-AE1-B03

103 TMU-SHH-24

Title: Psychometric evaluation in anxiety, depression and sleep quality after a mild traumatic brain injury: A 2 year follow-up study

Authors: *Y.-H. CHIANG[1], K.-Y. CHEN[1], J.-C. OU[4], C.-J. HU[2], K.-H. LIAO[5], C.-C. WU[3]
[2]Dept. of Neurol., [3]Dept. of Surgery, [1]Taipei Med. Univ., Taipei, Taiwan; [4]Dept. of Emergency Med., Shuang Ho Hospital, Taipei Med. Univ., Taipei, Taiwan; [5]Dept. of Neurosurg., Wan Fang Hospital, Taipei Med. Univ., Taipei, Taiwan

Abstract: Aim: More than a million mild traumatic brain injury (mTBI) patients are reported annually world-wide. mTBI may result in patients' cognitive, physical, and emotional welling rather than sever disability or death. Depression, anxiety, sleep problems are commonly reported. However, the long term effects for mTBI patients in Taiwan are limited and this report documents the results of mild traumatic brain injury patients. Method: A total of 440 mTBI patients and 73 normal controls were enrolled in this study thus far. 70 patients were followed-up for 2 years, and completed five assessments in this study. Four questionnaires, PSQI (Pittsburgh Sleep Quality Index), ESS (Epworth sleepiness scale), BAI (Beck's anxiety inventory), BDI (Beck's depression inventory), were used to evaluate sleep problems, daytime sleepiness, anxiety and depression, respectively. The comparison between different time points was evaluated by the ANVOA along with a significant level at 0.05. Result: There were 38 female and 32 male patients in this study, with no significant difference in age and injury mechanism. Female patients had higher scores in three of four questionnaires and male patients had higher score in daytime sleepiness. However, there is no significant between female and male patients. Overall, all of questionnaires have significant changes except daytime sleepiness 2 years post injury. Conclusion: Daytime sleepiness did not change significantly over time. Both anxiety and depression improved after two years while sleep quality deteriorated at second-year assessment. Continued recruitment will provide additional evidence in validating the results of this study with limited sample size.

Disclosures: Y. Chiang: None. **K. Chen:** None. **J. Ou:** None. **C. Hu:** None. **K. Liao:** None. **C. Wu:** None.

Poster

216. Traumatic Brain Injury: Human Studies I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 216.12/U10

Topic: C.09. Brain Injury and Trauma

Support: NIH/NIND Grant NS083377 to SH Frey

United States Army Medical Research Acquisition Activity Grant W81XWH-09-2-0114 to SH Frey

Title: Arm amputation impacts the relationships between neuronal metabolic state of the sensorimotor cortex and microstructural integrity of the major sensory tract in the ipsilateral hemisphere

Authors: *H. PENG[1], S. H. FREY[2], C. M. CIRSTEA[3]
[1]Psychological Sci., Univ. of Missouri Columbia, Columbia, MO; [2]Psychological Sci., [3]Physical Med. & Rehabil., Univ. of Missouri, Columbia, MO

Abstract: Background: Our recent MR Spectroscopy (MRS) study[1] indicates that chronic unilateral arm amputation is associated with lower levels of N-acetylaspartate (NAA) -a putative marker of neuronal metabolism and integrity- in the contralateral, but not in the ipsilateral, sensorimotor hand territory. Using diffusion tensor imaging (DTI), we and others found lower fractional anisotropy (FA) -a putative marker of axonal microstructural integrity- in contralateral white matter underlying the premotor cortex[2] and ipsilateral medial lemniscal (ML)[3] and corona radiata[2]. Are these NAA cortical-level changes precipitated by structural alterations in the white matter underlying the sensorimotor territory? If so, then we would expect a positive relationship between NAA in hand territory and FA of ML and/or corticospinal tract (CST), the major afferent and efferent pathways, in the hemisphere contralateral to amputation. **Methods:** MRS and DTI images were acquired in 15 (7 female) chronic (mean[SD]=12[13]years) unilateral right hand (dominant hand) adult amputees and 26 age/sex/handedness-matched controls. Absolute NAA levels were bilaterally quantified in the sensorimotor hand territories (LCModel software). Probabilistic tractography was used to delineate ML and CST in each hemisphere (FSL-TBSS). **Results:** We failed to find significant relationships between NAA and ML/CST FA in the hemisphere contralateral to amputation ($p \approx 0.3$-0.9). This result is similar with what we found in the dominant hemisphere in controls. Contrary, in the hemisphere ipsilateral to amputation, NAA was significantly correlated with the ML FA ($r=-0.60$, $p=0.02$). This finding suggests that higher neuronal metabolism is associated with less directionality of water diffusion, suggestive of increase in cell density or axonal/dendritic arborization. Such relationship was not found in controls. **Discussion:** The lack of significant correlations between the neuronal metabolic changes and the microstructure of the primary afferent/efferent pathways in the hemisphere

contralateral to amputation is unexpected. Yet, this could be due to insufficient reductions in efferent activity as a result of continued use of the residual arm and/or activity of the former hand territory when using the intact arm. Our results provide however initial evidence that the ipsilateral neuronal metabolic state is associated with the microstructure of the underlying major afferent pathway. This could be the result of experience-related changes in the sensorimotor intact hand territory and underlying white matter. Additional work is underway to decipher the functional implications of such relationships.

Disclosures: H. Peng: None. **S.H. Frey:** None. **C.M. Cirstea:** None.

Poster

216. Traumatic Brain Injury: Human Studies I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 216.13/U11

Topic: C.09. Brain Injury and Trauma

Support: NIH Grant HD51912

The Jerold B. Katz Foundation

The James S. McDonnell Foundation

NIH NCATS Grants UL1 TR000043 & UL1 TR000457-06

Title: Restoration of sleep dynamics may index recovery induced by central thalamic deep brain stimulation following severe brain injury

Authors: *J. L. GOTTSHALL[1,2], Z. M. ADAMS[2], P. B. FORGACS[2,3,4], N. D. SCHIFF[2,3,4]
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Abstract: Severe brain injuries often result in disorders of consciousness (DOC), a spectrum of chronic disorders in which consciousness level fluctuates and is often difficult to assess. Many DOC patients exhibit severe motor impairments, resulting in an inability to demonstrate overt cognitive recovery detectable by standard diagnostic tools. Furthermore, few treatments have been effective at facilitating recovery from DOC. Central thalamic deep brain stimulation (CT-DBS) has been proposed to mediate recovery of consciousness on the basis that the central thalamus plays a key role in maintaining synaptic activity across frontostriatal systems, which are uniquely vulnerable to dysfunction following severe brain injury. Recent studies suggest that sleep electrophysiology may be a reliable correlate of daytime cognitive functioning in both healthy individuals and DOC patients, potentially providing a sensitive indicator of recovery.

Here we report on a longitudinal study of CT-DBS in one DOC patient studied at five time points over the course of 8.5 years. Overnight video-EEG was collected at each time point, corresponding to pre-CT-DBS implantation (1 visit), active CT-DBS (3 visits), and post CT-DBS cessation (1 visit). In this patient, both visual inspection and spectral analysis revealed the presence of a unique electrophysiological sleep signature consisting of persistent and aberrant blending of elements of stage 2 and slow wave sleep (SWS). Notably, blending was significantly attenuated following CT-DBS onset, corresponding with improvements in subjective alertness and increased average spindle frequency, the latter notable as a reversal of expected trends due to aging (Adams et al., 2016). This effect localized to frontal channels, which exhibited significant suppression of aberrant frequency mixing during the CT-DBS "on" compared to CTS-DBS "off" conditions. As CT-DBS was only active during the daytime, these results likely indicate the effect of increased daytime frontostriatal excitability on sleep dynamics. Specifically, increases in neuronal firing across the frontal cortex may have resulted in the stabilization of sleep transitions from thalamically-driven stage 2 into more cortically-dependent SWS. Such a relationship between daytime synaptic activity and driving of sleep electrophysiology is both consistent with and provides novel evidence to support the synaptic homeostasis hypothesis. Collectively, our findings demonstrate the impact of CT-DBS on sleep processes and underscore the potential value of sleep dynamics as a measure to track covert functional recovery of frontostriatal systems in patients with DOC.

Disclosures: J.L. Gottshall: None. **Z.M. Adams:** None. **P.B. Forgacs:** None. **N.D. Schiff:** None.

Poster

216. Traumatic Brain Injury: Human Studies I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 216.14/U12

Topic: C.09. Brain Injury and Trauma

Title: Sex-related differences in self-reported personality traits in varsity concussed athletes

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Abstract: Recent studies have suggested that concussions can result in sex-related differences in emotional, behavioral and cognitive sequelae. Multi-concussed athletes and concussed females particularly are more likely to report more post-concussive symptoms of greater intensity. Although personality changes in moderate and severe traumatic brain injuries (TBI) are well documented, little is known about the effects of sport-related concussions on personality traits.

The objective of this study was to investigate sex-related differences in personality traits in asymptomatic concussed athletes relative to their unconcussed counterparts. A total of 118 varsity athletes (61 males) were recruited based on prior concussion history: Athletes presenting with at least one concussion (n = 69) and a control group consisting of unconcussed athletes (n = 49). Time since last concussion was more than three months (M = 28.56). After a concussion interview, participants filled out the NEO-PI-R, a self-perceived personality questionnaire based on the five-factor personality model consisting of Neuroticism, Extraversion, Openness, Agreeableness, and Conscientiousness. Overall, our results suggest that the effects of concussions differed between males and females on Agreeableness and Neuroticism in asymptomatic athletes. More specifically, concussed males perceived themselves significantly more negatively on both agreeableness and neuroticism personality traits relative to same-sex controls, whereas the reverse pattern was observed in concussed females relative to same-sex unconcussed teammates. In moderate and severe TBI, Neuroticism is typically found to increase, whereas Conscientiousness and Extraversion decreases, with Openness and Agreeableness remaining stable. Post-injury changes on the NEO-PI-R have been suggested to reflect emotional reactions to trauma rather than altered neural systems regulating social-emotional behavior. Future studies are therefore needed to investigate whether male-specific impairments of emotion recognition could be linked to personality traits changes after concussion.

Disclosures: **S. Guay:** None. **E. Léveillé:** None. **C. Beaulieu:** None. **L. De Beaumont:** None.

Poster

216. Traumatic Brain Injury: Human Studies I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 216.15/V1

Topic: C.09. Brain Injury and Trauma

Support: Own the Podium operating grant

Mitacs Accelerate Postdoctoral fellowship

Canadian Institutes of Health Research Postdoctoral Fellowship

Alberta Innovates Health Solutions Postdoctoral Fellowship

Canadian Academy of Sports Exercise Medicine Research Fund

Canadian Sport Institute Calgary

Jim Smith, Calgary

Title: Assessment of spatial working memory following sport-related concussion

Authors: *T. A. WHITTEN[1,2], C. MANG[1,2], M. S. COSH[4], S. H. SCOTT[5], S. P. DUKELOW[1,2], B. W. BENSON[1,3,4]
[1]Dept. of Clin. Neurosciences, Cumming Sch. of Med., [2]Hotchkiss Brain Inst., [3]Fac. of Kinesiology, Univ. of Calgary, Calgary, AB, Canada; [4]WinSport Med. Clinic, Winter Sport Inst., Calgary, AB, Canada; [5]Dept. of Anat. & Cell Biol., Queen's Univ., Kingston, ON, Canada

Abstract: BACKGROUND: Sport-related concussion is a heterogeneous injury, which can result in impairments across multiple modalities. Spatial working memory is one component of neurological function that is likely critical for skilled play in many sports, and deficits have been reported post-concussion. Therefore, impairments of spatial working memory should be tracked with reliable and sensitive methods following sport-related concussion to quantify impairments and help guide return-to-play decisions. In the current study, we assessed changes in spatial working memory in concussed athletes relative to baseline performance using the Spatial Span Task on a KINARM end-point robot. We hypothesized that athletes would be impaired on this task following concussion.
METHODS: In the Spatial Span Task, individuals were presented with a 3x4 grid of blocks. Blocks were lit up sequentially in a randomized order and participants were instructed to remember the sequence. Individuals then attempted to select the blocks in the correct order using the robotic arms. Sequence lengths started at 4 blocks and increased or decreased by one based on success on each trial, for a total of 18 trials. Subjects were assessed on Total Score (the sum of correct sequence lengths), Test Time and Time Per Target.
Test-retest reliability was assessed in seventy-nine healthy athletes (24F; Mean ± SD: Age 19.6 ± 5.4 years; Days between tests 337 ± 72) using intraclass correlation coefficients (ICCs: good reliability ICC ≥ 0.75; moderate reliability ICC ≥ 0.5). Reliable change indices (RCIs, 80% confidence interval) were calculated to determine the expected change from baseline in the absence of concussion. We then examined task performance in 46 other athletes (9F; 15.9 ± 2.5 years) who sustained a concussion after their first baseline test (acute timepoint 3.5 ± 1.8 days post-injury). Impairment was defined as a change in performance falling outside the RCI limits in the direction of a decrease in performance.
RESULTS: We found good reliability for Total Score (ICC = 0.78) and Test Time (ICC = 0.76), and moderate reliability for Time Per Target (ICC = 0.59). A small percentage of athletes were identified as impaired following concussion (Total Score: 13% impaired; Test Time: 11% impaired; Time Per Target: 6% impaired).
SUMMARY: The Spatial Span Task is not identifying impairments in a large percentage of athletes acutely following concussion. This suggests that either spatial working memory is not commonly affected by concussion, or that the Spatial Span robotic task is not a sufficiently sensitive measure. Future directions will evaluate other spatial working memory tasks using the KINARM robot.

Disclosures: T.A. Whitten: None. **C. Mang:** None. **M.S. Cosh:** None. **S.H. Scott:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BKIN Technologies Inc., Kingston, Canada. **S.P. Dukelow:** None. **B.W. Benson:** None.

Poster

217. Traumatic Brain Injury: Therapeutic Interventions I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 217.01/V2

Topic: C.09. Brain Injury and Trauma

Support: NIH grants R01NS060005, R01HD069620, HD069620-S1, R01NS084967 (AEK)

Title: Comparable impediment of cognitive function in female and male rats subsequent to daily administration of haloperidol after traumatic brain injury

Authors: *I. H. BLEIMEISTER[1,2], K. E. FREE[1,2], A. M. GREENE[1,2], H. L. RADABAUGH[1,2], P. B. DE LA TREMBLAYE[1,2], C. O. BONDI[1,2], N. LAJUD[3], A. E. KLINE[1]
[1]Univ. of Pittsburgh, Pittsburgh, PA; [2]Safar Ctr. for Resuscitation Res., Pittsburgh, PA; [3]Inst. Mexicano del Seguro Social, Morelia, Mexico

Abstract: Antipsychotic drugs, such as haloperidol (HAL), are prescribed in the clinic to manage traumatic brain injury (TBI)-induced agitation. While preclinical studies have consistently shown that once-daily administration of HAL hinders functional recovery after TBI in male rats, its effects in females are unknown. Hence, the objective of this study was to directly compare neurobehavioral and histological outcomes in both sexes to determine whether the reported deleterious effects of HAL extend to females. Anesthetized adult female and male rats received either a cortical impact or sham injury and then were randomly assigned to a dosing regimen of HAL (0.5 mg/kg, i.p.) or vehicle (VEH; 1 mL/kg, i.p.) that was initiated 24 hrs after injury and continued once daily for 19 consecutive days. Motor function was tested using established beam-balance/walk protocols on post-operative days 1-5 and acquisition of spatial learning was assessed with a well-validated Morris water maze task on days 14-19. Cortical lesion volume was quantified at 19 days. No statistical differences were revealed between the HAL and VEH-treated sham groups and thus they were pooled for each sex. HAL only impaired motor recovery in males ($p<0.05$), but significantly diminished spatial learning in both sexes ($p<0.05$). Females, regardless of treatment, exhibited smaller cortical lesions vs VEH-treated males. Taken together, the data show that daily HAL does not prohibit motor recovery in females, but does negatively impact cognition. These task-dependent differential effects of HAL in female vs male rats may have clinical significance as they can direct therapy.

Disclosures: I.H. Bleimeister: None. **K.E. Free:** None. **A.M. Greene:** None. **H.L. Radabaugh:** None. **P.B. de la Tremblaye:** None. **C.O. Bondi:** None. **N. Lajud:** None. **A.E. Kline:** None.

Poster

217. Traumatic Brain Injury: Therapeutic Interventions I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 217.02/V3

Topic: C.09. Brain Injury and Trauma

Support: NIH grants NS095950, NS099683, UPP/UPMC Academic Foundation, Univ. Pitt Rehabilitation Inst. (COB)

NIH Grants NS060005, HD069620 and NS084967 (AEK)

NIH Grants R01 HD075760, R01 NS084604 (MDM)

2016 AHA SURP award (DAO)

Title: Assessment of executive function after cardiac arrest and resuscitation in pediatric and adult rats

Authors: *D. A. O'NEIL[1,2,4], M. D. MANOLE[1,3,4], C. DEZFULIAN[1,3,4], A. E. KLINE[1,2,4], C. O. BONDI[1,2,4]
[2]Physical Med. and Rehabil., [3]Critical Care Med., [1]Univ. of Pittsburgh, Pittsburgh, PA; [4]Safar Ctr. for Resuscitation Res., Pittsburgh, PA

Abstract: Cognitive impairments are frequently reported after cardiac arrest (CA). These impairments prove ubiquitous throughout the life span in both pediatric and adult populations, typically presenting as deficits in attention, declarative memory, executive function, visuospatial abilities, and verbal fluency. The pathological changes that underlie these executive dysfunctions are relatively unknown and remain unstudied in the laboratory. This study utilizes the attentional set-shifting test (AST) to investigate age-dependent higher-order cognitive dysfunction following clinically-relevant CA in immature and adult rats. We hypothesized that rats resuscitated from CA will exhibit performance deficits on cognitive set-shifting compared to Sham controls. Potentially, adult rats recovering from CA may exhibit more pronounced cognitive dysfunction and behavioral inflexibility than adolescents who underwent pediatric CA procedures secondary to the enhanced neuroplasticity properties of the young, developing brain. CA and resuscitation procedures were performed in accordance with previously established methodology at the Safar Center. Rat pups (PND 16-18) underwent 9 or 12 minutes of asphyxial CA (moderate or severe duration, respectively). Adult rats received necessary adjustments in order to match reperfusion and other parameters between the two age groups. Sham control rats underwent anesthesia and surgery without CA or resuscitation. Rats were tested on the AST at four weeks post-cardiac arrest. The AST involves a series of increasingly difficult discriminative tasks to obtain food reward, including simple and compound discriminations, stimulus reversals, and intra- and

extradimensional shifts. Results suggest CA does not impair executive function in either age group, as measured via total trials to reach criterion, total errors or set-loss errors compared to sham-operated rats. Intriguingly, there seems to be a paradoxical improvement of performance in rats subjected to CA insult. Specifically, CA adult rats performed faster than SHAM group on the second stimulus reversal (n=6/group), while CA adolescents subjected to 9-min pediatric CA also performed better on the intradimensional shift stage (n=8-11/group, $p<0.05$). The surprising lack of detrimental cognitive outcome post-insult could be secondary to enhanced neuroplasticity properties, as well as elevated scanning attention or reduced impulsivity. Given that executive function post-CA has not been studied to date, by characterizing long-term higher order cognitive performance, the groundwork for future rehabilitative and preventative intervention can be established.

Disclosures: D.A. O'Neil: None. **M.D. Manole:** None. **C. Dezfulian:** None. **A.E. Kline:** None. **C.O. Bondi:** None.

Poster

217. Traumatic Brain Injury: Therapeutic Interventions I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 217.03/V4

Topic: C.09. Brain Injury and Trauma

Support: NIH grants HD069620, HD069620-S1, NS060005, NS084967 (AEK)

NIH grants NS094950, NS099683 (COB)

University of Pittsburgh Physicians /UPMC Academic Foundation (COB)

Title: Abbreviated EE and galantamine synergize to promote cognitive recovery after experimental brain trauma

Authors: J. WELLCOME[1], D. BERRY[1], E. SHARKEY[2], P. NIESMAN[2], K. NASSAU[2], H. RADABAUGH[2], J. P. CHENG[2], C. O. BONDI[2], *A. E. KLINE[2]
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Abstract: Environmental enrichment (EE) improves neurobehavioral performance after traumatic brain injury (TBI) when provided daily for 6-hrs, but not 2-hr or 4-hr. Hence, the goal of this current study was to determine if limited EE could become an effective therapy when combined with galantamine (GAL) and whether the combined group is better than the GAL-only group. Anesthetized rats received a cortical impact or sham injury and then were randomly assigned to receive GAL (2 mg/kg; i.p.) or saline vehicle (VEH; 1 mL/kg; i.p.) beginning 24-hr after surgery and once daily for 21 days while also receiving daily sessions of EE for 2-hr, 4-hr, or 24-hr. Motor and cognitive assessments were conducted on post-operative days 1-5 and 14-19,

respectively. Motor function was significantly improved in the TBI+EE (24-hr) group vs. the TBI+STD+VEH and TBI+STD+GAL groups [$p<0.05$]. Cognitive performance was increased in the continuous EE group, as well as in the TBI+STD+GAL and the 2-hr EE and 4-hr EE GAL-treated groups vs. TBI+STD+VEH [$p<0.05$]. Moreover, the 2-hr EE and 4-hr EE groups that also received GAL did not differ from the continuous EE group [$p>0.05$] and performed better than the GAL alone group [$p<0.05$], which support the hypothesis. Overall, the data demonstrate that continuous EE and once daily GAL promote cognitive recovery after TBI, which replicates previous studies, and extend the findings by showing that even sub-therapeutic doses of EE can become effective when combined with GAL. The findings have significant clinical relevance as often times only a brief amount of rehabilitation may be available. Augmenting brief or limited rehabilitation with a pharmacotherapy like GAL may lead to improved outcomes vs. either therapy alone.

Disclosures: J. Wellcome: None. **D. Berry:** None. **E. Sharkey:** None. **P. Niesman:** None. **K. Nassau:** None. **H. Radabaugh:** None. **J.P. Cheng:** None. **C.O. Bondi:** None. **A.E. Kline:** None.

Poster

217. Traumatic Brain Injury: Therapeutic Interventions I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 217.04/V5

Topic: C.09. Brain Injury and Trauma

Support: NIH grants NS095950, NS099683, UPP/UPMC Academic Foundation, Univ. Pitt Rehabilitation Inst. (Corina Bondi, Ph.D.)

NIH Grants NS060005, HD069620 and NS084967 (Anthony Kline, Ph.D.)

Title: Frontal lobe brain trauma impairs attentional set-shifting performance in male rats

Authors: *I. P. MARSHALL[1,2], L. KUTASH[1,2], M. NICHOLAS[1,2], D. A. O'NEIL[1,2], H. L. RADABAUGH[1,2], A. E. KLINE[1,2], C. O. BONDI[1,2]
[1]Univ. of Pittsburgh, Pittsburgh, PA; [2]Safar Ctr. for Resuscitation Res., Pittsburgh, PA

Abstract: More than 10 million people worldwide sustain a traumatic brain injury (TBI) each year. The majority of survivors suffer long-lasting cognitive impairments associated with frontal lobe disturbances, as well as psychological consequences, such as being vulnerable to developing a psychiatric disorder. Previously, we demonstrated that a controlled cortical impact (CCI) injury over the parietal cortex produced significant deficits in executive function in the attentional set-shifting test (AST) in rats, a complex cognitive paradigm analogous to the Wisconsin Card Sorting Test. This study aimed to investigate complex cognitive deficits after experimental TBI

in rats subjected to frontal lobe injury, a clinically relevant location, by testing the hypothesis that a frontal TBI will impair executive function and cognitive flexibility in a cortical deformation depth-dependent manner. Thirty-one isoflurane-anesthetized adult male rats were subjected to CCI injury (2.0, 2.2, and 2.4 mm cortical tissue deformation depth at a speed of 4 m/sec) or sham injury over the prefrontal cortex region in the right hemisphere. At 4 weeks post-surgery, rats were tested on the AST, which involves a series of increasingly difficult discriminative tasks for a food reward, such as simple and compound discriminations, stimulus reversals, and intra- and extradimensional (ED) shifts. Dependent measures include number of trials to reach criterion of six correct consecutive responses, number or total errors and number of set loss errors (i.e., after 50% or more of the contingency has been achieved). Frontal CCI produced significant deficits in attentional performance on the ED stage and stimulus reversals of AST, seen as significantly higher total trials to reach criterion and increased total errors compared to SHAM rats ($p<0.05$ for Injury, n=7-8/group). These effects were particularly robust in the two more severe injury groups, namely 2.2 and 2.4 mm cortical deformation depth ($p<0.05$). These results suggest that frontal lobe injury negatively impacts complex cognitive functioning. Ongoing and future studies will focus on further disentangling brain constructs and neurotransmitter alterations responsible for such attentional deficits following brain trauma. Considering that a large percentage of TBIs occur via direct impact to the frontal part of the skull (e.g., hitting the windshield during a car accident), this approach is clinically-relevant and may prove extremely valuable for successful translation from bench to bedside, identifying necessary pharmacotherapies for cognitive performance and advance rehabilitation research.

Disclosures: **I.P. Marshall:** None. **L. Kutash:** None. **M. Nicholas:** None. **D.A. O'Neil:** None. **H.L. Radabaugh:** None. **A.E. Kline:** None. **C.O. Bondi:** None.

Poster

217. Traumatic Brain Injury: Therapeutic Interventions I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 217.05/V6

Topic: C.09. Brain Injury and Trauma

Support: NIH Grant R01NS060005, R01HD069620, HD069620-S1, R01NS084967 (AEK)

Title: Intermittent administration of the antipsychotic drug haloperidol does not reduce the efficacy of neurorehabilitation

Authors: *G. C. BAO[1,2], P. J. NIESMAN[1,2], K. L. NASSAU[1,2], J. L. WELLCOME[1,2], I. H. BLEIMEISTER[1,2], J. P. CHENG[1,2], C. O. BONDI[1,2], A. E. KLINE[1,2]
[1]Univ. of Pittsburgh, Pittsburgh, PA; [2]Safar Ctr. for Resuscitation Res., Pittsburgh, PA

Abstract: Background: Traumatic brain injury (TBI) impairs functional outcome and induces agitation. Because of the difficulty in assessing and treating agitated patients, haloperidol (HAL) is used to manage the maladaptive behavior. Past research has shown that the chronic use of HAL impedes recovery and attenuates the efficacy of environmental enrichment (EE). However, HAL may not be provided every day, so whether intermittent administration is also detrimental to recovery is unknown. **Hypotheses:** Administering HAL intermittently to standard (STD)-housed controls will be less detrimental to recovery than chronic administration in STD rats and will not reduce the efficacy of EE. **Methods:** TBI and Sham groups receiving intermittent or chronic HAL (0.5 mg/kg, i.p.) or vehicle (saline 1 mL/kg, i.p.) were housed in EE or STD conditions. Motor and cognitive performance was assessed. **Results:** TBI rats that received HAL performed worse in the motor and cognitive tests than those who received TBIs with no HAL ($p<0.05$). Rats given HAL intermittently performed better than those given HAL continuously ($p<0.05$). Furthermore, rats exposed to EE performed better than STD ($p<0.05$). **Conclusions:** The results support the hypothesis that intermittent HAL is less detrimental than once daily administration and that EE supports recovery. Moreover, if HAL was administered continuously in EE, performance was better than those housed in STD conditions, indicating the significant role that EE has in aiding recovery. **Significance:** HAL may be used in rehabilitation to control TBI-induced agitation without negatively affecting outcome or the efficacy of rehabilitation, but only when provided intermittently.

Disclosures: G.C. Bao: None. **P.J. Niesman:** None. **K.L. Nassau:** None. **J.L. Wellcome:** None. **I.H. Bleimeister:** None. **J.P. Cheng:** None. **C.O. Bondi:** None. **A.E. Kline:** None.

Poster

217. Traumatic Brain Injury: Therapeutic Interventions I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 217.06/V7

Topic: C.09. Brain Injury and Trauma

Support: NIH grants HD069620, HD069620-S1, NS060005, NS084967 (AEK)

NIH Grants NS094950, NS099683 (COB)

University of Pittsburgh Physicians /UPMC Academic Foundation (COB)

Title: Albeit nocturnal, rats subjected to traumatic brain injury do not differ in neurobehavioral performance whether tested during the day or night

Authors: *P. J. NIESMAN[1,2], J. WEI[1,2], M. J. LAPORTE[1,2], J. P. CHENG[1,2], P. B. DE LA TREMBLAYE[1,2], N. LAJUD[3], C. O. BONDI[1,2], A. E. KLINE[1,2]

[1]Univ. of Pittsburgh, Pittsburgh, PA; [2]Safar Ctr. for Resuscitation Res., Pittsburgh, PA; [3]Inst. Mexicano del Seguro Social, Morelia, Mexico

Abstract: The majority of behavioral assessment studies are conducted during the day, which is not when rats are most active. This discrepancy may preclude optimal performance. Hence, the goal of this study was to determine if differences in neurobehavior exist in traumatic brain injured (TBI) rats when assessed during the day vs. night. The hypothesis was that the night group would perform better than the day group in all behavioral tasks. Anesthetized adult male rats received a cortical impact or sham injury and were randomly assigned to either day (1:00 - 3:00 p.m.) or night (07:30 - 09:30 p.m.) testing. Motor function (beam-balance and beam-walk) was conducted on post-operative days 1-5 and cognitive performance (acquisition of spatial learning) was assessed on days 14-18. CORT levels were quantified at 24 hr and 21 days after TBI. No significant differences were revealed between the TBI rats tested during the day vs. night for beam-balance, beam-walk, or water maze (p's<0.05). CORT levels were higher in the TBI and sham groups tested at night at 24 hr (p< 0.05), but returned to baseline and were no longer different by day 21 (p>0.05), suggesting an initial, but transient stress response, that did not affect neurobehavioral outcome. These data suggest that the time rats are tested has no impact on their performance, which does not support the hypothesis. The finding is important because it validates the interpretations from numerous studies conducted when rats were tested during the day vs. their biologically active period.

Disclosures: P.J. Niesman: None. **J. Wei:** None. **M.J. Laporte:** None. **J.P. Cheng:** None. **P.B. de la Tremblaye:** None. **N. Lajud:** None. **C.O. Bondi:** None. **A.E. Kline:** None.

Poster

217. Traumatic Brain Injury: Therapeutic Interventions I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 217.07/V8

Topic: C.09. Brain Injury and Trauma

Support: NIH grants NS095950, NS099683, UPP/UPMC Academic Foundation, Univ. Pitt Rehabilitation Inst. (Corina Bondi, Ph.D.)

NIH Grants NS060005, HD069620 and NS084967 (Anthony Kline, Ph.D.)

Title: Detrimental effects of traumatic brain injury on attentional set-shifting behavior in female rats

Authors: *M. NICHOLAS[1,2], H. M. TENNANT[1,2], K. E. FREE[1,2], I. NJOKU[1,2], J. B. LEARY[1,2], M. J. LAPORTE[1,2], J. P. CHENG[1,2], A. E. KLINE[1,2], C. O. BONDI[1,2]
[1]Univ. of Pittsburgh, Pittsburgh, PA; [2]Safar Ctr. for Resuscitation Res., Pittsburgh, PA

Abstract: Traumatic brain injuries (TBIs) are considered a significant healthcare burden, with cognitive impairment associated with prefrontal cortical dysfunction being a major component of long term disability for survivors. Specifically, executive function and cognitive flexibility represent sophisticated brain capabilities to use environmental feedback to “unlearn” a previously valid set of rules, switch gears and filter out unwanted distractions. Previously, we demonstrated that a controlled cortical impact (CCI) injury produced significant impairments in executive function and cognitive flexibility in the attentional set-shifting test (AST), a complex cognitive paradigm analogous to the Wisconsin Card Sorting Test, which is used to measure strategy-switching deficits in patients with frontal lobe damage, TBI, and psychiatric disorders. Females represent over 40% of the clinical TBI population and may outnumber males with regards to unfavorable outcomes post-injury, yet this group is largely understudied in models of experimental brain trauma. Hence, the hypothesis of this study was that executive function and behavioral flexibility performance in female rats will be impaired after TBI, when tested, for the first time, on AST. Isoflurane-anesthetized, normal cycling, adult female rats were subjected to CCI injury (2.8 mm cortical deformation depth at 4 m/s) or sham injury. Four weeks post-surgery, rats underwent verification of estrous stage and were tested on the AST, which involves a series of increasingly difficult discriminative tasks to obtain food reward, including simple and compound discriminations, stimulus reversals, and intra- and extradimensional (ED) shifts. TBI produced significant performance deficits in extradimensional set-shifting and reversal learning, seen as increased trials to reach criterion and total errors ($p's<0.05$). When separated by estrous stage, TBI rats in both diestrus and proestrus stages performed similarly worse than their sham counterparts. In summary, experimental brain trauma impaired attentional set-shifting performance in female rats at four weeks post-injury, which supported the hypothesis. While there are over 100 studies employing the AST in male rats, executive function performance in females has been reported only a handful of times, with controversial baseline behavior and without identification of estrous cycle phases. These novel findings demonstrate executive function and behavioral flexibility deficits in our animal model of CCI injury in female rats, rendering further assessments using pharmacological and rehabilitative therapies post-TBI as both timely and necessary.

Disclosures: M. Nicholas: None. **H.M. Tennant:** None. **K.E. Free:** None. **I. Njoku:** None. **J.B. Leary:** None. **M.J. Laporte:** None. **J.P. Cheng:** None. **A.E. Kline:** None. **C.O. Bondi:** None.

Poster

217. Traumatic Brain Injury: Therapeutic Interventions I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 217.08/V9

Topic: C.09. Brain Injury and Trauma

Support: NIH Grants NS095950, NS099683, UPP/UPMC Academic Foundation, Univ. Pitt Rehabilitation Institute (COB)

NS060005, HD069620 and NS084967 (AEK)

T32 AG021885 (PI: SG)

Title: Effect of galantamine on attentional set-shifting performance after experimental brain trauma

Authors: *I. NJOKU[1,2], L. KUTASH[1,2], D. A. O'NEIL[1,2], I. P. MARSHALL[1,2], H. L. RADABAUGH[1,2], J. P. CHENG[1,2], A. E. KLINE[1,2], C. O. BONDI[1,2]
[1]Univ. of Pittsburgh, Pittsburgh, PA; [2]Safar Ctr. for Resuscitation Res., Pittsburgh, PA

Abstract: Traumatic brain injuries (TBI) impact millions of Americans, with older patients being more likely to have a co-occurring condition, particularly dementia. Galantamine (GAL), a first-line drug used to treat dementia, acts primarily as an acetylcholinesterase inhibitor and has been reported to positively impact cognitive function in older adults. Previously, we demonstrated that a controlled cortical impact (CCI) injury produced significant impairments in executive function in the attentional set-shifting test (AST), a complex cognitive paradigm analogous to the Wisconsin Card Sorting Test, which is used to measure strategy-switching deficits in patients with frontal lobe damage, TBI, and psychiatric disorders. In the current study, we predicted that daily GAL injections would normalize AST performance after a parietal lobe TBI in rats. Isoflurane-anesthetized adult male rats were randomly assigned to either a CCI or sham group. Surgery was administered following a previously established CCI protocol. Following surgery, rats were randomly distributed into three treatment groups: saline or GAL (1 or 2 mg/kg/day), until the test day 4 weeks later. AST results indicated that TBI significantly impairs performance on the first reversal stage, deficits attenuated by both GAL chronic doses ($p<0.05$). In particular, GAL (2 mg/kg/day) also significantly reduced TBI-induced cortical lesion volumes ($p<0.05$). In summary, chronic GAL administration provides an efficacious treatment for higher-order cognitive recovery following TBI. Further studies will investigate whether these results are maintained when using aged Sprague-Dawley rats in order to mirror the elderly segment of adults typically treated with GAL in the clinic, as well as assess protein expression of brain cholinergic markers involved in the GAL mechanism of action for restoring executive function after TBI.

Disclosures: I. Njoku: None. **L. Kutash:** None. **D.A. O'Neil:** None. **I.P. Marshall:** None. **H.L. Radabaugh:** None. **J.P. Cheng:** None. **A.E. Kline:** None. **C.O. Bondi:** None.

Poster

217. Traumatic Brain Injury: Therapeutic Interventions I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 217.09/V10

Topic: C.09. Brain Injury and Trauma

Support: NIH grants NS095950, NS099683, UPP/UPMC Academic Foundation, Univ. Pitt Rehabilitation Inst. (Corina Bondi, Ph.D.), NIH Grants NS060005, HD069620 and NS084967 (Anthony Kline, Ph.D.), P30CA047904 (UPCI Cancer Biomarkers Facility)

Title: Interaction of brain trauma and chronic unpredictable stress on cognition, anxiety, and markers of neurotransmission and neuroinflammation

Authors: L. KUTASH, D. O'NEIL, P. B. DE LA TREMBLAYE, I. MARSHALL, M. NICHOLAS, H. RADABAUGH, J. CHENG, N. LAJUD, A. KLINE, *C. O. BONDI
Safar Ctr. for Resuscitation Res., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Traumatic brain injury (TBI) survivors endure long-lasting cognitive impairments associated with frontal lobe disturbances, while also being vulnerable to neuropsychiatric disorders. Research has highlighted the importance of chronic unpredictable stress (CUS) as a major risk factor for many psychopathological conditions. Herein, we began to assess clinically-relevant cognitive- and anxiety-like dimensions sensitive to both TBI and CUS. We hypothesized that moderate TBI produced by controlled cortical impact (CCI) injury, as well as CUS exposure, will render cognitive impairments in rats in an attentional set-shifting test (AST), reduced sucrose preference, open field exploration, blunted weight gain, as well as increased inflammatory markers and altered brain markers for various neurotransmitters, such as dopamine or serotonin. Isoflurane-anesthetized adult male rats were subjected to CCI (2.8 mm cortical deformation depth) or sham injury, and were assigned to receive CUS (21 days) or handling (CTRL). Rats were then tested for anxiety (open field) and anhedonia (sucrose preference), as well as on AST, which involves a series of increasingly difficult tasks for food reward, such as simple and compound discriminations, stimulus reversals, and intra- and extradimensional (ED) shifts. A separate cohort was sacrificed post-stress for serum corticosterone (CORT) and cytokine analyses, as well as brain monoamine protein markers relevant to neurotransmitter synthesis, release and reuptake in multiple brain regions, such as prefrontal cortex, striatum or hippocampus. CUS resulted in 5-10% weight reduction compared to CTRL, yet the combination of TBI and CUS did not negatively impact the open field test or sucrose preference (n=8-12/group), albeit it rendered a near-significance elevation in CORT ($p=0.056$). TBI and CUS induced cognitive deficits as expected on AST stages such as ED and stimulus reversals, when each was given alone, but not when given in combination, suggesting a resilience effect or

compensatory interaction. Similarly, proinflammatory markers such as IL-1β, IL-6 or TNF-α were paradoxically decreased in the combined TBI + CUS group compared to Sham + CTRL rats. This project provides outcomes pertaining to cognition, anxiety, depression and neuroinflammation following overlapping chronic stress and the recovery phase of TBI, with ongoing directions involving environmental enrichment as a preclinical model of neurorehabilitation.

Disclosures: L. Kutash: None. **D. O'Neil:** None. **P.B. de la Tremblaye:** None. **I. Marshall:** None. **M. Nicholas:** None. **H. Radabaugh:** None. **J. Cheng:** None. **N. Lajud:** None. **A. Kline:** None. **C.O. Bondi:** None.

Poster

217. Traumatic Brain Injury: Therapeutic Interventions I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 217.10/V11

Topic: C.09. Brain Injury and Trauma

Support: NIH grants HD069620, HD069620-S1, NS060005, NS084967 (AEK)

NIH grants NS094950, NS099683 (COB),

University of Pittsburgh Physicians /UPMC Academic Foundation (COB)

Title: Role of cannabinoid CB1 receptors in modulating long-term effects of adolescent chronic stress on cognitive and emotional impairments in adult male TBI rats

Authors: *P. BARRA DE LA TREMBLAYE[1], H. L. RADABAUGH[1], K. L. NASSAU[1], J. L. WELLCOME[1], J. P. CHENG[1], C. O. BONDI[1], A. E. KLINE[1,2]
[1]Physical Med. & Rehabil., Univ. of Pittsburgh, Pittsburgh, PA; [2]Upmc, Safar Ctr. for Resuscitation Res., Pittsburgh, PA

Abstract: Endocannabinoids are involved in the adaptation of the brain's response to stress through cannabinoid type 1 (CB1) receptors. CB1 activation has also been implicated in the neuropathology of traumatic brain injury (TBI), and has shown promise as a potential therapeutic target. However, it is unknown whether CB1 activation can reverse the long-term effects of adverse stress exposure during adolescence on adult TBI emotional and cognitive recovery. In the current study, adolescent male Sprague-Dawley rats were exposed to 4 weeks of chronic unpredictable stress (CUS) on postnatal day (PND) 30-60. After an additional 4 weeks of resting (PND 60-90), rats were anesthetized and receive either a controlled cortical impact of moderate severity (2.8 mm tissue deformation at 4m/s) or sham injury, immediately followed by daily pharmacological treatment with either ACEA (1 mg/kg), AM251 (2 mg/kg) or vehicle (1 ml/kg), which were administered intraperitoneally for 7 consecutive days. After this week of recovery,

rats were behaviorally assessed for anxiety in the elevated plus maze (EPM) and the open field test (OFT), sociability in the three-chamber social approach test, anhedonia in the sucrose preference test (SPT), and cognitive performance in the novel object recognition (NOR) test, and Morris water maze (MWM). CUS exposure in adolescence increased time spent in the anxiogenic zones of the OFT and EPM and decreased sociability in sham rats, but improved NOR memory after a 24 hour delay, and reduced time to reach the platform in the MWM in both sham and TBI groups, effects which were mediated by CB1 receptors. The results demonstrate that chronic unpredictable stress selectively impairs emotional responses, while providing some cognitive benefits, which may be context-dependent. Furthermore, CB1-mediated neurotransmission may effectively reverse the deleterious effects of adolescent -stress on behavioral recovery post TBI in adulthood.

Disclosures: P. Barra De La Tremblaye: None. **H.L. Radabaugh:** None. **K.L. Nassau:** None. **J.L. Wellcome:** None. **J.P. Cheng:** None. **C.O. Bondi:** None. **A.E. Kline:** None.

Poster

217. Traumatic Brain Injury: Therapeutic Interventions I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 217.11/V12

Topic: C.09. Brain Injury and Trauma

Support: NIH UH3 NS095554

Title: How reliable is tractography-based targeting during central thalamic deep brain stimulation for the treatment of traumatic brain injury?

Authors: *A. JANSON[1,2], J. M. HENDERSON[3], N. D. SCHIFF[4], J. L. BAKER[5], J. SU[6], B. RUTT[6], C. R. BUTSON[1,2]
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Abstract: Deep brain stimulation (DBS) in the central thalamus is currently undergoing clinical investigation for the treatment of cognitive impairments due to traumatic brain injury (TBI). The proposed target for this therapy is a fiber pathway in the ascending arousal network which projects through the central thalamus and into the frontal cortex. In order to target this fiber pathway, diffusion tensor imaging (DTI) is acquired along with structural imaging to reconstruct patient-specific fiber tracts. However, DTI acquisitions are susceptible to inaccuracies due to field distortions and the choice of diffusion gradient directions. The goal of this study was to compare fiber tractography results after varying three parameters: 1) the amount of diffusion

weighting during acquisition (b-value), 2) the number of acquired diffusion directions, and 3) the correction of distortion introduced by eddy currents and phase encoding. We found that increasing the number of diffusion gradients increased the number of distinct fiber pathways that can be reconstructed, thereby allowing us to identify our proposed target with more confidence. In addition, distortion correction has a major impact on the location of fiber pathways relative to structural anatomy (Figure 1). The tractography results also show that more pathways were reconstructed and were less diffuse with the distortion corrected versus the uncorrected acquisitions. We anticipate that this study will provide guidance on the choice of appropriate DTI acquisition parameters and tractography analyses for patient-specific DBS surgical planning to treat TBI cognitive impairments.

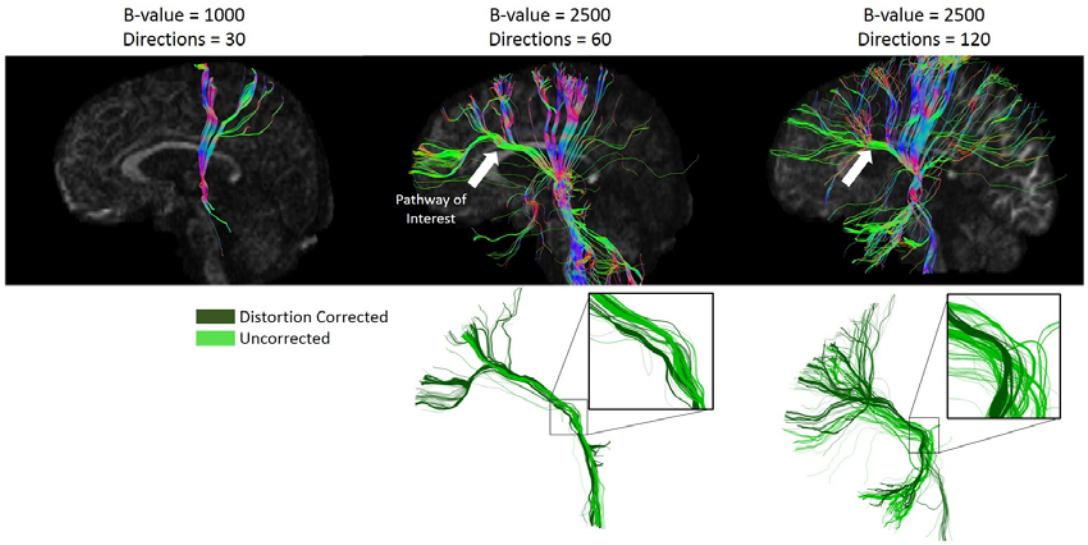

Figure 1. The top row shows the distinct fiber pathways that can be reconstructed in three different distortion corrected DTI acquisitions, each seeded in the same central-thalamic region. The bottom row shows the effect distortion correction has on the quality and location of reconstructed fiber pathways. No pathways are shown for the 30 gradient direction acquisition because we were unable to reconstruct our pathway of interest.

Disclosures: **A. Janson:** None. **J.M. Henderson:** None. **N.D. Schiff:** None. **J.L. Baker:** None. **J. Su:** None. **B. Rutt:** None. **C.R. Butson:** None.

Poster

217. Traumatic Brain Injury: Therapeutic Interventions I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 217.12/V13

Topic: C.09. Brain Injury and Trauma

Support: MOST-104-2923 -B-038-001-MY3, Taiwan

RO1NS094152, NIH, USA

Title: Therapeutic effect of intravenous pomalidomide on traumatic brain injury through multiple mechanisms to reduce neuronal death and improve behavioral deficits

Authors: *J. WANG[1], Y. LIU[1], J. WANG[1], D. TWEEDIE[2], N. GREIG[2]
[1]Grad. Inst. of Med. Sci. TMU, Taipei, Taiwan; [2]Drug Design & Develop. Section, Translational Gerontology Branch, Intramural Res. Program, Natl. Inst. on Aging, NIH, Baltimore, MD

Abstract: Traumatic brain injury (TBI) is a risk factor for neurodegenerative diseases and mortality worldwide. Using an animal model of TBI by subjecting Sprague-Dawley rats to controlled cortical impact (CCI), we have previously shown that pomalidomide (Pom), an FDA (USA)-approved immunomodulatory agent used in the treatment of multiple myeloma and other cancers, mitigates neuronal loss, neuroinflammation and behavioral impairments induced by traumatic brain injury. Post-treatment with Pom (0.5 but not 0.1 mg/kg, i.v.) administered at 5 hr after CCI reduced contusion volume and improved functional deficits by reducing neuronal apoptosis after TBI. The aim of the present study is to further investigate whether the beneficial effects of Pom are related to a reduction in neuroinflammation, oxidative stress and autophagy after TBI. Immunofluorescence staining of 3-nitrotyrosine (3-NT, markers of oxidative products of protein) and 4-hydroxynonenal (4-HNE, lipid peroxidation product) indicated that both 3-NT and 4-HNE significantly elevated by TBI and were both suppressed after Pom treatment. Autophagy related-gene 7 (ATG7) and the ratio of LC3-II/I protein level, indicators for early- and late-stage autophagy respectively, were increased by TBI but decreased by Pom treatment. Elevated protein expression of heme oxyenase-1 (HO-1), which mediates cellular responses to oxidative stress, and spectrin breakdown products (SBDPs), a marker for cell death by TBI, were suppressed by posttreatment with Pom. Our results suggest that administration of Pom after TBI reduces contusion volume and elicits anti-inflammatory, anti-oxidative and protective effect on autophagic neurons, as well as improvement of functional deficits in rat models. Our data suggest that multiple mechanisms such as anti-neuroinflammation, anti-oxidation, and anti-autophagy may contribute to the beneficial effects of Pom on TBI. (supported by MOST-104-2923 -B-038-001-MY3, Taiwan and RO1NS094152, NIH, USA.)

Disclosures: **J. Wang:** None. **Y. Liu:** None. **J. Wang:** None. **D. Tweedie:** None. **N. Greig:** None.

Poster

217. Traumatic Brain Injury: Therapeutic Interventions I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 217.13/V14

Topic: C.09. Brain Injury and Trauma

Support: TTUHSC Seed grant

TTUHSC Start-up fund

Title: Anti-glioma nanoparticles for brain targeted delivery

Authors: *H. DOU, L. ZOU, G. PAYNE, T. THOMAS
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Abstract: Nanotechnology and convection-enhanced delivery have been developed in recent years for treatment of glioma, each with highly desirable strengths in certain aspects, but limitations in other aspects. The development of an effective brain-glioma targeting delivery system for glioma therapy is much needed. We developed a novel drug carrier that can combine the advantages of both liposomes and polymeric NPs to target brain-tumor associated macrophages (TAMs). Nanoparticles (NPs) containing mixed lipid monolayer shell, biodegradable polymer core were conjugated with rabies virus glycoprotein (RVG) peptide as brain targeting ligand. Anti glioma drug, paclitaxel (PTX), was loaded to RVG-NPs to treat malignant glioma. Characterization by AFM, nanosizer and HPLC assays showed that the size-controlled RVG-PTX-NPs had the desirable size (~140 nm), narrow size distribution and spherical shape. With size of 140 nm, RVG-PTX-NPs prevented uptake by neurons and selective targeting to the brain TAMs with controlled release and tumor specific toxicity. In vivo studies revealed that RVG-PTX-NPs were significant to cross the blood-brain barrier (BBB) and had specific targeting to the brain. Most importantly, RVG-PTX-NPs showed effectiveness for anti-glioma therapy on human glioma of mice model. We concluded that RVG-PTX-NPs provided an effective approach for brain-TAMs targeted delivery for the treatment of glioma.

Disclosures: H. Dou: 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.; TTUHSC Seed Grant, TTUHSC start-up fund. **L. Zou:** None. **G. Payne:** None. **T. Thomas:** None.

Poster

217. Traumatic Brain Injury: Therapeutic Interventions I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 217.14/V15

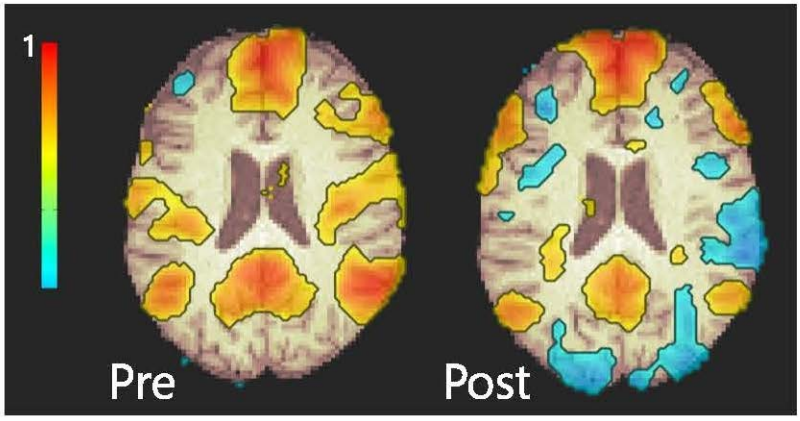
Topic: C.09. Brain Injury and Trauma

Title: Mri and neuropsychological assessment outcomes following cognitive rehabilitation training in traumatic brain injury: A multiple case study

Authors: *A. L. MOORE[1], C. LEDBETTER[2], D. M. CARPENTER, III[3]
[1]Gibson Inst. of Cognitive Res., Colorado Springs, CO; [2]LSU Hlth. Sci. Ctr. - Shreveport, Shreveport, LA; [3]Univ. of Colorado Colorado Springs, Colorado Springs, CO

Abstract: BACKGROUND: Cognitive rehabilitation training is a promising technique for remediating functional cognitive deficits and neural pathology associated with traumatic brain injury.
OBJECTIVE: The current study examined the MRI, qEEG, and neuropsychological outcomes for five cases with varying degrees of traumatic brain injury following 60 hours of intensive, metronome-based cognitive rehabilitation training with ThinkRx, a clinician-delivered training program.
METHODS: Using a multiple case study design with start point randomization, baseline and outcome measures using MRI, qEEG, standardized neuropsychological tests including the Woodcock Johnson IV Tests of Cognitive Abilities, Conners Continuous Performance Test (CPT-3), Gibson Test of Cognitive Skills, and a functional TBI rating scale were collected. Each participant attended 40 training sessions of 90 minutes each over a four month period. The training procedures were delivered one-on-one by a cognitive trainer and targeted multiple cognitive skills including working memory, long-term memory, processing speed, visual processing, auditory processing, logic and reasoning, and attention.
RESULTS: Training effects included substantial gains on neuropsychological outcome measures, markedly reduced symptom reporting, and a normalizing of resting state networks including the default mode network (Figure 1). Functional changes on the MRI also correlated with changes in cognitive test scores.
CONCLUSION: The improvements across outcome measures following ThinkRx cognitive rehabilitation training suggests that an intensive, metronome-based cognitive training intervention may be a viable option for remediating the cognitive, functional, and neural deficits associated with traumatic brain injury. The results support investment in a larger clinical trial.
Figure 1. DMN Resting State Connectivity Pre and Post Cognitive Training

Figure 1. DMN Resting State Connectivity Pre and Post Cognitive Training



Disclosures: **A.L. Moore:** A. Employment/Salary (full or part-time):; Gibson Institute of Cognitive Research at LearningRx. **C. Ledbetter:** None. **D.M. Carpenter:** None.

Poster

217. Traumatic Brain Injury: Therapeutic Interventions I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 217.15/V16

Topic: C.09. Brain Injury and Trauma

Support: NIH/NIGMS Grant # P20GM103444

Title: Dexamethasone-PEG hydrogel reduces secondary injury and promote motor function after TBI

Authors: *J. LEE[1], D. JEONG[1], S. BAE[1], C. MACKS[1], J. WHITAKER[1], M. LYNN[2], K. WEBB[1]
[1]Bioengineering, Clemson Univ., Clemson, SC; [2]Neurosurg., Grennville Hlth. Syst., Greenville, SC

Abstract: Neuro-inflammation can be detrimental to repair brain function after TBI and neuroprotective treatments based on anti-inflammatory drugs may minimize the neurotoxic effects and improve functional recovery. Dexamethasone (DXM), a steroidal anti-inflammatory agent is known to attenuate early expression of proinflammatory cytokines associated with activated microglia/macrophages. In this study, we investigated the effects of dexamethasone-conjugated hyaluronic acid (HA-DXM) combined with hydrolytically degradable, photo-cross-linkable PEG-bis-(2-acryloyloxy propanoate) (PEG-bis-AP) hydrogel in a controlled cortical impact (CCI) TBI rat model. The release of DXM from the hydrogel was evaluated in PBS and PBS containing enzymes in vitro. Rat TBI model was created by CCI devise armed with a 3mm tip (3.5 m/sec, depth: 2mm). Animals were divided to 4 groups: 1) Sham: craniotomy only, 2) untreated TBI, 3) PEG/HA gel, and 4) PEG/HA-DXM gel treated group. At 7 days post-injury, brains were harvested for analysis. RT-PCR was conducted to evaluate expression of inflammatory cytokines. Nissl staining was conducted to measure cavity area. TUNEL assay were performed for the apoptosis. Functional recovery was evaluated by beam walk test. PEG-bis-AA/HA-DXM hydrogel treatment exhibited significantly lower level of inflammatory cytokines, IL-1β, TGF-β1, TNF-α and IL-10 relative to TBI untreated group. The cavity sizes in HA-DXM treated group was significantly reduced compared to untreated TBI group by Nissl staining. For histological analysis, substantially fewer $ED1^+$ cells were observed in the PEG-bis-AA/HA-DXM treated group compared to untreated TBI group. Moreover, the number of $NeuN^+$ cells was significantly increased in the PEG-bis-AA/HA-DXM treatment group. In the results of TUNEL staining, substantially fewer apoptotic cells were observed in the PEG/HA-DXM treated group compared to untreated TBI group. In the behavioral tests, the time to traverse the beam in PEG-bis-AA/HA-DXM gel treated group was not significantly different with that in sham animal group, while that is significantly longer in untreated TBI animals during 6 days after surgery. In

conclusion, PEG-bis-AA/HA-DXM hydrogel treatment immediately after injury reduced inflammatory responses and improved neuronal cell survival as well as motor function after TBI.

Disclosures: J. Lee: None. **D. Jeong:** None. **S. Bae:** None. **C. Macks:** None. **J. Whitaker:** None. **M. Lynn:** None. **K. Webb:** None.

Poster

217. Traumatic Brain Injury: Therapeutic Interventions I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 217.16/V17

Topic: C.09. Brain Injury and Trauma

Support: EVER Pharma

Title: A prospective, randomized, blinded, and placebo-controlled study of Cerebrolysin dose response effects on long-term functional outcomes in rats with mild traumatic brain injury

Authors: *Y. ZHANG[1], M. CHOPP[2,4], Z. ZHANG[2], Y. ZHANG[2], L. ZHANG[2], M. LU[3], T. ZHANG[3], S. WINTER[5], H. BRANDSTÄTTER[5], A. MAHMOOD[1], Y. XIONG[1]
[1]Neurosurg., [2]Neurol., [3]Biostatistics and Res. Epidemiology, Henry Ford Hosp., Detroit, MI; [4]Physics, Oakland Univ., Rochester, MI; [5]EVER Pharma GmbH, Unterach, Austria

Abstract: Cerebrolysin is a neuropeptide preparation mimicking the effects of neurotrophic factors and has beneficial effects on the treatment of neurodegenerative diseases, stroke, and traumatic brain injury (TBI). To further standardize treatment schemes, we assessed the dose response of Cerebrolysin on functional improvement in a rat model of mild TBI (mTBI).This dose response study was a prospective, randomized, blinded, and placebo-controlled preclinical experiment. Male Wistar adult rats, subjected to mTBI induced by a closed head impact, were randomly treated with Cerebrolysin doses of 0.8, 2.5, 7.5 ml/kg or placebo, 4 hours after mTBI and daily for a total of 10 consecutive days. A battery of cognitive and sensorimotor functional tests were performed over the 90 day study. The primary outcome was functional improvement over the 90 days; animal weight and mortality were secondary and safety outcomes, respectively. There was a significant ($p<0.001$) dose effect of Cerebrolysin on cognitive recovery at 3 months after injury. Cerebrolysin at a dose of ≥ 0.8 ml/kg significantly ($p<0.001$) improved cognitive outcome. The higher dose (7.5 ml/kg) resulted in better cognitive recovery compared to the lower doses (0.8 ml/kg); however, there was no significant difference in cognitive recovery between 2.5 and 7.5 ml/kg doses Cerebrolysin at doses of 2.5 and 7.5 ml/kg also resulted in diverse onset times of significant improvement in sensorimotor function. There were no differences in body weight among groups. There was no mortality after mTBI and during the 90 day study. Collectively, our preclinical study following a randomized, placebo-controlled, and blinded design with a clinically relevant treatment scheme demonstrates that Cerebrolysin at

doses of 0.8-7.5 ml/kg, administered 4 hours after mTBI for a total of 10 consecutive days, improved functional outcomes at 3 months.

Disclosures: **Y. Zhang:** None. **M. Chopp:** None. **Z. Zhang:** None. **Y. Zhang:** None. **L. Zhang:** None. **M. Lu:** None. **T. Zhang:** None. **S. Winter:** None. **H. Brandstätter:** None. **A. Mahmood:** None. **Y. Xiong:** None.

Poster

217. Traumatic Brain Injury: Therapeutic Interventions I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 217.17/V18

Topic: C.09. Brain Injury and Trauma

Title: Adaptation of virtual environment for training of wheelchair users with visual impairments supported by electroencephalography

Authors: *E. S. SOUZA, SR[1], E. LAMOUNIER[2], A. CARDOSO[3]
[1]ENGINEERING, UNIVERSIDADE FEDERAL DE UBERLANDIA, Santos, Brazil; [2]COMPUTER GRAPHICS, [3]UNIVERSIDADE FEDERAL DE UBERLÄNDIA, UBERLÂNDIA, Brazil

Abstract: Many difficulties are encountered by people with disabilities, when diagnoses are made up of more than one dysfunction, for instances, in the case of wheelchair users with visually impaired. In fact, this picture generate incapacity for the performance of them activities. The treatments of disabled patients are performed in an individualized manner according to the clinical aspects. People with visual and motor disabilities have restrictions to navigate independently. In this scenario of navigation require interactions, that requirement justify the use of Virtual Reality (VR). In addition, locomotion needs to have a natural control to be incorporated, based on such condition, Electroencephalography (EEG) shows advances in the area of health with spontaneous brain signals. This research demonstrate an experiments of a wheelchair adapted with support of VR and EEG for the training of locomotion and interaction individualized of wheelchair user with visually impaired, in order to provide an efficient interactions allowing social inclusion of patients considered unable. This project was based on follow criteria like natural control, feedback, stimuli, and safety. A computer rehabilitation system multi-layer was developed incorporating natural interaction supported by EEG activating the movements in the Virtual Environment and real wheelchair with experiments successfully performed. This research consists of elaborating a suitable approach for patient's wheelchair users and visual impairment. The results of this research demonstrated that the use of Virtual Reality with EEG signals has the potential to improve the quality of life and independence of a wheelchair users who is at the same time visually impaired.

Disclosures: **E.S. Souza:** None. **E. Lamounier:** None. **A. Cardoso:** None.

Poster

217. Traumatic Brain Injury: Therapeutic Interventions I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 217.18/V19

Topic: C.09. Brain Injury and Trauma

Support: Neuroscience Institute-JFK Medical Center Startup fund

Title: Nrf2 signaling as a therapeutic target against Traumatic Brain Injury

Authors: *M. ABDUL MUNEER PERINGADY, R. K. PATEL, N. BRISKI, D. HALDAR
Neurosci., JFK Med. Ctr., Edison, NJ

Abstract: Traumatic brain injury (TBI) is a leading cause of death and disability in worldwide. Recent studies from our group and others have demonstrated that oxidative stress, Ca^{2+} signaling, and neuroinflammation are major mechanisms contributing post-traumatic neurovascular impairments and neurodegeneration. Thus, we are pursuing with the overall idea that up-regulation of endogenous antioxidants have greater potential in developing viable therapeutic strategies against TBI associated neurological/neurovascular complications. Nrf2 (nuclear factor E2-related factor 2, a transcriptional factor) transcriptional system is the major regulator of endogenous defense mechanisms operating within the cells. Nrf2 boosts the expression of several major detoxifying, cytoprotective, and anti-inflammatory genes by interacting with the antioxidant response element (ARE) in their regulatory regions, thus it can be exploited for developing novel and clinically relevant therapeutic strategy against TBI. In the current project, using an *in vitro* stretch-injury model in rat neuronal cultures and the *in vivo* fluid percussion injury (FPI) model in rats, we evaluated the role of Nrf2 in promoting major endogenous antioxidants by treating injured animals with Nrf2 activator III peptide (a synthetic cell penetrating peptide, 50 μM). Our study demonstrated the neuroprotective efficacy of Nrf2 activator III peptide by evaluating the rate of apoptosis as evidenced by the expression level of annexin V (an apoptosis marker). Further, we analyzed the expression of oxidative radical inducing enzyme, NOX1 (NADPH oxidase 1) in rat brain cortical neurons and cortex tissue sections. Both immunofluorescence and western blotting data showed that the expression level of NOX1 significantly decreased with Nrf2 activator III peptide treatment (50 μM) compared to the untreated stretch injured cells. Further, the expression level of genes coding for endogenous scavenging enzymes (antioxidants) such as superoxide dismutase (SOD), heme-oxygenase 1 (HO-1), catalase, and glutathione modulators such as glutathione peroxidase 1 (GPx1) and glutathione s-transferase mu-1 (GSTm1) were upregulated in Nrf2 activator III peptide treated animal samples. *In vitro*, treating CPUY192018 (inhibitor of Keap1-Nrf2 protein-protein interaction), transfection of Nrf2 siRNA or Keap1 siRNA, we established the neuroprotective

role of Nrf2. In conclusion, this study could establish the significance of Nrf2 in promoting regeneration and functional recovery after TBI.

Disclosures: M. Abdul Muneer Peringady: None. **R.K. Patel:** None. **N. Briski:** None. **D. Haldar:** None.

Poster

217. Traumatic Brain Injury: Therapeutic Interventions I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 217.19/V20

Topic: C.09. Brain Injury and Trauma

Support: NRF

Title: Inhibition of c-Jun N-terminal kinase protects against brain damage and improves learning and memory after traumatic brain injury in adult mice

Authors: *M.-O. KIM, S. U. REHMAN, T. ALI, G.-H. YOON
Col. of Nature Sci., Dept. of Biol., Gyeongsang Natl. Univ., Gajwa 900, Jinju, Korea, Republic of

Abstract: Traumatic brain injury (TBI) is a global risk factor that leads to long-term cognitive impairments. To date, the disease remains without effective therapeutics because of the multifactorial nature of the disease. Here, we demonstrated that activation of the c-Jun N-terminal kinase (JNK) is involved in multiple pathological features of TBI. Therefore, we investigated the disease-modifying therapeutic potential of JNK-specific inhibitor (SP600125) in TBI mice. Treating two different models of TBI mice with SP600125 for 7 days dramatically inhibited activated JNK, resulting in marked reductions of APP expression level and in amyloid beta (Aβ) production and hyperphosphorylated tau and regulation of the abnormal expression of secretases. Furthermore, SP600125 strongly inhibited inflammatory responses, blood brain barrier breakdown, apoptotic neurodegeneration, and synaptic protein loss, regulated prosurviaval processes and improved motor function and behavioural outcomes in TBI mice. More interestingly, we found that SP600125 treatment ameliorated amyloidogenic APP processing and promoted the non-amyloidogenic pathway in TBI mouse brains. Our findings strongly suggest that active JNK is critically involved in disease development after TBI and that inhibition of JNK with SP600125 is highly efficient for slowing disease progression by reducing multiple pathological features in TBI mouse brains and regulating cognitive dysfunction. (supported by NRF)

Disclosures: M. Kim: None. **S.U. Rehman:** None. **T. Ali:** None. **G. Yoon:** None.

Poster

217. Traumatic Brain Injury: Therapeutic Interventions I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 217.20/V21

Topic: C.09. Brain Injury and Trauma

Support: Dr. Miriam and Sheldon G. Adelson Medical Research Foundation (AMRF) to ES and AS

Title: Pharmacological inhibitors of chemokine receptors type 4 and 5 (CXCR4 and CCR5) stimulate recovery from traumatic brain injury

Authors: *Y. FRIEDMAN-LEVI[1], E. L. KESNER[2], D. SHABASHOV-STONE[2], G. GINCBERG[2], S. LIRAZ-ZALTSMAN[3], A. SILVA[4], E. SHOHAMI[1]
[1]Hebrew Univ., Jerusalem, Israel; [2]Pharmacol., Hebrew university, Jerusalem, Israel; [3]Neurosci. Ctr., Sheba Med. Ctr., Ramat-Gan, Israel; [4]Dept Neurobiol, UCLA Med. Ctr., Los Angeles, CA

Abstract: **Background:** Long term learning and memory (L&M) disabilities are a major concern in patients suffering from Traumatic Brain Injury (TBI). NMDAR signaling, and in particular subunit 1 (NR1), plays a key role in long term potentiation and in L&M processes. C-C chemokine receptor 5 signaling is a newly described molecular memory system, recently identified as one of the strongest negative effectors of L&M in amygdala, hippocampal and cortical circuits. We have found that its suppression by transfecting the CA1 hippocampus with *ccr5* shRNA before injury enhances recovery of L&M after closed head injury in mice. Lately, several studies have shown that CCR5 and C-X-C chemokine receptor type 4 (CXCR4) are connected to neurocognitive deficits in a mechanism that involves inhibition of the obligatory NR1 subunit phosphorylation. Here we aimed to target CCR5 and CXCR4 after TBI with pharmacological antagonists in order to preserve post traumatic L&M. Maraviroc, an FDA approved CCR5 antagonist is an antiretroviral drug used in HIV patients as a virus entry inhibitor, and Plerixafor, an FDA approved CXCR4 antagonist is used as immunostimulator in cancer patients. **Methods:** Mice were subjected to closed head injury and treated during the following 5 days with either Maraviroc, Plerixafor or their respective vehicles. Their neurobehavioral function was tested using NSS (Neurological Severity Score), and L&M functions were evaluated by Novel Object Recognition Test, Y-maze and Barnes maze. Levels of phosphorylated and total NR1 in ipsilateral cortex and hippocampus were also measured using biochemical analysis methods. **Results:** Treated mice displayed significantly improved performance in Barnes maze, Y maze and Novel Object Recognition Test, as compared to vehicle treated controls, namely improved L&M function. In contrast to Maraviroc, Plerixafor treated animals also showed significant improvement in motor skills. Western blot analysis confirmed that improved L&M after injury is correlated with increased NR1 phosphorylation in

cortical and hippocampal areas while total levels of NMDAR remains markedly unchanged. **Conclusions:** These results indicate that inhibition of chemokine receptors CCR5 and CXCR4 preserves post traumatic L&M, in a mechanism that involves maintaining NR1 subunit phosphorylation. CCR5 and CXCR4 are promising translational targets for functional neural repair after TBI, and since Maraviroc and Plerixafor are approved for human use they can be readily translated to TBI patients who suffer from cognitive decline, and probably other neurodegenerative disorders.

Disclosures: Y. Friedman-Levi: None. **E.L. Kesner:** None. **D. Shabashov-Stone:** None. **G. Gincberg:** None. **S. Liraz-Zaltsman:** None. **A. Silva:** None. **E. Shohami:** None.

Poster

217. Traumatic Brain Injury: Therapeutic Interventions I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 217.21/V22

Topic: C.09. Brain Injury and Trauma

Support: CNRM Grant R0704254

CNRM Grant G1703898

Title: Human induced pluripotent stem cell-derived neural cell grafts survive and modulate gliosis following cortical contusion injury in the mouse

Authors: M. D. NIEVES[1], *O. FURMANSKI[1], M. DEWAN[2], Q. ZHOU[2], M. L. DOUGHTY[2]
[1]Ctr. for Neurosci. and Regenerative Medcine, [2]Anatomy, Physiology, and Genet., Uniformed Services Univ. of Hlth. Sci., Bethesda, MD

Abstract: Traumatic brain injury (TBI) results in both acute primary damage and persistent secondary injury mechanisms which prolong neuronal death and dysfunction. Sustained neuroinflammation following trauma, perpetuated by chronic astroglial and microglial activation, is a key component of secondary injury mechanisms in TBI. Stem cell engraftment-based therapies have shown promise in attenuating secondary injury mechanisms to improve outcomes in experimental models of TBI. Although most pre-clinical efforts have utilized mesenchymal stem cells (MSCs) or embryonic stem cells (ESCs), human induced-pluripotent stem cells (iPSC) offer the greater therapeutic potential. iPSCs circumvent issues of ethics associated with ESCs, have unlimited cell source availability, and unlike MSCs can be differentiated into defined neural lineages for autologous cell-based regenerative strategies. We sought to determine whether human iPSC-derived NSCs, neurons, or astrocytes would survive differently and/or exert different effects in the injured mouse brain. We have generated isogeneic neurons and astrocytes from iPSC-derived neural stem cells (NSCs) with cell type-specific phenotypic characteristics in

morphology, gene expression, and physiology. Cohorts of mice received either craniotomy alone (sham) or combined with a single, mild open-skull controlled cortical impact (CCI) contusion to the somatosensory cortex. We then micro-injected iPSC-derived neurons, astrocytes, or NSCs into the deep layers (-1.4mm) of the cortex at day 1 post-injury. Preliminary stereological data reveal ≈ 65% of engrafted cells remained at 7-days post-graft in shams and that cell graft survival was lower at ≈ 40% in mice that had received a CCI. The majority of engrafted iPSCs resided in and along the corpus callosum and external capsule, indicating iPSC-derived neural cells home to host white-matter structures. iPSC-derived NSC and neuron grafts, but not astrocyte grafts, reduced astrogliosis (GFAP+ cell density) in the injured cortex and striatum, respectively. Despite these clear results on inflammation, microgliosis (Iba1+ cell density) was not significantly impacted by engraftment treatment in either brain area. Neither astrocyte nor microglial cell density was affected in the ipsilateral hippocampal CA1 field or dentate gyrus. Determining the extents to which iPSC-derived neural grafts are able to tolerate the injured microenvironment and concurrently modulate host-tissue pathology will be important information in the long-term development of regenerative stem cell-based therapies to treat TBI.

Disclosures: **M.D. Nieves:** None. **O. Furmanski:** None. **M. Dewan:** None. **Q. Zhou:** None. **M.L. Doughty:** None.

Poster

217. Traumatic Brain Injury: Therapeutic Interventions I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 217.22/V23

Topic: C.09. Brain Injury and Trauma

Title: N-Docosahexaenoylethanolamine (synaptamide) suppresses astrocyte and microglial activation after repetitive mild traumatic brain injury

Authors: *H. CHEN
NIAAA/NIH, Rockville, MD

Abstract: Recent studies have demonstrated that *N*-docosahexaenoylethanolamine (synaptamide), an endogenous metabolite of docosahexaenoic acid (DHA), increases neurogenesis, neuritogenesis and synaptogenesis in cultured cortical neurons and neural stem cells, and modulates neuroinflammation in LPS-induced microglia. It has been also demonstrated that GPR110 is the target receptor of synaptamide. In this study, we investigated the effect of synaptamide on neuropathology in a mouse model of traumatic brain injury (TBI), repeated Closed-Head Impact Model of Engineered Rotational Acceleration (rCHIMERA), and explored the underlying mechanisms. Adult C57BL/6 male wild-type (WT) and GPR110 knock-out (GPR110 KO) mice were subjected to CHIMERA injury and sham treatment for three consecutive days at 24 h interval. Immediately after each impact, mice were injected with

synaptamide (5 mg/kg) or vehicle intraperitoneally. The brains were collected for neuropathological evaluation one week after the last treatment. Immunohistochemical and Western blot analyses were performed to assess astrocyte and microglial activation, GFAP and Iba-1 protein levels, respectively. We found that rCHIMERA injury resulted in activation of microglia in optic tract, corpus callosum and cerebral cortex, and astrocyte in optic tract from both genotype mice. Synaptamide treatment of rCHIMERA-injured WT mice significantly suppressed the activated microglia and astrocyte. GFAP and Iba-1 protein levels in cortex of synaptamide-treated WT mice compared with vehicle-treated WT mice were also reduced. However, synaptamide treatment did not produce any inhibition of microglial and astrocyte activation in these areas from GPR110 KO mice. Together, these data suggest that synaptamide may provide neuroprotective effect against repetitive mild TBI by suppressing astrocyte and microglial activation in a GPR110-dependent manner.

Disclosures: H. Chen: None.

Poster

217. Traumatic Brain Injury: Therapeutic Interventions I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 217.23/V24

Topic: C.09. Brain Injury and Trauma

Support: MOST 105-2221-E-010-003

Title: Effect of ultrasound treatment in traumatic brain injury mice

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Abstract: Traumatic brain injury (TBI) leads to high rate of mortality and disability in the world every year, but there is still no effective therapeutic strategies for the patients after brain injury. They can only accept rehabilitation therapy for recovering limited cognition and motor function. This study demonstrated a novel treatment on experimental traumatic brain injury animal model. We utilized low-intensity pulsed ultrasound (LIPUS) on lesion to protect normal brain tissue from secondary injury via increasing endogenous neurotrophic factors such as brain-derived neurotrophic factor (BDNF),glial cell line-derived neurotrophic factor (GDNF),vascular endothelial growth factor (VEGF),etc. We evaluated the outcome improvement by brain water content, blood brain barrier permeability, neurological functional evaluation, western blot, histochemistry and magnetic resonance T2W imaging.Neurological functional evaluation contain rotarod test, beam walk test, modified neurological severity score (mNSS) and performed at 1, 4,

7, 14, 21, 28 days after injury.
Results showed that LIPUS treatment alleviated edema and blood brain barrier disruption at day1 after injury. We also found BDNF, GDNF and VEGF expression significantly increased at day1 and day4 after treatment. 28 days multiple treatments later, LIPUS improved functional outcomes and decreased cortical contusion volume by cresyl violet staining after traumatic brain injury. Our findings indicated that low-intensity pulsed ultrasound treatment may become a potential therapeutic strategy for traumatic brain injury.

Disclosures: **W. Su:** None. **C. Wu:** None. **S. Chen:** None. **F. Yang:** None.

Poster

217. Traumatic Brain Injury: Therapeutic Interventions I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 217.24/V25

Topic: C.09. Brain Injury and Trauma

Support: MOST 101-2314-B-350-001-MY3

Title: Deletion or inhibition of soluble epoxide hydrolase protects against brain damage and reduces microglia-mediated neuroinflammation in traumatic brain injury

Authors: *C.-H. WU[1], T.-H. HUNG[3], S.-K. SHYUE[4], C.-C. CHEN[5], C.-C. LIN[5], C.-F. CHANG[6], S.-F. CHEN[5,2]
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Abstract: Microglia-induced neuroinflammation after traumatic brain injury (TBI) causes secondary injury progression and subsequently leads to neuronal damage and neurological deficits. Soluble epoxide hydrolase (sEH) is a potential mediator of brain injury via its metabolism of anti-inflammatory epoxyeicosatrienoic acids (EETs). The present study investigated the involvement of sEH in neuroinflammation and brain damage in a mouse model of TBI and in microglial cultures. Both wild-type C57BL/6 mice and sEH knockout mice were subjected to controlled cortical impact over the right parietal cortex (4m/s velocity, 2mm deformation). The effects of genetic deletion of sEH and treatment with an sEH inhibitor, 12-(3-adamantan-1-yl-ureido)-dodecanoic acid (AUDA, 10 μM in 0.5μL of 1% DMSO, i.c.v. injection, 30 min before injury, 24 h, 48 h and 72h post-injury), on neurological recovery, brain damage and inflammatory responses were evaluated. The anti-inflammatory effects of AUDA and mitogen-associated protein kinase (MAPK) signaling were also investigated in the BV2

microglial cell line and primary microglial cultures stimulated by lipopolysaccharide (LPS) - or interferon (IFN) -γ.
The results showed that sEH protein levels were up-regulated from 1 h to 4 days after TBI and expressed in microglia. Deletion of sEH significantly alleviated TBI-induced neurological deficits and brain tissue damage up to 28 days post-injury. Brain tissue damage, neuron death, brain edema, and blood-brain-barrier disruption were also reduced in sEH knockout mice at 1 and 4 days. These protective effects were associated with marked reductions in microglial activation, neutrophil infiltration, matrix metalloproteinase-9 activity, inflammatory cytokine expression, and reduced degradation of EETs at 1 and 4 days. Treatment with AUDA reduced brain edema, apoptosis, up-regulation of inflammatory cytokines and degradation of EETs at 4 days . *In vitro*, either LPS or IFN-γ treatment for 24 h induced a significant increase of sEH protein expression in BV2 microglial cell line. AUDA attenuated LPS- or IFN -γ-stimulated nitric oxide production and reduced LPS- or IFN-γ-induced P38 MAPK and NF-κB signaling in primary microglial cultures. Moreover, AUDA attenuated N2A neuronal death induced by BV2 microglial conditioned media.These data show that gene deletion or pharmacological inhibition of sEH protects against TBI. This neuroprotective effect is at least in part mediated by inhibition of P38 and NF-κB signaling in activated microglia. This suggests that inhibition of sEH may provide a potential therapy for TBI by modulating the cytotoxic functions of microglia.

Disclosures: C. Wu: None. **T. Hung:** None. **S. Shyue:** None. **C. Chen:** None. **C. Lin:** None. **C. Chang:** None. **S. Chen:** None.

Poster

217. Traumatic Brain Injury: Therapeutic Interventions I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 217.25/V26

Topic: C.09. Brain Injury and Trauma

Support: Utah NASA Space Grant Consortium Fellowship

Title: A quantitative motor assessment for TBI: Toward linking results to underlying neural injury

Authors: *P. K. JOHNSON[1], C. J. KINCAID[2], N. M. MUNCY[3], S. K. CHARLES[2]
[1]Physiol. and Developmental Biol., [2]Mech. Eng. and Neurosci., Brigham Young Univ., Provo, UT; [3]Psychology, Brigham Young Universtiy, Provo, UT

Abstract: Purpose: There is a recognized need for sensitive, quantitative evaluations of neuromuscular health. Existing exams tend to be subjective, often fail to detect subtle abnormalities, and provide little insight into neurophysiological lesions underlying the abnormalities. We previously developed a quantitative motor assessment (QMA) battery using a

quick, low-cost, accurate motion capture system and custom software, and we established normative data based on a healthy population. Here we report on 1) the sensitivity of the QMA to identify motor deficits, and 2) the feasibility of linking the results of the QMA with the brain areas underlying QMA abnormalities. **Methods:** Twelve 18-37 year-old individuals who have suffered a traumatic brain injury (TBI) were recruited to 1) perform the QMA and 2) undergo MR imagining of their brain, which included T1- and T2 weighted structural images and diffusion tensor imaging (DTI). We compared QMA results from the TBI group to the normative standards to identify motor deficits. From the DTI, we identified areas of white matter tracts showing a difference in fractional anisotropy (FA) values between the subjects with mild TBI (8) vs. moderate-to-severe TBI (4). We performed a regression analysis to compare the measures of damage extracted from the DTI data to the QMA measures from the TBI group. **Results:** QMA results from the TBI group compared to normative standards varied across individuals; however, they generally fell outside of the 25 - 75 percentiles of the three QMA measures analyzed to-date (dysmetria, reaction time, and postural sway). The FA of the moderate-to-severe group differed from that of the mild group in the motor portion of the corpus callosum and two areas in the corticospinal tract. However, these differences did not correlate with the abnormalities in dysmetria, reaction time or postural sway observed in these twelve participants. **Discussion:** Based on the preliminary analysis, there is evidence that the QMA is a sensitive tool for identifying motor deficits. However, deficits involving dysmetria, reaction time and postural sway did not appear to be related to damage in the motor area of the corpus callosum, nor in areas of the the right and left corticospinal tracts. Failure to find a link between these brain areas and QMA measures may be due to lack of power. With a complete set of QMA measures and a more comprehensive analysis of the MR data (including additional data from T1- and T2-weighted images) from a larger number of participants, we expect to have sufficient power to test if the motor deficits are correlated with abnormalities in MRI.

Disclosures: P.K. Johnson: None. **C.J. Kincaid:** None. **N.M. Muncy:** None. **S.K. Charles:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SK Charles is a scientific advisor to, and holds stock in, Vykon Technologies LLC. This company has licensed technology invented by SK Charles to develop markerless monitoring of movement disorders, i.

Poster

217. Traumatic Brain Injury: Therapeutic Interventions I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 217.26/W1

Topic: C.09. Brain Injury and Trauma

Title: Risk of concussion associated with progressive body checking for Bantam (13-14 year olds) hockey players

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Abstract: Purpose: The Ice Hockey Federation in the province of Québec implemented a new set of rules that progressively introduce body checking in the Bantam category (13-14 year olds). Specifically, the players in the class CC do not body check, those in the class BB have restricted body checking, and those in the classes AA-AAA have complete body checking. The goal of the present study was to determine if the restriction reduces the risk of concussion.
Method: This observational study took place during the championship organised by the provincial Ice Hockey Federation. Three observers were present at each game to identify injuries. A first responder was also present and was required to complete the injury questionnaire. There was a follow-up (one month later) to get more information about possible concussions. In all, 906 players participated to a total of 4023 minutes of player-expositions.
Results: Risk of concussion is superior for the classes playing with body checking (3.00 / 1000 players injured / minutes) compared to the restricted body checking group (0/1000) and the no body checking group (1.83 / 1000). There is a total of 9 concussions reported (7 for body checking group and 2 for non body checking group). About 5 / 7 of the concussions in the body checking group occurred following a body check. Surprisingly, up to 50% of players with a suspected concussion who reported symptoms returned to play.
Conclusions: The new set of rules (body check restriction) seem to reduce the risk of concussions. The number of concussions is probably underestimated when considering that some players with symptoms returned to play without consulting any professional.

Disclosures: G. Lavoie: None. **D. Ellemberg:** None.

Poster

217. Traumatic Brain Injury: Therapeutic Interventions I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 217.27/W2

Topic: C.09. Brain Injury and Trauma

Title: Dimethyl fumarate attenuates neuroinflammation and neurobehavioral deficits induced by experimental traumatic brain injury

Authors: G. CASILI[1], M. CAMPOLO[1], *I. PATERNITI[2], M. LANZA[1], A. FILIPPONE[1], S. CUZZOCREA[1], E. ESPOSITO[1]
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Abstract: TBI is a serious neuropathology that causes secondary injury mechanisms, including dynamic interplay between ischemic, inflammatory and cytotoxic processes. Moreover, the

damage induces massive cell death and outcomes in extensive dendrite degeneration leading to persistent cognitive, sensory and motor dysfunction and resulting in a permanent neurobiological alteration. Fumaric acid esters (FAEs) showed beneficial effects in preclinical models of neuroinflammation, neurodegeneration and toxic oxidative stress, so the aim of the present work was to evaluate the potential beneficial effects of dimethyl fumarate (DMF), the most pharmacologically effective molecules among the FAEs, in a murine model of TBI induced by controlled cortical impact (CCI). Mice were orally administered with DMF at the doses of 1, 10 and 30 mg/Kg, 1h and 4h after CCI. DMF treatment notably reduced histological damage and improved behavioral function, observed by Rotarod and Elevated Plus Maze (EPM) tests. Moreover, DMF treatment was able to reduce edema and brain infarctions as evidenced by decreased 2,3,5-triphenyltetrazolium chloride staining (TTC) and a blocked apoptosis process increasing B-cell lymphoma 2 (Bcl-2) expression in the injured cortex. Furthermore, DMF treatment up-regulated Nrf-2 pathway, inducing activation of manganese superoxide dismutase (Mn-SOD) and heme-oxygenase-1 (HO-1). Also, regulating NF-κB pathway, DMF treatment decreased the severity of inflammation through a modulation of neuronal nitrite oxide synthase (nNOS), interleukin 1 (Il-1β), tumor necrosis factor (TNF-α) and ionized calcium-binding adapter molecule 1 (Iba-1) expression, and cyclooxygenase 2 (COX-2) and myeloperoxidase (MPO) activity. Our results showed important protective effects of DMF in an animal model of TBI, sustaining the thesis that DMF could provide a valuable support to the therapies for brain trauma avaible today.

Disclosures: G. Casili: None. **M. Campolo:** None. **I. Paterniti:** None. **M. Lanza:** None. **A. Filippone:** None. **S. Cuzzocrea:** None. **E. Esposito:** None.

Poster

217. Traumatic Brain Injury: Therapeutic Interventions I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 217.28/W3

Topic: C.09. Brain Injury and Trauma

Support: Swiss National Science Foundation 31003A-140945/165834 and 320030/159997

Association Française contre les Myopathies (AFM-Téléthon)

Novartis foundation

Title: The self-inactivating KamiCas9 sytem for the editing of CNS disease genes

Authors: G. VACHEY[1], N. MERIENNE[1], L. DE LONGPREZ[3], C. MEUNIER[4], V. ZIMMER[1], G. PERRIARD[2], M. CANALES[2], A. MATHIAS[2], L. HERRGOTT[1], T. BELTRAMINELLI[1], T. DEQUESNE[1], C. PYTHOUD[1], M. REY[1], L. PELLERIN[4], E. BROUILLET[3], A. PERRIER[5], R.

DU PASQUIER[2], *N. DEGLON[1]
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Abstract: Neurodegenerative disorders are a major public health problem because of the high frequency of these devastating diseases in the population. Genome editing with the CRISPR/Cas9 system is making it possible, for the first time, to modify the sequence of genes linked to these diseases in the adult brain. Here, a self-inactivating CRISPR/Cas9 system, kamiCas9, was designed for transient expression of the Cas9 protein and high editing efficiency. In the first application of this technology to neurodegenerative disorders, the gene responsible for Huntington's disease (HD) was targeted in adult mouse neuronal and glial cells. Mutant huntingtin (*HTT*) was efficiently inactivated in mouse models of HD, leading to an improvement in key markers of the disease. Sequencing of potential off-targets with the constitutive Cas9 system in differentiated human iPS cells, revealed a very low incidence with only one site above background level. Importantly, the off-target frequency was drastically reduced with the kamiCas9 system. These results demonstrate the potential of the self-inactivating CRISPR/Cas9 editing for applications in the context of neurodegenerative diseases.

Disclosures: G. Vachey: None. **N. Merienne:** None. **L. de Longprez:** None. **C. Meunier:** None. **V. Zimmer:** None. **G. Perriard:** None. **M. Canales:** None. **A. Mathias:** None. **L. Herrgott:** None. **T. Beltraminelli:** None. **T. Dequesne:** None. **C. Pythoud:** None. **M. Rey:** None. **L. Pellerin:** None. **E. Brouillet:** None. **A. Perrier:** None. **R. du Pasquier:** None. **N. Deglon:** None.

Poster

217. Traumatic Brain Injury: Therapeutic Interventions I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 217.29/W4

Topic: C.09. Brain Injury and Trauma

Support: VA Grant 1I01RX002334

Title: Nilvadipine ameliorates repetitive mild TBI-induced memory impairment in aged mice

Authors: *A. MORIN[1,2], B. C. MOUZON[1,2,3], S. FERGUSON[1,2,3], D. PARIS[1,2,3], F. C. CRAWFORD[1,2,3]
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Abstract: Mild TBI (mTBI) is the most common form of brain trauma worldwide. The effect of mTBI is not well-studied within the elderly population, yet it constitutes a significant part of all mTBI patients. The rate of hospitalization for the mTBI population aged over 65 is two times higher than it is for younger adults, with ground falls and motor vehicle accidents as primary reasons. Age alone is known to slow neurorecovery and exacerbate cognitive decline but also dramatically worsens mTBI outcomes. However, preclinical studies focusing on geriatric TBI and its treatment are scant and are limited to moderate and severe injuries only. We hypothesize that mTBI pathophysiology in the aged brain has distinct characteristics from mTBI in younger adults due to pre-exiting age-related deteriorations and might require different therapeutic interventions. Herein, we present a study of 24 months old aged hTau mice after sham injuries or repetitive mTBI (r-mTBI, 5x), modeling forces common in human mTBI with or without nilvadipine treatment. Furthermore, we investigated the effects of three weeks of treatment with Nilvadipine, a spleen tyrosine kinase inhibitor which has been shown to block amyloid production, tau hyperphosphorylation and inflammation in mouse models of Alzheimer's Disease and Tauopathy. Nilvadipine is currently under investigation to treat AD in a Phase III trial in Europe. In our r-mTBI mice we observed that nilvadipine reversed memory impairments and showed a trend in the reduction of inflammation and tau pathology. To our knowledge, this is the only preclinical study focusing on the treatment of r-mTBI in the aged and these results highlight the therapeutic potential of nilvadipine in this situation. Additional studies are ongoing to investigate the effects of nilvadipine on other outcomes and in other injury paradigms.

Disclosures: A. Morin: None. **B.C. Mouzon:** None. **S. Ferguson:** None. **D. Paris:** None. **F.C. Crawford:** None.

Poster

217. Traumatic Brain Injury: Therapeutic Interventions I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 217.30/W5

Topic: C.09. Brain Injury and Trauma

Support: Australian Research Council Future Fellowship (FT120100030).

Title: Trehalose; a natural compound with neuroprotective properties for neurodegeneration

Authors: *S. D. PORTBURY, C. SGAMBELLONI, K. PERRONNES, A. J. PORTBURY, D. FINKELSTEIN, P. A. ADLARD
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Abstract: Trehalose is a stable disaccharide found predominantly in lower-order organisms that has purported therapeutic efficacy in neurodegenerative cell culture and transgenic mouse models through a diverse array of mechanisms including autophagy, growth factor promotion

and oxidative stress reduction. We therefore aimed to assess whether trehalose could reverse the cognitive decline in three mouse models of neurodegeneration; namely, the Tg2576 and rTg4510 transgenic lines, which recapitulate the amyloid and tau pathology that is characteristic of Alzheimer's disease and other disorders of the nervous system respectively, and also in a model of controlled cortical impact traumatic brain injury (TBI) in wildtype animals. Transgenic mice received a daily 2% trehalose solution via oral gavage for a period of 30 days, with TBI mice commencing the same dosing schedule 24 hours post-TBI. Behavioural assessments occurred at various time points 2 weeks after commencement of dosing and included the Morris water maze, y-maze and open field tests. In conjunction, western blotting was utilized to assess relevant changes in proteins likely associated with improved cognition. Whilst results varied between each animal model, trehalose treated animals consistently demonstrated significantly improved behavioural outcomes that were concomitant with animal model specific increases in the growth factors brain derived neurotrophic factor and progranulin, the pre-synaptic protein synaptophysin, as well as doublecortin, a reliable marker of neurogenesis. Our results indicate that trehalose, a readily available and FDA-approved compound, may be of benefit in ameliorating the cognitive deficits that characterise multiple neurodegenerative diseases and other disorders of the nervous system. Further studies are underway to determine whether these benefits extend to disease modification.

Disclosures: S.D. Portbury: None. **C. Sgambelloni:** None. **K. Perronnes:** None. **A.J. Portbury:** None. **D. Finkelstein:** None. **P.A. Adlard:** None.

Poster

218. Spinal Cord Injury: Models and Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 218.01/DP04/W6 (Dynamic Poster)

Topic: C.09. Brain Injury and Trauma

Support: UW RRF

UW Neurological Surgery

Title: Contrast-enhanced ultrasound to visualize and quantify local blood perfusion after spinal cord injury

Authors: *Z. Z. KHAING[1], L. N. CATES[1], D. M. DEWEES[1], M. F. BRUCE[2], A. HANNAH[2], C. TREMBLAY-DARVEAU[3], C. P. HOFSTETTER[4]
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Abstract: Traumatic spinal cord injury (tSCI) often leads to debilitating loss of sensory and motor function at and below the site of injury. In patients with tSCI also suffer from autonomic dysfunction, chronic pain, and loss of bladder, bowel and sexual function. It is known that tSCI causes an almost complete loss of blood flow at the site of injury (primary injury) as well as significant ischemia in the penumbra of the injury, which may contribute to progressive cell death over time (secondary injury). Neuroprotecitve treatment strategies seek to limit secondary injury. However, techniques to simultaneously monitor temporal and spatial patterns of blood flow in the contused spinal cord are lacking. Here, we present a pre-clinical tool enabling visualization of perfusion changes in a rat injury model utilizing contrast enhanced ultrasound imaging (CEUS). CEUS provides high resolution and real-time information of perfusion changes in and around regions of tSCI. Utilizing an ultrasound research platform (Verasonics Vantage, USA) combined with a 18MHz linear array transducer (Vermon, France), plane-wave nonlinear Doppler acquisitions enabled visualization of blood flow in the rat spinal cord using 10KHz pulse repetition frequencies. Spinal cords were imaged before and 15 minutes after injury (calibrated compression for 30 seconds at T7/T8). The resulting images acquired over 300 milliseconds before and after injured showed marked reductions in volume blood flow in the injured area following injury (*~35%;* n = 4*)*. These images also allowed for real-time mapping of hypoperfused areas along the length of the spinal cord (3 mm rostral and caudal to injury/lesion). Next, we examined the effects of decompression of the spinal cord by the opening of dura and pial membranes, and found that this resulted in increased volume local blood flow compared to immediately after injury (*~13%;* n = 5). These findings showed for the first time that high frequency CEUS could be used to visualize local blood flow and perfusion after tSCI, and that surgical decompression may enhance re-perfusion of the injured spinal cord. The results also suggest that CEUS may be useful for clinic application to determine injury extent and severity in patients.

Disclosures: Z.Z. Khaing: None. **L.N. Cates:** None. **D.M. Dewees:** None. **M.F. Bruce:** None. **A. Hannah:** None. **C. Tremblay-Darveau:** None. **C.P. Hofstetter:** None.

Poster

218. Spinal Cord Injury: Models and Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 218.02/W7

Topic: C.09. Brain Injury and Trauma

Support: NIH/NINDS R01NS085426

NIH/NINDS P01NS055976

NIH P50NS038370

Title: Combing constitutively-active Rheb expression and chondroitinase treatment promotes functional axonal regeneration following a cervical level 2 hemisection

Authors: *D. WU[1], M. C. KLAW[1], N. G. KHOLODILOV[2], R. E. BURKE[2,3], T. M. CONNORS[1], M.-P. COTE[1], V. J. TOM[1]
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Abstract: After spinal cord injury (SCI), severed axons in the adult mammalian central nervous system (CNS) are unable to mount a robust regenerative response. In addition, the glial scar at the lesion site further restricts the regenerative potential of axons, leading to permanent functional deficiencies. Previously, we found that providing a growth permissive environment, i.e. a predegenerated peripheral nerve graft (PNG) to span incomplete cervical injury sites along with digesting the scar-associated, growth-inhibitory chondroitin sulfate proteoglycans (CSPGs) with the bacterial enzyme chondroitinase ABC (ChABC) at the distal PNG interface results in some functional axonal regeneration. In a complete thoracic SCI model, axon regrowth out of a PNG and across a ChABC-treated scar interface is further augmented when we also tackle the intrinsic obstacles, i.e. transducing neurons rostral to the SCI site to express constitutively active Rheb (caRheb; Ras homolog enriched in brain), a GTPase that directly activates mammalian target of rapamycin (mTOR), to enhance the intrinsic growth ability of adult axons. In the current study, we adapted a similar strategy to treat animals after a cervical level 2 hemisection (C2Hx). We hypothesized that caRheb expression would provide more incentive for injured axons to grow out of a PNG and beyond a ChABC-treated scar interface and to reinnervate the distal spinal cord, improving functional recovery. To test our hypotheses, we intraspinally injected AAV-caRheb rostral to a C2Hx to transduce neurons within the spinal cord and brainstem, grafted a growth-supportive predegenerated PN bridge into the lesion cavity, and digested the inhibitory CSPGs at the distal PNG/spinal cord interface with ChABC. By comparing four groups: 1) GFP+PBS; 2) caRheb+PBS; 3) GFP+ChABC; 4) caRheb+ChABC, we found that expressing caRheb in neurons post-SCI did not enhance ingrowth into the graft but did result in modestly yet significantly more axons regenerating across a ChABC-treated distal graft interface into caudal spinal cord than either treatment alone. In addition, we found that caRheb+ChABC animals significantly improved the animals' ability to use the affected forelimb. Lastly, electrical stimulation of the PN bridge in caRheb+ChABC animals activated significantly more neurons (as indicated by c-Fos induction) than after either treatment alone, indicating that expressing caRheb potentiates the ability of axons that emerge from the graft to form synapses with host spinal neurons.

Disclosures: D. Wu: None. **M.C. Klaw:** None. **N.G. Kholodilov:** None. **R.E. Burke:** None. **T.M. Connors:** None. **M. Cote:** None. **V.J. Tom:** None.

Poster

218. Spinal Cord Injury: Models and Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 218.03/W8

Topic: C.09. Brain Injury and Trauma

Support: NIH 2R01NS028785-25

Craig H. Neilsen ID#259350

Title: A new microtubule-based approach for augmenting nerve regeneration

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Abstract: Most studies on microtubules in the nervous system have focused on the dynamic properties of the microtubules, with stabilization by taxol and related drugs being proposed as a therapeutic for nerve injury. However, while initial indications were hopeful, more recent observations have called into question whether such drugs directly help nerves to regenerate or if they only provide a small advantage by reducing proliferation within the glial scar. In particular, there is concern that microtubule-stabilizing drugs will impede the ability of the regenerating axon to navigate to its target, given that microtubule dynamics are known to be important for growth cone guidance. Even so, microtubules remain a worthy target, given that they are downstream of many of the growth factors and cell signaling pathways that have already been shown to be relevant to nerve regeneration. We hypothesize that a better approach than microtubule stabilization may be to boost the levels of the more dynamic component of the microtubule mass, which is more akin to how axons grow and navigate during development. Previously we showed in work on fetal neurons that fidgetin is a microtubule-severing protein that pares down the dynamic portions of microtubules in the axon, such that depleting fidgetin results in an increase in dynamic microtubule mass and improved axon growth. Using AAV5 to transduce adult dorsal root ganglion neurons with fidgetin shRNA, we have now tested whether fidgetin knockdown assists axon regeneration in a novel *in vitro* system in which the cells are plated on a laminin substrate with spots of aggrecan, which is a growth-inhibitory component of glial scarring after spinal cord injury. When dried onto glass coverslips, the spots create a gradient of aggrecan and lamanin that increases from the inside-out. Fidgetin knockdown resulted in faster-growing axons off the spots, as well as more crossing of axons through the laminin-aggrecan border, in both directions. With fidgetin depleted, axons of neurons on the spots grew against the concentration gradient of aggrecan, unlike their control counterparts. In

addition, the fidgetin-depleted axons had less dystrophic growth cones than controls, with microtubules that invaded into the peripheral regions of broader growth cones than controls. These in vitro results bode well for improved regeneration in an in vivo model for nerve regeneration that we are currently pursuing.

Disclosures: A.J. Matamoros: None. **D. Wu:** None. **V.J. Tom:** None. **L. Baker:** None. **D. Sharp:** None. **P.W. Baas:** None.

Poster

218. Spinal Cord Injury: Models and Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 218.04/W9

Topic: C.09. Brain Injury and Trauma

Support: NEUROREC 01-16

Title: Identification of stimulating/inhibitors factors in OEGs using nanotechnology

Authors: M. Y. SANCHEZ-MOLINA[1], *R. M. GOMEZ[1], O. CHAPARRO[2], M. F. QUIROZ-PADILLA[3], R. H. BUSTOS[4]
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Abstract: The olfactory ensheathing cells (OEGs) are promoters of cell regeneration in the nervous system due to its inherent ability to support continuous regeneration of olfactory neurons. These cells secrete proteins such as growth factors, angiogenic and pro angiogenic factors, which help neuroregeneration processes to occur but they also secrete factors that are inhibitory to these processes. The main goal was aimed at the quantitative evaluation and *in vitro* expression of soluble growth factors promoters such as Acidic fibroblast growth factor, Neurotrophin-3 and Neurotrophin-4 as well as soluble protein inhibitor factors as Myelin-associated glycoprotein MAG among them NOGO-A, using a nanobiosensing technology. OEGs in suspension was obtained from primary cultures of lamina propria (LP) and neonatal Wistar rat olfactory bulb (BO) and transfected OEGs (TEG3) obtained from the BO of adult Wistar rats. Neurotrophin-3 was identified, as the promoter factor in OEGs LP with the highest concentration, while the inhibitor factor with the highest concentration was NOGO-A. The results showed for all concentrations of the promoters and inhibitory factors a highly significant difference ($p<0.01$) between the cells conditioned BO and LP in relation to time. Additionally, in OEGs as analyte significant difference ($p<0.05$) in the expression of NOGO-A, other factors had similar concentrations in both cell types (LP/BO) with a ($P>0.05$). Finally, as the analyte TEG3. NOGO-A had a concentration of 3.35ug/mL and other factors presented very low concentrations.

Experimental results from this research indicate that the use of NT-3 as stimulating factor and the modulation of NOGO-A inhibitor factor, in OEGs obtained from neonatal LP, would be ideal therapeutic targets in experimental models of neuroregeneration.

Disclosures: M.Y. Sanchez-Molina: None. **R.M. Gomez:** None. **O. Chaparro:** None. **M.F. Quiroz-Padilla:** None. **R.H. Bustos:** None.

Poster

218. Spinal Cord Injury: Models and Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 218.05/W10

Topic: C.09. Brain Injury and Trauma

Title: Neural and synaptic guidance by molecular machines

Authors: *J. GIRON[1], N. ZILONY[2], H. SCHORI[2], O. SHEFI[2], I. BACHELET[1]
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Abstract: The ability to artificially regenerate nerve connections and functions after injury or disease is still at its infancy and is mostly limited to the peripheral nervous system. Our goal in this research was to design and study a radical approach for this challenge, based on guiding the growth of neurons and the formation of functional synapses via programmable molecular machines. These machines were fabricated from DNA and RNA by molecular self-assembly, and are capable of manipulating nerve cell biology through spatially and temporally controlled presentation of ligands to cell surface receptors. Our research focuses on high-resolution characterization and imaging of the machine-nerve cell interface. Programming the machines to control each aspect of the three-dimensional space between the points of neuron growth origin and destination during the guidance process. Our design was evaluated using PC-12 and mouse dorsal root ganglion (DRG) cells. DNA/RNA tiles were used as carriers for nerve growth factor (NGF), a well characterized differentiation and axonal guidance factor. In both neuronal systems tested, positive results were found, PC-12 cell line showed typical differentiation response as a result to the exposure to the NGF-carrying machines while the DRG cells displayed directional growth along the NGF-machine concentration gradient. The present study shows a draft strategy for implementing molecular machines in nerve regeneration by exerting logical autonomous control over neuronal growth. In vivo studies are underway to evaluate its future potential in therapy. Additionally, the DNA machines can be loaded with further programmable features that will be able to identify specific cells or locations after injury and deliver relevant substances to impacted areas.

Disclosures: **J. Giron:** A. Employment/Salary (full or part-time):; Augmanity. **N. Zilony:** None. **H. Schori:** None. **O. Shefi:** None. **I. Bachelet:** A. Employment/Salary (full or part-time):; Augmanity.

Poster

218. Spinal Cord Injury: Models and Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 218.06/W11

Topic: C.09. Brain Injury and Trauma

Support: TWU Department of Biology

The Southeast Missouri State University Department of Physics and Engineering Physics

TWU Research Enhancement Program

Title: Neuronal delivery of Y27632 ROCK inhibitor using nanocarriers

Authors: *S. SEBASTIAN[1], R. AMMASSAM VEETTIL[1], D. HYNDS[1], S. GHOSH[2]
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Abstract: Rho kinase (ROCK), known as Rho-associated coiled-coil forming protein serine/threonine kinase or Rho-associated kinase, is one of the central regulatory molecules for cytoskeleton control, cell adhesion process and gene expression. ROCK II isoform of Rho kinase is preferentially expressed in brain. ROCKs are downstream effectors of RhoA GTPase in axonal growth inhibition and it causes rapid growth cone collapse, neurite retraction, and neurite growth inhibition. ROCK up-regulation has been found in spinal cord injury. It has been reported that ROCK inhibitors were able to improve neural function recovery after nerve damage or after brain ischemia/reperfusion injury in animals. A ROCK inhibitor that has been widely used in axon growth and regeneration research is Y27632. Y27632, specifically inactivates ROCK and thereby promotes growth of neurites, both on permissive substrates and on growth inhibitory substrates. Using a nano drug carrier to deliver Y27632 to the therapeutic target and to release the drug in a controlled and sustained manner would be appropriate to reduce the dosage and side effects. We have developed a biocompatible polymer encapsulated magnetic nanocarrier system (PE-MNC) to meet this purpose. In the present study, we are determining the optimum concentration of Y27632 that can be loaded to our PE-MNCs. We treated B35 neuroblastoma cells with different concentrations of Y27632 and quantified the neurite outgrowth using Nikon A1 confocal microscope system. In future, PE-MNCs will be loaded with optimum concentration of Y27632 and its release profile will be tested in rat cortical neurons.

Disclosures: **S. Sebastian:** None. **R. Ammassam Veettil:** None. **D. Hynds:** None. **S. Ghosh:** None.

Poster

218. Spinal Cord Injury: Models and Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 218.07/W12

Topic: C.09. Brain Injury and Trauma

Support: NSF GRFP DGE-1247271

NIH R01 NS092754

Title: IL-4 releasing biomaterials reduce inflammation to promote regeneration after spinal cord injury

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Abstract: Introduction: During the first few hours following spinal cord injury (SCI), the lesion becomes pro-inflammatory; the recruited M1 macrophages secrete pro-inflammatory cytokines and produce reactive oxygen species. This environment is not permissive of axonal extension. Electrospun fibers are used as guidance scaffolds to promote neural regeneration following SCI. However, little is known about the ability of electrospun fibers to modulate intraspinal inflammation, and few studies have used fibers in an attempt to modulate macrophage recruitment and polarization. In this study, we use a combinatorial approach to shift macrophage polarization and direct axonal extension using interleurkin-4 (IL-4)-releasing polymer films with electrospun fibers on top. We hypothesize that the IL-4-releasing films will shift macrophage polarization towards a regenerative phenotype and increase neurite extension along fibers. **Materials and Methods**: Poly-L-lactic acid was electrospun onto poly(lactic-co-glycolic acid) films loaded with IL-4. IL-4 release was assessed using a Bio-Plex Pro™ Mouse Cytokine Bead Array (CBA). Peritoneal macrophages (PMACs) were polarized to a M1 phenotype using interferon-γ (100 ng/mL) for 24 hours then cultured on the fiber-film surfaces. Polarization state was assessed using qPCR and a multiplex cytokine bead array. In future experiments, the macrophage supernatant will be cultured with murine dorsal root ganglion (DRG), and neurite outgrowth will be assessed. ANOVA ($p<0.05$) followed by Tukey's HSD test will be used to analyze results. **Results**: Based on CBA results, IL-4 burst-released from films and then gradually released during the following 120 hours. M1-polarized PMACs cultured on the IL-4-releasing films had increased RNA expression of arginase-1 (Arg-1), an M2 marker; however,

this was lower than the Arg-1 expression of PMACs cultured on control films with soluble IL-4. Protein cytokine levels will also be used to assess the polarization state. **Conclusions**: IL-4 was released quickly from films and increased Arg-1 RNA expression, demonstrating an anti-inflammatory shift. IL-4 release levels were lower than expected, and strategies to stabilize IL-4 will be studied next. Future studies will also examine the effect of this macrophage phenotypic shift on DRG neurite outgrowth. Modulation of macrophage phenotype and neurite outgrowth using this combinatorial anti-inflammatory/guidance scaffold provides a greater chance of achieving functional recovery after SCI than biomaterial or pharmacological therapies alone.

Disclosures: A. D'Amato: None. **A.M. Ziemba:** None. **D.L. Puhl:** None. **T. MacEwan:** None. **A. Koppes:** None. **R. Koppes:** None. **M. Lennartz:** None. **R.J. Gilbert:** None.

Poster

218. Spinal Cord Injury: Models and Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 218.08/W13

Topic: C.09. Brain Injury and Trauma

Support: NIH NINDS R21NS62392

NSF 1150125

Title: The effect of fiber diameter on astroglial morphology and glutamate transporter production

Authors: *C. JOHNSON, R. J. GILBERT
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Abstract: Introduction: After spinal cord injury, lysed and apoptotic cells release glutamate into the injury environment, causing excitotoxic death of exposed neurons. The death of neurons releases more glutamate into the environment, spurring further dieback. This is one part of the secondary injury cascade that increases the lesion volume after injury[1]. Astroglia are capable of removing glutamate from the environment through glutamate transporters - glutamate aspartate transporter (GLAST) and glutamate transporter 1 (GLT-1). Recently, our lab found that astroglia cultured on electrospun fibers change to a morphology that is associated with increased glutamate uptake by increasing GLT-1 expression[2]. But, nothing is known about the effect of fiber diameter on astroglial glutamate uptake. We prepared fibers with two distinct diameters to test how fiber diameter affects astroglial morphology and glutamate transporter levels. This study is impactful because the diameters represent changes in axon caliber as neurons mature. **Materials and Methods:** Aligned 400nm diameter small fibers (**SF**) and 800nm diameter large fibers (**LF**) were electrospun and analyzed with scanning electron microscopy. Primary astroglia

were isolated from p2 Sprague Dawley rats and cultured on fibronectin coated LF, SF, and Film control surfaces for 24 or 96 hours (n=3). Astrocytes were fixed and immunostained for glial fibrillary acid protein (GFAP) to determine morphology. Western blots were performed (n=6) for GFAP and glutamate transporters (GLAST, GLT-1). Astroglial morphology and protein expression were measured using ImageJ, and samples were analyzed with an ANOVA followed by a Tukey HSD. **Results:** Astroglia cultured on LF scaffolds were consistently more elongated compared to those cultured on the SF scaffolds and films, for all time points. The differences in morphology became most apparent after 24 hours in culture, while the differences in glutamate transporter protein expression became most apparent after 96 hours. Astroglia on LF and SF scaffolds showed significant ($p < 0.05$) increases in GLT-1 over film controls, but were not significantly different from each other. GFAP and GLAST expression were not significantly different at any measured time point. **Conclusion:** Fibrous substrates increase astroglial glutamate uptake by increasing GLT-1 production, but they do not significantly affect GFAP or GLAST levels. Astroglial morphology is sensitive to changes in fiber diameter between 400nm and 800nm, but the morphology change is not coupled with increased glutamate transporter production.

Disclosures: C. Johnson: None. **R.J. Gilbert:** None.

Poster

218. Spinal Cord Injury: Models and Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 218.09/W14

Topic: C.09. Brain Injury and Trauma

Support: NIH 5R01NS064004-07

Craig H Neilsen Foundation #261214

Title: Microglia and complement mediate loss of premotor cholinergic innervation in spinal cord deprived of corticospinal projection

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Abstract: The corticospinal tract (CST) is the major descending motor pathway controlling voluntary movement. Spinal interneurons play critical roles in conveying CST inputs to motor neurons. One subset of interneuron, Pitx2 cholinergic interneurons, which are located in the medial intermediate zone of spinal cord, has been recently identified as a key premotor interneuron class. These interneurons receive direct CST projections, form large cholinergic terminals, C bouton, on motoneurons, and modulate motoneuron excitability by reducing spike

after-hyperpolarization and increasing motoneuron firing. Studies in developing animals revealed parallel changes in cholinergic interneurons with manipulation of corticospinal activity.
We examined the spinal cord of adult rats after unilateral pyramidal tract lesion (PTX), focusing on 3 groups: day3 and day10 after lesion, and PTX+systemic minocycline, a microglia inhibitor. ChAT, OX42, CD68, and C1q antibodies were used to detect cholinergic interneurons and C boutons, microglia and C1q. M1 muscimol infusion, which inactivates motor cortex, was used to investigate activity dependence.
We found that there is a substantial reduction in cholinergic interneurons and C boutons after PTX. We found this down-regulation of cholinergic interneurons and C boutons starts at day 3 and exacerbates until day10 post-PTx. Microglial activation showed a similar timeline. In contrast, C1q expression, both intracellular (ChAT interneurons, motoneurons) and in extracellular spaces, show significant increases at day 3 and a return to baseline by day 10. Microglial engulfment of cholinergic interneurons and C boutons can be detected from day 3. Systemic minocycline significantly reduces microglial activation and C1q overexpression, and rescued the downregulation of cholinergic interneuron and C-boutons. In muscimol inactivation animals, we found slightly decreased C bouton numbers, mild microglial activation, and increased C1q expression in the spinal cord.
We show for the first time a reduction in the premotor cholinergic innervation after PTX. Our findings suggest that microglial activation and C1q are both required for this reduction. We propose the following model. CS injury or inactivation induces early microglia activation and a transient C1q overexpression. C1q triggers activation of the complement cascade that, in turn, drives more microglia activation, proliferation, and migration and this initiates the start of cholinergic interneuron and C-bouton engulfment. This process results in a progressive downregulation of the cholinergic innervation of motoneurons and a reduction in C1q by day 10.

Disclosures: Y. Jiang: None. **A. Sarkar:** None. **J.H. Martin:** None.

Poster

218. Spinal Cord Injury: Models and Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 218.10/W15

Topic: C.09. Brain Injury and Trauma

Title: Evaluating the temporal sequence of cell death in a rodent SCI model with extended morphine treatment

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Abstract: Opioids are among the most effective and commonly prescribed analgesics for the treatment of acute pain after spinal cord injury (SCI). We have shown, however, that administration of morphine in the early phase of SCI undermines locomotor recovery in a rodent contusion model. Further, we found that morphine administration is associated with decreased expression of neuronal and astrocytic markers post SCI. Increased neuronal death may lead to further loss of function. Whether morphine increases cell death or decreases the expression of cell specific markers is unknown. To test this, the current study used Caspase-3, as an apoptotic marker, together with specific neuronal and astrocytic markers, and analyzed the temporal sequence of cell loss with morphine administration. Subjects were given a moderate spinal contusion injury or were sham controls. On the day following surgery, half of the subjects in each injury condition were treated with 10 mg of morphine (i.v.) on days 1-2, 20 mg on days 3-4, and 30 mg on days 5-7. The remaining subjects served as controls, receiving an equivalent volume of 0.9% saline across days. To assess the temporal sequence of cell loss, subjects were euthanized on days 2, 4, or 8 (24 hrs after the final dose of morphine). A 1.5 cm section of injured spinal cord was collected and sectioned for immunohistochemistry. We found that morphine-treated subjects had increased co-localization between Caspase-3 and NeuN at 4 days post injury, relative to controls. By contrast, morphine did not increase co-localization between GFAP and Caspase-3, despite the decreased expression of astrocytes at 7 days. These data suggest that while morphine may induce apoptosis in neurons in vivo, astrocyte loss might be mediated by an alternate mechanism. Given the clinical utility of opioid analgesics, it is imperative that we identify the molecular mechanisms mediating the adverse effects of morphine in the rodent SCI model. We must develop safe and effective therapeutic strategies for the use of opioids in pain management after SCI.

Disclosures: M.N. Terminel: None. **M. Aceves:** None. **M. Hook:** None.

Poster

218. Spinal Cord Injury: Models and Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 218.11/W16

Topic: C.09. Brain Injury and Trauma

Support: DOD SCI 150225 to LMC

Title: Spinal cord injury causes selective loss of gastrin releasing peptide in spinal ejaculation generator in rats

Authors: J. W. WIGGINS[1], G. G. WILSON[1], *L. M. COOLEN[2]
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Abstract: Chronic spinal cord injury (SCI) causes ejaculatory dysfunction in men. Ejaculation is a reflex mediated by a spinal ejaculation generator (SEG) in the lumbosacral spinal cord. A principle component of the SEG is a neuronal population located in spinal levels L3-4 and named for their projections to the thalamus (lumbar spinothalamic cells: LSt cells). In rat, LSt cells co-express the neuropeptides galanin, gastrin releasing peptide (GRP), enkephalin, and cholecystokinin. LSt cells integrate sensory inputs during sexual activity to coordinate autonomic and motor outputs required for ejaculation, via interspinal connections and the release of neuropeptides onto spinal target neurons. We recently showed that SCI caused long term changes in the rat SEG. Contusion injury ablated ejaculatory reflexes triggered by sensory stimulation and were observed after acute removal of supraspinal inputs, hence due to long term changes within the SEG itself. Here, we tested the hypothesis that SCI caused long term reduction in the expression of GRP and galanin in LSt cells, thereby disrupting ejaculatory reflexes. Male Sprague Dawley rats received either a contusion injury at spinal levels T6-7 or sham surgery. Six weeks following contusion or sham injury, animals were perfused and spinal cords were immunoprocessed for galanin and GRP. Quantitative analysis of numbers of cells single or double labeled for galanin and GRP showed that SCI significantly reduced labeling for GRP, but not for galanin, and fewer galanin-labeled cells co-localized GRP. This effect was seen primarily in the LSt cells located in the caudal portion of the population, with intact GRP expression in rostral L3 cells. In addition, qualitative analysis showed an apparent loss of GRP axon connections to the sacral parasympathetic and motor neurons. It has previously been shown that GRP in LSt cells is regulated by testosterone acting on androgen receptors (AR). Therefore, to rule out that SCI decreased GRP via reduced testosterone or AR expression, spinal cords from sham and SCI males were immunostained for galanin and AR. Results showed that 100% of LSt cells expressed AR and that SCI did not affect co-localization. In addition, there no differences in testes weights, suggesting that reduction of GRP is not caused by reduced testosterone actions. Since our prior studies have shown GRP to be a powerful facilitative neuropeptide for control of ejaculation, selective loss of GRP could contribute to the disruption of ejaculation seen in male SCI rats and human patients.

Disclosures: J.W. Wiggins: None. **G.G. Wilson:** None. **L.M. Coolen:** None.

Poster

218. Spinal Cord Injury: Models and Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 218.12/W17

Topic: C.09. Brain Injury and Trauma

Support: DOD Grant SCIRP W81XWH-12-1-0563

NIH Grant F32NS096883

Title: Diclofenac induces L-selectin shedding on circulating and infiltrated neutrophils and non-classical monocytes, implicating multiple roles for L-selectin in inflammation following spinal cord injury

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Abstract: Spinal cord injury (SCI) elicits a robust acute inflammatory response that is marked by aggressive invasion of myeloid cells and secondary tissue damage. We have previously shown that L-selectin, an adhesion and signaling molecule broadly expressed on myeloid cells, is a determinant of neurological recovery in a murine model of SCI. We have also found that diclofenac, an FDA-approved non-steroidal anti-inflammatory drug (NSAID), improves tissue sparing and longer-term recovery when administered early after SCI. While diclofenac is known to be a potent inducer of L-selectin shedding via activation of cell surface metalloproteinases, the mechanisms by which diclofenac confers neuroprotection, including the cell types involved, remain unclear. To address this, we first administered diclofenac (40 mg/kg) or vehicle into uninjured male C57BL/6J mice and assessed L-selectin (CD62L) levels on myeloid cell subtypes from the peripheral blood by flow cytometry at 8 and 24 hours post injection. At each of these time points, diclofenac treatment reduced L-selectin levels on circulating neutrophils ($Ly6C^{low}/Ly6G^{+}$), but not inflammatory ($Ly6C^{hi}/Ly6G^{-}$) or non-classical monocytes ($Ly6C^{low}/Ly6G^{-}$), compared to vehicle. To determine the effect of diclofenac on L-selectin levels after SCI, contusive injury was performed at thoracic vertebral level 9 and diclofenac was administered immediately after injury. Peripheral blood and spinal cord tissue were collected 24 hours later. Diclofenac reduced L-selectin levels on circulating neutrophils and non-classical monocytes, but did not alter accumulation of myeloid subtypes, compared to vehicle-treated mice. Infiltrated myeloid subtypes retained considerable levels of L-selectin, raising the possibility that this molecule may participate in post-recruitment adhesive and signaling activies. Consistent with this possibility, diclofenac further reduced L-selectin on infiltrated neutrophils and non-classical monocytes compared to vehicle-treated mice. Our findings suggest that L-selectin on neutrophils and/or nonclassical monocytes may participate in post-recrutiment signaling functions in the injured spinal cord. These findings are the first to show cell type specificity for L-selectin shedding induced by diclofenac and implicate a novel mechanism by which NSAIDs attenuate secondary damage after SCI. Supported by: Department of Defense SCIRP W81XWH-12-1-0563 and National Institutes of Health NINDS F32NS096883.

Disclosures: D.A. McCreedy: None. **S.D. Rosen:** None. **L.J. Noble-Haeusslein:** None.

Poster

218. Spinal Cord Injury: Models and Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 218.13/W18

Topic: C.09. Brain Injury and Trauma

Support: NIH grant RO1 AG034113 to J.K.

Title: Structural and functional features of spinal cord meningeal lymphatic vessels

Authors: *J. HERZ[1], M. DONG[2], I. SMIRNOV[2], A. LOUVEAU[3], J. KIPNIS[1]
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Abstract: There is an accumulating body of evidence that lymphatic vessels in the meninges of the brain function as a pipeline for the removal of waste but also traveling immune cells during homeostasis and states of disease. To address if the spinal cord communicates through these brain meningeal lymphatics or if a separate lymphatic system exists, we applied an array of imaging techniques and stained for a variety of hallmark markers of lymphatic endothelium. We found a continuous network of bona-fide lymphatics in the cervical area of the spinal cord meninges. In addition, a previously unknown lymphatic system containing vessels with similar characteristics was found along the dorsal nerve roots of the cervical, thoracic and lumbar region of the cord. Here the lymphatic vessels lie embedded into the dural and arachnoid layer and fluorescent particles or tracers introduced subdurally pass through the CSF-filled space and reach the draining lymph nodes. These findings are significant because they provide a new pathway for central nervous and immune system to communicate. We are currently investigating the role of spinal cord meningeal lymphatic vessels after spinal cord injury.

Disclosures: J. Herz: None. **M. Dong:** None. **I. Smirnov:** None. **A. Louveau:** None. **J. Kipnis:** None.

Poster

218. Spinal Cord Injury: Models and Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 218.14/W19

Topic: C.09. Brain Injury and Trauma

Support: NIH Grant R01GM100474

NIH Grant R01GM072611

Title: Novel survival factor for infiltrating macrophages in the injured spinal cord

Authors: *A. J. ROLFE[1], L. SUN[1], Y. CHI[2], X. SUN[2], Y. REN[1]
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Abstract: In the United States alone, there are an estimated 17,000 new spinal cord injury cases each year. Even with timely medical interventions, the primary injury is often exacerbated by a period of inflammation and pathological vascular changes that result in additional secondary injuries. During both the primary and secondary injuries, substantial quantities of myelin debris is generated from dying glia and neurons. While it is known that myelin debris clearance by professional phagocytes such as macrophages (Mϕ) is a prerequisite for inflammation resolution, it is unclear how to mitigate the deleterious effects that accompany an increased Mϕ presence in the lesion. We previously demonstrated that bone marrow derived macrophages (BMDMϕ), but not resident microglia, are the primary phagocytes in the injured spinal cord. Following recruitment from the blood, BMDMϕ are retained in the lesion epicenter for protracted periods of time where they engulf myelin debris and become myelin laden macrophages (Mye-Mϕ) which contribute to the secondary injury. We have also found that exposure to myelin debris supports long-term BMDMϕ survival, prolonging their potential to induce damage. Thus, the therapeutic manipulation of infiltrating BMDMϕ represents a means to limit secondary injuries and promote functional recovery.

Disclosures: A.J. Rolfe: None. **L. Sun:** None. **Y. Chi:** None. **X. Sun:** None. **Y. Ren:** None.

Poster

218. Spinal Cord Injury: Models and Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 218.15/W20

Topic: C.09. Brain Injury and Trauma

Support: SAF-2016-79774-R

Title: Differential effects of IL-4 and IL-13 after spinal cord contusion in mice

Authors: *J. AMO-APARICIO, R. LÓPEZ-VALES
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Abstract: Spinal cord injury (SCI) elicits an inflammatory response that comprises mainly microglia and peripheral blood-derived macrophages. These cells contribute directly or indirectly

to tissue damage and functional loss; however, they can also promote repair. These paradoxically conflicting roles of microglia and macrophages depend on their polarization state: In response to interferon gamma or lipopolysaccharide, macrophages and microglia undergo “classical” M1 polarization. Contrary, upon interleukin 4 (IL-4) or interleukin 13 (IL-13) stimulation, macrophages and microglia acquire “alternative” M2 polarization. M1 macrophages and microglia release high levels of pro-inflammatory cytokines and free radicals. These compounds are crucial for killing microbes and tumour cells, but they also induce damage in healthy neighbouring cells and are associated with cell loss and secondary damage after SCI. Contrary, M2 macrophages release anti-inflammatory cytokines and are involved in parasite containment, tissue repair and remodelling events after injury. Importantly, the finding of this macrophage dichotomy was originally described using *in vitro* systems. *In vivo*, macrophages are influenced by multiple additional factors leading to a wide spectrum of intermediate phenotypes, where the M1 and M2 archetypal states are located at the ends of this range. We have previously demonstrated that aberrant induction of M2 polarizing cytokines after SCI hampers microglia and macrophages to express M2 markers. In this line, we found that local administration of IL-4 in the injured spinal cord induced the expression of the M2 markers, Arg1 and CD206, in microglia and macrophages, and led to functional recovery and reduced tissue damage. Here, we investigate whether IL-13, another M2 polarizing factor, has similar effects on microglia and macrophages and leads to functional recovery after SCI.We first evaluated the expression of IL-13 receptor (IL-13Rα1) and found it is induced in microglia and macrophages following contusion injury. Interestingly, we observed that the administration of IL-13 into the contused spinal cord increases levels of the M2 marker Arg1, but not CD206, in microglia and macrophages. However, administration of IL-13, contrary to IL-4, did not confer protection against functional deficits and secondary tissue damage. This study reveals that the presence of M2 markers in microglia and macrophages after SCI is not necessarily associated with locomotor recovery. Further studies are therefore needed to elucidate specific markers for protective phenotypes of microglia and macrophages after SCI.

Disclosures: J. Amo-Aparicio: None. **R. López-Vales:** None.

Poster

218. Spinal Cord Injury: Models and Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 218.16/W21

Topic: C.09. Brain Injury and Trauma

Title: F11 and Neuro2a cell line-derived neurons in an *In vitro* model of the glial scar

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Abstract: Spinal cord injury (SCI) is a debilitating medical condition resulting from severe trauma to the spinal cord. SCI can lead to permanent neurological deficits, muscle weakness, disturbance to the autonomic nervous system, abnormal or absent sensory reception, and complete paralysis. Research on the regeneration of the spinal cord is necessary to advance rehabilitation for those suffering from SCI. At the lesion site, the glial scar is formed by hypertrophic astrocytes releasing inhibitory chondroitin sulfate proteoglycans (CSPGs) into the extracellular matrix. Axons encountering high levels of CSPGs typically form dystrophic endings or turn away. To further study the impact of glial scar formation on neuronal regeneration, an *in vitro* model of the glial scar called the spot assay was utilized. The assay combines laminin, a growth-promoting substrate, and aggrecan, a highly inhibitory CSPG, to create spots with an increasing aggrecan gradient to form a high-aggrecan/low laminin rim. Using this assay, we compared differentiated neurons from two cell lines: Neuro2a mouse neuroblastoma cells and F11 rat/mouse hybrid dorsal root ganglion sensory neurons (DRGs). The neurons were visualized using immunofluorescence and wide-field microscopy to quantify the number of axons that crossed the inhibitory rim of the spot at various cellular concentrations. Both cell types crossed the inhibitory rim at low levels. We are currently investigating how this behavior changes by altering the substrate type. Further study of the glial scar could allow us to develop therapies for the treatment of SCI.

Disclosures: **J.G. Bracamonte:** None. **A. Diaz:** None. **A.L. Hawthorne:** None.

Poster

218. Spinal Cord Injury: Models and Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 218.17/W22

Topic: C.09. Brain Injury and Trauma

Support: TWU Research Enhancement Program

TWU Department of Biology

Title: Cell targeting of surface functionalized nanoparticles in neuronal cells

Authors: *C. MENGJIE[1], D. L. HYNDS[2], R. AMMASSAM VEETTIL[3], S. GHOSH[4], T. MCALLISTER[4]
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Abstract: Damage to axons of corticospinal tract neurons leads to permanent loss of voluntary fine motor control. In recent years, nanoparticle (NP) has becomes more widely used in

therapeutic fields and serve as a vehicle to deliver drugs to the damaged neuron cells across the blood brain barrier (BBB). In this study, we used -COOH and -NH_2 surface functionalized nanoparticles (SFNPs) to study the mechanism of cell targeting in B35, PC12, and corticospinal tract (CST) neurons. We hypothesize that these thermo-responsive PEG coated MNPs with -COOH and -NH_2 surface functionalized nanospheres would be internalized by neurons compared to the other, such as glial cells, in a mixed cortical culture. Different antibody such as βIII-Tubulin, Actin, Ctip2 /Otx1, and GABAergic will be used. In this case, the targeting efficiency of nanospheres by different cell types in a mixed cortical culture will be determined as well. In the future study, targeting the nanospheres using BDNF, NGF, NT3 or other targeting molecules specifically for the neurons would allow us to direct the nanospheres to the target neurons. We suggest that our nanoparticle drug delivery systems are able to target specific neurons and provide on-demand release of a specific drug. Therefore, these systems provide potential therapies for encouraging axon regeneration in spinal cord injury and degenerative diseases of the central nervous system.

Disclosures: C. Mengjie: None. **D.L. Hynds:** None. **R. Ammassam Veettil:** None. **S. Ghosh:** None. **T. McAllister:** None.

Poster

218. Spinal Cord Injury: Models and Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 218.18/W23

Topic: C.09. Brain Injury and Trauma

Title: Modeling the dynamics of the neural circuitry controlling micturition

Authors: *V. GUNTU[1], C. GARROW[2], D. SCHULZ[3], S. NAIR[1]
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Abstract: We report results from an interdisciplinary study focused on an understudied but crucial aspect of how spinal cord injury (SCI) alters the properties and activity of uninjured neural networks below the site of injury, focusing on the rodent lower urinary tract (LUT, composed of the bladder and urethra). The study involves both biological experimentation and computational modeling, with the latter being the primary focus of this poster. Our hypothesis is that neurons are fundamentally altered when inputs are removed by injury. Understanding how and why these neurons and networks are altered by denervation as a result of injury is essential for studies aimed at restoring function. Computational models complement biological experiments very well in such a study. The sympathetic pathway controls bladder filling and includes sympathetic pre-ganglionic neurons in the spinal cord and post-ganglionic cells of the inferior mesenteric ganglion. Sacral parasympathetic outflow controls bladder voiding, and this

pathway includes the parasympathetic pre-ganglionic cells and the post-ganglionic neurons of pelvic ganglia. While urine storage mechanisms are largely dependent on spinal reflex pathways, urine voiding is dependent on a rapid switch from filling to voiding mediated by descending supraspinal inputs. Sensory information regarding bladder fullness is conveyed to the spinal cord through the sacral pelvic and lumbar splanchnic nerves. We have developed models of the cells in the ganglia using information from the literature and first-hand biological recordings pelvic ganglia neurons from our Lab. Sensory afferents are modeled presently using a regression fit with filling rate. A mechanistic model of the bladder reported in the literature has been used, with a simple neurogenic logic for the supraspinal input cited earlier, to switch between modes. The model successfully reproduced the bladder volume and pressure patterns with the switch. With the base model, we are presently exploring the relative strength/balance of inhibition and excitation across pathways required for normal bladder function, and the level of integration of the supraspinal input necessary to coordinate the switch from filling to voiding. We will be improving our model to show guarding reflex and investigate further how it works and problems associated with improper execution of guarding reflex (Ex: detrusor-sphincter dyssynergia) at neuronal level. This improved model will then be modified for SCI studies by disconnecting the top down control and investigate mechanisms that might restore the reflex arc.

Disclosures: V. Guntu: None. **C. Garrow:** None. **D. Schulz:** None. **S. Nair:** None.

Poster

218. Spinal Cord Injury: Models and Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 218.19/W24

Topic: C.09. Brain Injury and Trauma

Support: NINDS RO1NS091582-01A1

Title: Myelin modulates macrophage responses after spinal cord injury

Authors: *T. J. KOPPER[1,2,3], B. ZHANG[1,2,3], J. C. GENSEL[1,2,3]
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Abstract: Spinal cord injury (SCI) produces chronic inflammation largely mediated by resident microglia and infiltrating monocytes (here, collectively referred to as macrophages). These activated SCI macrophages eventually adopt a pro-inflammatory, pathological state that continues long after the initial injury. Pro-inflammatory macrophages potentiate secondary damage and impair SCI recovery, yet the mechanisms driving chronic pathological SCI macrophage activation are poorly understood. After SCI, macrophages clear and accumulate extensive myelin debris. Published data demonstrates that myelin debris can directly stimulate macrophages to adopt different activation states. We hypothesize that myelin, in combination

with inflammatory stimuli within the SCI lesion environment, increases pro-inflammatory macrophage activation. To test this hypothesis we stimulated bone marrow derived macrophage with pro-inflammatory stimuli (LPS+INF-gamma) in vitro in the presence or absence of myelin. Myelin co-stimulation significantly increased pro-inflammatory IL-12 cytokine production, decreased anti-inflammatory IL-10 production, and increased reactive oxygen species production relative to unstimulated or LPS+INF-gamma treated controls. One potential mechanism for the myelin-mediated pro-inflammatory potentiation is increased activation of the enzyme cytosolic phospholipase A2 ($cPLA_2$) within macrophages. This enzyme has the potential to modify membrane lipids into direct and indirect pro-inflammatory stimuli. Indeed, through immunohistochemical analyses of spinal cord tissue sections after T9 contusion SCI in female C57BL/6 mice we observed $cPLA_2$ activation in myelin-laden macrophages at both 7 and 28 days post injury. Ongoing studies aim to link this continued $cPLA_2$ activity to potentiated pro-inflammatory macrophage activation and explore potential therapeutics to block these pathways after SCI.

Disclosures: **T.J. Kopper:** None. **B. Zhang:** None. **J.C. Gensel:** None.

Poster

218. Spinal Cord Injury: Models and Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 218.20/W25

Topic: C.09. Brain Injury and Trauma

Title: Differential neurite outgrowth of F11- and Neuro2a-derived neurons on inhibitory and growth-promoting substrates

Authors: *J. K. KING[1], L. M. WILSON[2], A. W. HOARD[2], B. Y. AINUZ[2], A. L. HAWTHORNE[2]
[1]Burnett Sch. of Biomed. Sci., Univ. of Central Florida, Rockledge, FL; [2]Burnett Sch. of Biomed. Sci., Univ. of Central Florida, Orlando, FL

Abstract: After spinal cord injury, neuroregeneration in the central nervous system (CNS) is limited due in part to the inhibitory lesion environment. The glial scar contains an increased concentration of inhibitory chondroitin sulfate proteoglycans (CSPGs). Aggrecan, possessing a high number of glycosaminoglycan side chains, has been shown to be one of the highly inhibitory CSPGs present in a CNS lesion. Laminin, an extracellular matrix (ECM) trimeric glycoprotein, provides adhesion and promotes the regrowth of neurons. The lesion environment coupled with the intrinsic potential of the neuron determines successful regrowth. Our goal was to investigate the growth of cell line-derived neurons for *in vitro* regeneration studies using growth-promoting and growth-inhibitory substrates. We differentiated two different cell lines: Neuro-2a (N2a) cells, derived from mouse neuroblastoma, and F11 cells, a fusion of rat

embryonic dorsal root ganglion (DRG) and mouse neuroblastoma. Neurons differentiated with forskolin were grown on three different concentrations of ECM proteins: 10 µg/ml laminin, 1 µg/ml laminin, or 1 µg/ml laminin mixed with 50 µg/ml aggrecan. After four days, cells were fixed and immunostained for β-tubulin III and dapi. Then, the lengths of the neurites were quantified using NeuronJ. N2a-derived neurons followed the expected trend of decreased outgrowth when grown on the inhibitory aggrecan/laminin mixture. F11-derived neurons grew significantly longer than N2a's in the presence of aggrecan, indicating that the F11 neurons may have increased propensity for growth. It is possible that the F11's retained some embryonic growth potential, while N2a's may more closely resemble adult neurons. The differences may also be attributed to cell type: brain-derived versus sensory neurons. Through ongoing studies, we aim to examine differences in the intrinsic growth potential by investigating the gene expression of F11 and N2a cell lines. Overall, identifying a neuronal cell line that most closely mimics adult neuronal behavior in a model of the glial scar can serve as a model for future regenerative studies.

Disclosures: **J.K. King:** None. **L.M. Wilson:** None. **A.W. Hoard:** None. **B.Y. Ainuz:** None. **A.L. Hawthorne:** None.

Poster

218. Spinal Cord Injury: Models and Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 218.21/W26

Topic: E.09. Spinal Cord Injury and Plasticity

Support: National Natural Science Foundation of China 81650007, 31500968

Natural Science Foundation of Jiangsu BK20151127

Fundamental Research Funds for the Central Universities JUSRP51619B

Title: Neuropeptide Y facilitates locomotor recovery and regeneration after spinal cord injury in adult zebrafish

Authors: L.-F. WANG, P. ZHAO, C. CUI, X. CHEN, H.-D. ZHAO, C.-J. LIU, S.-X. PENG, S.-B. HUANG, *Y.-Q. SHEN
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Abstract: Following injury, the spinal cord of adult zebrafish is capable of regeneration, which is in stark contrast to the limited repair within the mammalian central nervous system. In the present study, we evaluate the effects of neuropeptide Y (NPY) on zebrafish spinal cord injury (SCI) by swimming ability, axon regrowth and motor neuron proliferation. We found that NPY morpholino (MO) treatment resulted in retarding both axon regrowth and locomotor recovery in

the injured zebrafish spinal cord. NPY protein expression substantial increased at 6 d, 11 d, and 21 d after SCI and expressed in the cytoplasm of spinal cord motoneurons, moreover, immunostaining of PCNA and motoneuron study showed motoneuron proliferation after SCI. The western blot and immunofluorescence results suggested that NPY could promote motoneuron proliferation. In addition, immunofluorescence staining of GFAP (a marker for radial glial cell) and motoneuron results suggested that the newly formed motoneurons might be derived from GFAP positive cells, and NPY could influence regeneration by activating the Y1 receptor subtype. Collectively, our data suggest that NPY promotes locomotor recovery and axon regrowth by regulating motoneuron proliferation through activation of the Y1 receptor.

Disclosures: L. Wang: None. **P. Zhao:** None. **C. Cui:** None. **X. Chen:** None. **H. Zhao:** None. **C. Liu:** None. **S. Peng:** None. **S. Huang:** None. **Y. Shen:** None.

Poster

218. Spinal Cord Injury: Models and Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 218.22/W27

Topic: C.09. Brain Injury and Trauma

Support: The Veterans Administration

Wings for Life

UCSD FISP

Nakajima Foundation

Title: Synaptic connectivity between host and neural progenitor cell-derived neurons after spinal cord injury

Authors: *S. L. CETO[1], K. J. SEKIGUCHI[3], A. NIMMERJAHN[3], M. H. TUSZYNSKI[2]
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Abstract: Neural stem cells (NSCs) grafted into sites of spinal cord injury (SCI) may act as new electrophysiological relays between host neurons above and below the lesion. Host axons regenerate robustly into NSC grafts and form synapses; in turn, graft axons extend long distances into host white and gray matter caudal to the injury and form synapses. To investigate potential functionality of these new synaptic pathways, we performed calcium imaging and whole-cell patch clamp recordings in mice with NSC grafts after SCI. We placed T12 dorsal column lesions and acutely grafted embryonic day thirteen (E13)-derived spinal cord neural progenitor cells (NPCs) expressing the calcium indicator GCaMP6f into the lesion site. From 6 to 8 weeks later,

we imaged the activity of populations of neurons within NPC grafts in acute spinal cord slices, anesthetized, or awake behaving animals.
In acute spinal cord slices, grafted neurons exhibited spontaneous activity. Moreover, dorsal column stimulation evoked responses in grafted cells. In vivo imaging revealed spontaneous activity in both neurons and glia, as well as hindpaw pinch- and cold air puff-evoked responses. Activity patterns included both large-scale events and independent, single-neuron activity. We are currently optimizing methods for interrogating host-to-graft inputs through optogenetic techniques. We are also planning to probe the host response to graft output by stimulating graft axons and imaging host cells in the areas that they innervate. Additionally, using cell type-specific transgenic Cre lines to drive GCaMP expression in grafts, we will assess the activities of different graft cell types.

Disclosures: S.L. Ceto: None. **K.J. Sekiguchi:** None. **A. Nimmerjahn:** None. **M.H. Tuszynski:** None.

Poster

218. Spinal Cord Injury: Models and Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 218.23/W28

Topic: C.09. Brain Injury and Trauma

Support: NIH NS042291

VA Gordon Mansfield Consortium

NIH NCRR P51 OD011107-56

Craig H. Neilsen Foundation

Spitzer Family Trust

Dr. Miriam and Sheldon G. Adelson Medical Research Foundation

Christopher and Dana Reeve Foundation

Title: Chondroitinase improves anatomical and functional outcomes after primate spinal cord injury

Authors: *E. S. ROSENZWEIG[1], E. A. SALEGIO[2], J. J. LIANG[1], J. L. WEBER[1], C. WEINHOLTZ[1], J. H. BROCK[1,3], R. MOSEANKO[2], S. HAWBECKER[2], R. PENDER[2], J. F. IACI[4], A. O. CAGGIANO[4], A. R. BLIGHT[4], B. HAENZI[5], J. R. HUIE[6], L. A. HAVTON[7], Y. S. NOUT-LOMAS[8], J. W. FAWCETT[5], A. R. FERGUSON[6], M. S. BEATTIE[6], J. C. BRESNAHAN[6], M. H. TUSZYNSKI[1,3]

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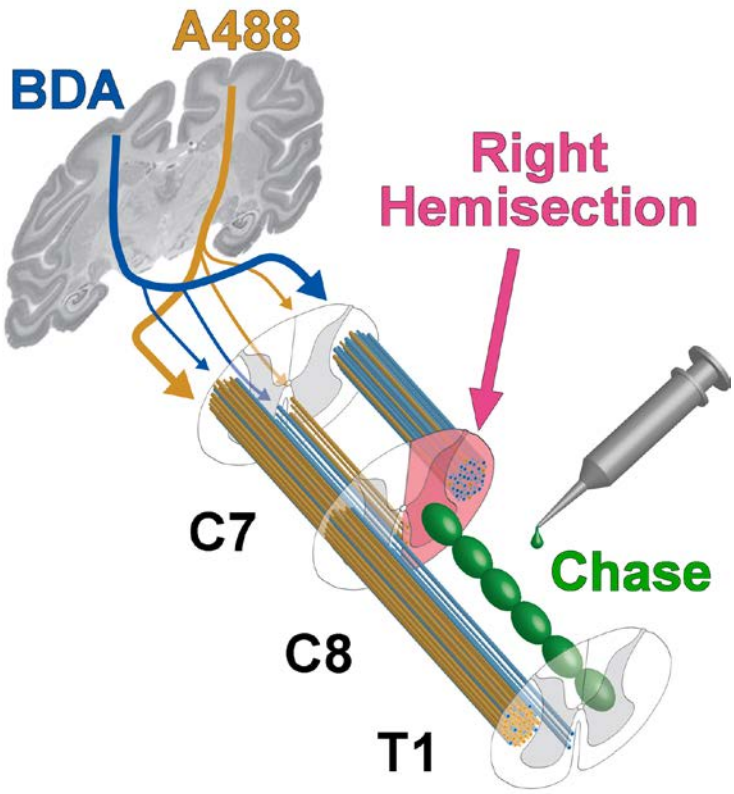
Abstract: Inhibitory chondroitin sulfate proteoglycans (CSPGs) in the extracellular matrix hinder axonal regeneration after spinal cord injury (SCI). In particular, CSPGs form 'peri-neuronal nets' that may limit axonal regrowth and synaptic plasticity. Moreover, CSPGs are newly synthesized at sites of central nervous system injury and directly block axon growth. Administration of the enzyme chondroitinase (Chase) degrades inhibitory portions of CSPGs and improves axonal sprouting and functional recovery after SCI in rodents. Here we show for the first time that Chase treatment is also effective in a non-human primate model of SCI. Adult rhesus monkeys received C7 spinal cord lateral hemisection lesions. Four weeks later, subjects received intraparenchymal spinal cord injections of 20 U/ml Chase (or saline) caudal to the lesion. Five µl of Chase / saline were injected at each of 10 sites (spaced 1.5 mm apart in the rostrocaudal axis) on the right side of the spinal cord from C7-T1. This effectively targets spinal cord circuits below the lesion that control hand function. Hand function and locomotion were assessed weekly in a large enriched environment and in a cage-based Brinkman task (retrieval of small food items from wells in a board). Corticospinal axons were labeled with dextran-conjugated tracer injections into right and left motor cortices 6 weeks before sacrifice. Chase-treated monkeys recovered hand function (but not locomotion) better than control monkeys (Condition x Time, $P<0.001$, Linear Mixed Model [LMM]). The fact that the beneficial effect is specific to hand function is consistent with the hypothesis that Chase increases axonal sprouting in the treated region (segments C7-T1). Indeed, Chase increased corticospinal axon growth ($P=0.036$, LMM) and the number of corticospinal synapses ($P=0.001$, LMM) in gray matter caudal to the lesion. Thus, intraparenchymal Chase is an effective treatment in a primate model of SCI that recapitulates some aspects of traumatic human SCI. Chase treatment for SCI therefore warrants further research and translational development.
Fig. 1:



Disclosures: **E.S. Rosenzweig:** None. **E.A. Salegio:** None. **J.J. Liang:** None. **J.L. Weber:** None. **C. Weinholtz:** None. **J.H. Brock:** None. **R. Moseanko:** None. **S. Hawbecker:** None. **R. Pender:** None. **J.F. Iaci:** A. Employment/Salary (full or part-time):; Acorda Therapeutics, Inc. **A.O. Caggiano:** A. Employment/Salary (full or part-time):; Acorda Therapeutics, Inc. **A.R. Blight:** A. Employment/Salary (full or part-time):; Acorda Therapeutics, Inc.. **B. Haenzi:** None. **J.R. Huie:** None. **L.A. Havton:** None. **Y.S. Nout-Lomas:** None. **J.W. Fawcett:** F. Consulting Fees (e.g., advisory boards); Acorda Therapeutics, Inc.. **A.R. Ferguson:** None. **M.S. Beattie:** None. **J.C. Bresnahan:** None. **M.H. Tuszynski:** F. Consulting Fees (e.g., advisory boards); Acorda Therapeutics, Inc..

Poster

218. Spinal Cord Injury: Models and Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 218.24/W29

Topic: E.09. Spinal Cord Injury and Plasticity

Support: NIH Grant R01 NS 082463

Barrow Neurological Foundation

Title: Associations between motoneuron discharge and afterhyperpolarization properties following incomplete spinal cord injury

Authors: *V. V. TURKIN, D. O'NEILL, T. M. HAMM
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Abstract: We have examined the discharge properties of hindlimb motoneurons following incomplete spinal cord injury (iSCI). We asked whether the association between discharge properties and characteristics of the afterhyperpolarization (AHP) or the distribution of discharge properties within motoneuron pools was altered after iSCI. Two groups of iSCI rats were studied: a group housed in standard cages and an exercise group housed in cages with running wheels starting at 1 week after injury. Rats with sham injuries served as controls. Discharge properties were determined in response to intracellular injection of 5-second current triangles, measuring primary range frequency-current (f-I) slope, transition frequency (discharge rate at the start of the primary range), and mean discharge frequency in the primary range. Transition frequency and mean primary range discharge frequency were inversely correlated with input resistance (R_N), a measure of motoneuron size, in control rats and in each of the iSCI groups. F-I slope was directly correlated with R_N, although this correlation tended to be weaker in the standard-cage iSCI group. The distribution of primary range f-I slopes was the same in control and iSCI groups. Transition frequency and mean primary range discharge rate tended to be lower in the iSCI exercise group. However, this tendency was not significant in either the whole population or in type F motoneurons (AHP half decay < 20 ms), in which AHP amplitude increases in iSCI exercise rats (Turkin et al., 2016). Primary range f-I slope was not correlated with either AHP amplitude or half-decay time in any group. Transition frequency and mean primary range frequency are inversely correlated with AHP amplitude in all groups. Both are also inversely correlated with AHP half-decay time in control and iSCI exercise groups. They are not correlated with AHP half-decay time in the iSCI standard group, however. Overall, the distribution of discharge properties of rat hindlimb motoneurons is largely preserved following iSCI, and AHP amplitude remains a primary determinant of discharge rates. However, the associations of primary f-I slope with R_N and discharge rates with AHP half-decay time tend to weaken or be lost following iSCI, while exercise reduces these effects. This effect of iSCI seems consistent with changes in the expression of the SK3 isoform of Ca2+ activated K+ channels in lumbar motoneurons following iSCI (Romer et al., 2017).

Disclosures: V.V. Turkin: None. **D. O'Neill:** None. **T.M. Hamm:** None.

Poster

218. Spinal Cord Injury: Models and Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 218.25/W30

Topic: E.09. Spinal Cord Injury and Plasticity

Support: Grant P01 NS 057228

Grant R01 NS 082463

Barrow Neurological Foundation

Title: Alterations in postsynaptic Ca2+-activated K+ channels in rat hindlimb motoneurons following incomplete spinal cord injury

Authors: S. H. ROMER[1], A. S. DEARDORFF[1], V. V. TURKIN[2], D. O'NEILL[2], R. E. W. FYFFE[1], *T. M. HAMM[2]
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Abstract: Differential expression of SK2 and SK3 isoforms of the Ca^{2+}-activated K^+ channels contribute critically to the spectrum of rat α-motoneuron properties by mediating the afterhyperpolarization (AHP). Specifically, the SK3 isoform is predictive of slow-twitch motoneurons (MNs) being found in smaller MNs that have longer AHP durations and larger AHP amplitudes (Deardorff et al., 2013). We analyzed lumbar spinal cords for SK3 immunohistochemistry following completion of physiological studies to determine whether incomplete spinal cord injury (iSCI) produces changes in the expression of these channels. Spinal cords were obtained from control rats (sham injury) and two groups of rats with iSCI, one housed in standard caging and one given access to exercise by placement in cages with running wheels starting 1 week after injury. Lumbar spinal cord sections (75 μm) were processed for SK3 and VAChT immunohistochemistry from 11 animals from each of the three experimental groups. All analysis was blinded to experimental group. SK3 channels were expressed heterogeneously within lateral motoneurons pools. In all experimental groups, SK3 channels were primarily observed in large, membrane-bound clusters composed of "threadlike" bands of immunoreactivity and always juxtaposed to large, VAChT+ C-boutons. In control animals, approximately 25% of MNs sampled expressed SK3 immunoreactivity, consistent with previous observations (Deardorff. et al., 2013). However, following iSCI, 37% of MNs expressed SK3, a significant increase (ANOVA). SK3 immunoreactivity was found in 34% of sampled MNs in the exercise iSCI group, a value that was not significantly different from either the control or the standard iSCI group. No correlation was found between the proportion of SK3 immunoreactivity and the distance run by the animals in the exercise group. We also observed a decrease in the number of MNs observed with Nissl staining following injury, dropping from 50 lateral column MNs per section in the control group to 41 per section in the standard iSCI group. The loss of MNs in the exercise iSCI group was less apparent, with 46 lateral column MNs per section. This increase in the proportion of motoneurons expressing SK3 after injury suggests an up-regulation of SK3 in larger MNs, although a selective loss of larger MNs following injury cannot be excluded. An expansion of SK3 channel expression into a wider range of MNs would be consistent with alterations in the distribution of AHP properties and AHP-discharge correlations that occur after spinal cord injury (Turkin et al., 2016, 2017).

Disclosures: **S.H. Romer:** None. **A.S. Deardorff:** None. **V.V. Turkin:** None. **D. O'Neill:** None. **R.E.W. Fyffe:** None. **T.M. Hamm:** None.

Poster

218. Spinal Cord Injury: Models and Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 218.26/W31

Topic: C.09. Brain Injury and Trauma

Support: Commonwealth of Kentucky Challenge for Excellence Trust Fund

Leona M. and Harry B. Helmsley Charitable Trust

NIH Grant 5 P30 GM103507

Craig H. Neilsen Foundation

University of Louisville Foundation

Jewish Hospital and St. Mary's Foundation

Kentucky Spinal Cord Injury Research Center

Title: Short-term blood pressure regulation after complete and incomplete spinal cord injury

Authors: *S. WANG[1,1], S. C. ASLAN[1,4], D. LORENZ[2], A. V. OVECHKIN[1,4], G. HIRSCH[3], S. J. HARKEMA[1,4]
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Abstract: Background: Cardiovascular complications represent challenging clinical conditions after spinal cord injury (SCI). Orthostatic hypotension (OH) occurs often after severe SCI, affecting rehabilitation, health and quality of life. Evaluating the severity of OH and understanding the mechanisms are warranted in order to effectively treat this condition. We previously found that the patterns of cardiovascular responses during sit-up orthostatic stress test among 84 individuals with SCI were diverse and could be classified into three main groups by cluster analysis: a severe drop in blood pressure (BP) (SEVERE), mild drop or no change in BP (MILD) and normal increase in BP (NORMAL), which could not be predicted by the classification of sensorimotor completeness of injury. The current goal is to understand the underlying mechanisms of abnormal cardiovascular responses. **Methods**: Continuous BP and electrocardiography were monitored in 84 individuals with cervical, upper thoracic (UT) or lower thoracic-lumbar (LT) SCI with AIS grade A, B, C or D, and 20 non-injured volunteers,

during orthostatic stress test: 15 minutes supine rest followed by a passive position change to a seated position (SIT) lasting for another 15 minutes. Heart rate and BP variability (n=73 analyzable for SCI and n=20 for non-injured), were calculated during the last 5 minutes of supine rest and during the 3 minutes with the lowest systolic BP at SIT, including low frequency (LF, 0.04-0.15 Hz) and high frequency (0.15-0.4 Hz) spectral power of RR interval (RRI), systolic BP (SBP) and diastolic BP (DBP). Baroreflex sensitivity and effectiveness were determined with sequence method. **Results:** Heart rate and BP variability's were lower in SCI than in non-injured individuals at SIT. As expected, higher injury level resulted in higher degree of impairment; LF RRI power was lower in cervical than in UT SCI, and LF DBP power and baroreflex effectiveness was lower in cervical than in LT SCI, at the lowest 3 minutes of SIT. LF RRI power and LF DBP power were lower in C1-4 injury levels than in C5-8 injury levels at SIT. In individuals with cervical injury, LF SBP and LF DBP powers were lower in AIS A than in AIS D; LF SBP power was lower in AIS B than in AIS D. The SEVERE group had lower LF DBP power, baroreflex sensitivity and effectiveness than the NORMAL group at SIT. The SEVERE group also had lower baroreflex sensitivity and effectiveness than the MILD group. **Conclusions**: OH in individuals with SCI was associated with low peripheral vasomotor tone and abnormal baroreflex function, which could not be totally explained by sensorimotor completeness of injury.

Disclosures: S. Wang: None. **S.C. Aslan:** None. **D. Lorenz:** None. **A.V. Ovechkin:** None. **G. Hirsch:** None. **S.J. Harkema:** None.

Poster

218. Spinal Cord Injury: Models and Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 218.27/W32

Topic: C.09. Brain Injury and Trauma

Support: CH Neilsen Foundation 295319

NIH NS49177

Title: Acute experimental spinal cord injury provokes luminal hypoxia and tissue remodeling within the colon

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Abstract: Bowel dysfunction is a widely prevalent, yet profoundly understudied, comorbidity following spinal cord injury (SCI). Our previous data has identified diminished mesenteric

perfusion along the entire gastrointestinal (GI) tract following experimental SCI in rats. The GI tract is highly dependent upon adequate blood flow for proper functioning and even brief episodes of GI hypoxia lead to GI dysmotility, inflammation and neuromuscular remodeling. While our previous data has demonstrated diminished mesenteric blood flow following SCI, direct evidence of tissue hypoxia has not been demonstrated. We hypothesized that decreased blood flow provokes increased levels of tissue hypoxia and remodeling within the colon of adult male Wistar rats following a 300kdyn T3-SCI. Three days post-injury, both injured and age-matched controls underwent *in vivo* experimentation to quantify hypoxia in colonic tissue by immunostaining for bound Pimonidazole Hydrochloride (60mg/kg, iv). One hour following infusion, tissue was harvested for histological evaluation. Compared to surgical controls, the colonic epithelium of rats 3 days post-SCI was significantly more hypoxic. Conversely, the level of hypoxia within the myenteric ganglia was significantly lower in T3-SCI rats than in the controls. In conjunction, T3-SCI rats displayed significant morphological changes within the colon such as a decrease in the height and width of colonic crypts, an increase in the thickness of the muscularis propria, and an increase in collagen deposition within the muscularis propria. During states of normoxia, there is an oxygen gradient seen throughout the GI tract, where luminal epithelial cells naturally have lower levels of oxygen compared to those closer to the serosa; however, our data suggests that following SCI, the immediate decrease in mesenteric blood flow exacerbates the oxygen gradient, resulting in an acute state of hypoxia. The morphological changes seen within the mucosal crypts and muscularis propria are also suggestive of colonic tissue hypoxia. Lower levels of hypoxia within the myenteric ganglia point toward a possible protective mechanism activated during states of hypoxia, but this remains unclear and requires further investigation.

Disclosures: **A.R. White:** None. **E.N. Blanke:** None. **E.M. Besecker:** None. **G.M. Holmes:** None.

Poster

218. Spinal Cord Injury: Models and Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 218.28/W33

Topic: C.09. Brain Injury and Trauma

Support: R00- HL 111215

The Kentucky Spinal Cord and Head injury Trust

The Commonwealth of Kentucky Challenge for Excellence

the Rebecca F Hammond Trust

RCS-VA RR&D B9249S

Title: Cervical hemisection increases upper airway activity in breathing and swallow

Authors: *A. HUFF[1,2], C. GREENE[1], K. CHEFFER[1], W. O'STEEN[1], D. HOWLAND[1], T. PITTS[1]
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Abstract: The effects of cervical hemisection on swallow have not been determined. We hypothesized that cervical hemisection would increase swallow excitability and shift the pattern of swallow breathing coordination to maintain pharyngeal clearance. Electromyograms of the mylohyoid, geniohyoid, thyrohyoid, thyroarytenoid, thyropharyngeus, cricopharyngeus and diaphragm (costal and crural) muscles were recorded in anesthetized, spontaneously breathing cats prior to and after a C2 hemisection. Swallow was elicited by infusion of 3ccs of water into the oropharynx. Acute C2 cervical hemisection significantly increased EMG amplitudes across all upper airway muscles during swallow, and swallow frequency increased from 3.3 $\pm$1.2 to 8 $\pm$1.4 per infusion. Significant changes in swallow-breathing coordination were noted with all swallows occurring in E1 (as opposed to late E2), significantly increasing the risk for potential aspiration. These results support a theory of spinal cord inhibition/modulation of the swallow pattern generator and upper airway muscle excitability, as well as the importance of its role in swallow/breathing integration. Supported by R00- HL 111215, The Kentucky Spinal Cord and Head injury Trust, The Commonwealth of Kentucky Challenge for Excellence, the Rebecca F Hammond Trust and RCS-VA RR&D B9249S. The contents of this abstract do not represent the views of the DVA or US government.

Disclosures: A. Huff: None. **C. Greene:** None. **K. Cheffer:** None. **W. O'Steen:** None. **D. Howland:** None. **T. Pitts:** None.

Poster

218. Spinal Cord Injury: Models and Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 218.29/W34

Topic: E.09. Spinal Cord Injury and Plasticity

Support: CIHR MOP44358

Title: Spinal contusion at T10 in the cat : Recovery of locomotion

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Abstract: After a limited surgical lesion at the spinal thoracic level (i.e. lateral, dorsal or ventral hemisection), cats can regain quadrupedal locomotion on a flat treadmill (FTM). To approximate more extended bilateral lesion often found clinically, we submitted cats to a severe spinal contusion at T10. We evaluated cat's locomotor performance on a FTM, but also in more challenging conditions, such as obstacles avoidance and precise foot placement on a ladder treadmill (LTM; see Escalona et al, J. Neuroscience 2017). Twelve cats were implanted chronically with electromyographic (EMG) electrodes. Video recordings synchronized to the EMGs were acquired before the contusion (i.e. baseline values). The spinal cord was impacted bilaterally using an Infinite Horizon impactor allowing the application of a calibrated 800kdynes (8N) force for 30s using a 5mm diameter flat circular surface. Thereafter, during 5 weeks, cats were trained 5 times a week on a FTM and complete extensive recordings were made every week. Histological analyses revealed that the lesions were very large and generally affected all quadrants bilaterally (see Dea et al, twin poster). For 8/12 cats, hindlimb paralysis was complete during the first week but quadrupedal locomotion gradually recovered thereafter. After 5 weeks, 9/12 cats could walk without any assistance on all four limbs at speeds of up to 0.5 m/s, although some locomotor deficits remained: Fore-hindlimb were uncoupled on 11/12 cats, showing a 3:2 forelimb / hindlimb steps ratio on average; Foot drag gradually diminished throughout the recovery but remained in 11/12 of the cats after 5 weeks; Step length and duration were increased compare to the baseline values, in 8/12 cats. Cats also demonstrated a clear voluntary control of their hindlimbs. Indeed, 5 weeks after the contusion, cats could effectively step over a 5cm obstacle fixed to the belt with each limb smoothly clearing the obstacle without touching it. On the LTM, cats were unable to walk for the first few weeks post lesion. After a few weeks, cats could place correctly the forepaws on the rungs but not the hindpaws. Five weeks post-contusion, 10% to 25% of hindlimb steps were correctly placed on rungs. We conclude that after 5 weeks of daily training on a FTM following a large spinal contusion at T10, involving important damages to various spinal quadrants, cats could regain unaided quadrupedal locomotion on FTM, were able to step over a single obstacle fixed to the treadmill belt and could recover some voluntary steps of the hindlimbs on a LTM. This method provides a way to assess the overall locomotor capability of cats after lesions of the CNS.

Disclosures: H. Delivet-Mongrain: None. **M. Dea:** None. **J. Gossard:** None. **S. Rossignol:** None.

Poster

218. Spinal Cord Injury: Models and Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 218.30/W35

Topic: E.09. Spinal Cord Injury and Plasticity

Support: CIHR MOP44358

Title: Spinal contusion at T10 in the cat : Histological assessment

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Abstract: In recent years, we have studied the locomotor recovery of cats after various lesions affecting the spinal cord to inactivate known pathways coursing through different quadrants. It is often very difficult to establish a correlation between the apparent size of the lesion and the motor deficits. Spinal lesions are most often described through a representation of the maximal damage taken at the epicenter of the lesion on coronal slices. But on a given coronal slice, a quadrant may appear little affected whereas at other levels the same quadrant may be more damaged. In that context, it is important to assess as completely as possible the spinal lesion. In this study, we performed a contusion at T10-11 in 12 cats using the Infinite Horizon Impactor with a force of 800kdynes (8N) for 30s using a 5mm diameter flat circular tip. After 5 weeks, the extent of contusion was first evaluated by cresyl staining and the epicenter of lesion was further characterized for myelin for reactive astrocytes by various staining methods. Using the cresyl sections, a complete 3D reconstruction of all the contusive lesions was achieved using a neuroanatomical reconstruction system (Neurolucida, MicroBright-Field, USA) associated with a microscope (Olympus BX51, Japan). The produced lesions were substantial and affected all quadrants of the spinal cord, with no residual grey matter at the epicenter, which was occupied mostly by a large central cavity and a variety of smaller secondary cavities extending caudally. Primary cavities extended between 5,5 and 10 mm and the total length presenting any size cavity between 7 and 26,5 mm. The total volume of cavities ranged from 3,3 mm^3 to 34,2 mm^3. At epicenter, where the primary cavity was most extensive in every cat, it occupied 13 - 40 % of the spinal cord area. The results underline the inherent variability of contusive lesions and also highlight the small amount of possibly “normal” fibers left after 5 weeks, which were mostly located in the ventral quadrants. Remarkably, most of the cats could walk unaided on all four limbs and could even step over small obstacles placed on the treadmill (see Delivet-Mongrain et al. SFN 2017). We now have a set of histological tools to accurately describe and quantify the remnant and lesioned spinal cord tissue, including glial cells, following a contusion of the thoracic cord in a mammal model. These findings will help us elucidate potential links between the recovery and deficits of locomotor parameters and remnant and/or damaged pathways produced by the contusion.

Disclosures: **M. Dea:** None. **H. Delivet-Mongrain:** None. **S. Rossignol:** None. **J. Gossard:** None.

Poster

219. Somatosensation: TRP Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 219.01/W36

Topic: D.03. Somatosensation: Pain

Support: R01DE17794

R01DE22743

R01NS87988

R01NS89479

Title: MiRNA let-7b induces chronic itch via TLR7 and TRPA1

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Abstract: MicroRNAs (miRNAs) are 18-25 nucleotide noncoding RNAs. Increasing evidence supports an important role of miRNAs in regulating pain and itch via gene regulation. It is well established that intracellular miRNAs bind the 3' untranslated regions of mRNAs to regulate gene expression post-transcriptionally. miRNAs have also been detected in body fluids such as serum, CSF, saliva, and urine, and circulating miRNAs have been implicated as biomarkers for different diseases. However, the function of extracellular circulating miRNAs in itch regulation is unknown. In this study, we discovered that miRNA let-7b contributes to acute and chronic pruritus. Intradermal injection of let-7b elicited marked acute itch, which was reduced in *Tlr7* and *Trpa1* knockout mice. This result suggests that both TLR7 and TRPA1 are required for let-7b-induced itch. Interestingly, a single intradermal injection of let-7b also induced chronic itch for several days and further caused pathological changes in the back skin, with increased thickness of epidermis. Dry skin injury increased miRNA let-7b levels in the skin, and blockade of extracellular let-7b with its specific inhibitor reduced scratching behavior in the dry skin model. Collectively, this is the first report to demonstrate an important role of a specific miRNA, let-7b in persistent itch, which may provide a novel approach for treating chronic itch symptoms.

Disclosures: Q. Han: None. **R. Ji:** None.

Poster

219. Somatosensation: TRP Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 219.02/X1

Topic: D.03. Somatosensation: Pain

Title: Evaluation of anti-pruritic effect of TRPA1 inhibitor

Authors: *Y. MAJIMA, M. KONNO, K. SERIZAWA, M. MORIYAMA, N. YUZAWA, K. NAKANAGA, T. SUZUKI, M. KAINOH
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Abstract: Chloroquine(CQ) causes robust scratching in naïve mice via the Mas-related G protein-coupled receptor A3(MRGPRA3) and it is well known that MRGPRA3 activates Transient receptor potential cation channel, member A1(TRPA1). In this study, to evaluate effects of TRPA1 inhibitor on histamine-independent itch, we used three compounds of TRPA1 inhibitor. All the compounds inhibited Allylisothiocyanate(TRPA1 activator)-induced Ca^{2+} signal in TRPA1 expressing A549 cell. Furthermore, these compounds also suppressed CQ induced Ca^{2+} signal in TRPA1 positive primary cultured DRG neurons but not TRPA1 negative neurons. These results suggest that CQ activate not only TRPA1 but also other channels. Moreover, we evaluated anti-pruritic effect of these compounds on CQ induced scratching behavior. However, all compounds did not suppress itch related-behavior. Our findings demonstrate that only inhibition of TRPA1 is insufficient for diminishing CQ induced (histamine-independent) itch.

Disclosures: **Y. Majima:** A. Employment/Salary (full or part-time):; Toray Industries, Inc. **M. Konno:** A. Employment/Salary (full or part-time):; Toray Industries, Inc. **K. Serizawa:** A. Employment/Salary (full or part-time):; Toray Industries, Inc. **M. Moriyama:** A. Employment/Salary (full or part-time):; Toray Industries, Inc. **N. Yuzawa:** A. Employment/Salary (full or part-time):; Toray Industries, Inc. **K. Nakanaga:** A. Employment/Salary (full or part-time):; Toray Industries, Inc. **T. Suzuki:** A. Employment/Salary (full or part-time):; Toray Industries, Inc. **M. Kainoh:** A. Employment/Salary (full or part-time):; Toray Industries, Inc.

Poster

219. Somatosensation: TRP Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 219.03/X2

Topic: D.03. Somatosensation: Pain

Support: NIH Grant NS087542

Title: Lidocaine derivative QX-314 permeates TRPM8 channels to produce long lasting cold specific local anesthesia

Authors: *S. ONGUN[1], D. D. MCCOY[1], R. PALKAR[2], Y. YANG[1], S. YAMAKI[1], D. D. MCKEMY[3]
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Abstract: Most novel approaches to alter cold pain rely on local anesthetics that are intracellular sodium channel blockers, which non-selectively diffuse through cell membranes due to their hydrophobic nature. The charged lidocaine derivative QX-314 is a prominent alternative to the existing sodium channel blockers. Unlike most local anesthetics that block excitability of all neurons, the cell impermeant QX-314 allows targeting of certain subsets of sensory neurons when provided opportune cell entry sites. Recently certain non-selective cation channels were shown to be capable of passing large cations such as QX-314 (265Da), including members of the transient receptor potential (TRP) channel superfamily, the pain receptor, TRPV1 and the irritant mustard oil receptor, TRPA1. However, it was not clear if the principal mediator of cold stimuli TRPM8 was capable of permeating QX-314 and produce cold-specific local anesthesia. Recently, we have revealed that both heterologous cells and native sensory neurons expressing TRPM8 channels allow permeation of a large fluorescent cation Po-Pro3 (351 Da). Here we show that like Po-Pro3, the charged sodium channel blocker QX-314 can be targeted into cold sensitive neurons by administration of TRPM8 agonists to produce a cold-specific local anesthesia. Hindpaw injections of QX-314 together with TRPM8 agonist WS-12 in mice produces a long lasting decrease in cold-sensitivity, while having no effect on mechanical and heat responses. Moreover, cold specific local anesthesia is achieved in the absence of a TRPM8 agonist by simply cooling the QX-314 injection site. These results demonstrate that the ability of somatosensory TRP channels to promote the permeation of charged sodium channel blockers includes TRPM8, suggesting that selectively relieving cold pain without heat and mechanical deficits can be achieved via targeted delivery of QX-314.

Disclosures: S. Ongun: None. **D.D. McCoy:** None. **R. Palkar:** None. **Y. Yang:** None. **S. Yamaki:** None. **D.D. McKemy:** None.

Poster

219. Somatosensation: TRP Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 219.04/X3

Topic: D.03. Somatosensation: Pain

Support: MINECO Grant SAF2016-77233-R

MINECO Grant SEV- 2013-0317

MINECO Grant SVP-2014-068588

Title: Agonism of tacrolimus, an immunosuppressant macrolide, on thermally gated TRPM8 channels

Authors: J. ARCAS, A. GOMIS, *F. VIANA
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Abstract: Transient receptor potential melastatin 8 (TRPM8) is a non-selective cation channel activated by cold temperature and cooling agents (e.g. menthol). TRPM8 is expressed in small-diameter cold-sensitive sensory neurons where it plays a critical role in the detection of environmental cold. We found that TRPM8 is a pharmacological target of tacrolimus (FK506), a macrolide immunosuppressant with several clinical uses, including the treatment of allograft rejection following solid organ transplants, treatment of atopic dermatitis and dry eye disease. Tacrolimus is an inhibitor of the phosphatase calcineurin, an action shared with cyclosporine.
In patch clamp and calcium imaging experiments of HEK293 cells expressing mouse TRPM8 we found that tacrolimus activates a TRPM8-like current and evokes calcium transients. Tacrolimus also potentiated TRPM8-mediated cold responses in a dose-dependent manner. Tacrolimus induced a leftward shift of the voltage-dependent activation curve, moving the opening of TRPM8 towards physiological values. During whole-cell recordings at -60 mV, tacrolimus activated an inward current and potentiated the current evoked by a cold ramp, causing a shift in the temperature activation threshold. In contrast, cyclosporine did not show any effect on TRPM8 channels, suggesting an effect of tacrolimus on TRPM8 independent of calcineurin signaling. The menthol-insensitive mutant TRPM8-Y745H was also activated by tacrolimus although the response, normalized to the effects of cold, was reduced when compared to wildtype channels. Moreover, mutant channels did not show a potentiation of the cold response in the presence of tacrolimus.
In line with these findings, in mouse DRG cultures, tacrolimus (30 μM) evokes an increase in intracellular calcium levels exclusively in cold-sensitive neurons (32/35). In contrast, no cold-insensitive neurons were activated by tacrolimus (0/130). Moreover, the effects of tacrolimus were fully prevented by the TRPM8 blockers BCTC and AMTB. Consistent with the

pharmacological results, in TRPM8 KO mice DRG cultures, the percentage of responses to tacrolimus were strongly reduced, while responses to other TRP agonist remained unaltered. In the presence of lower concentrations of tacrolimus (10 μM) cold responses of neurons were sensitized, shifting their average threshold temperature to warmer values.
Together our results identify TRPM8 channels in sensory neurons as molecular targets of the immunosuppressant tacrolimus. The mechanism of action seems independent of calcineurin. The actions of tacrolimus on TRPM8 resemble those of menthol but may involve interactions with other channel residues.

Disclosures: J. Arcas: None. **A. Gomis:** None. **F. Viana:** None.

Poster

219. Somatosensation: TRP Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 219.05/X4

Topic: D.03. Somatosensation: Pain

Support: FONDECYT 11130144

CONICYT 21161660

Title: Protein kinase C negatively modulates TRPM8 channel activity

Authors: *B. O. RIVERA, SR, R. MADRID, M. CAMPOS, B. LAVANDEROS, M. PERTUSA
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Abstract: Transient receptor potential melastatin 8 (TRPM8) channel is expressed in primary somatosensory neurons and is activated by cold, cooling compound such as menthol, and by voltage. Several studies showed that protein kinases participate in the modulation of TRPM8 activity in both cold thermoreceptors and recombinant systems. In inflammatory conditions, the release of bradykinin activates Gq-coupled receptors and PKC, suggesting that this kinase could play a role in the modulation of TRPM8 in inflammation. To further explore the effect of PKC activation on TRPM8 function, we used either phorbol esters (PMA) and the proinflammatory mediator bradykinin, in combination with calcium imaging in native, recombinant systems and extracellular recordings in corneal free nerve endings of cold thermoreceptors. Our results show that the activation of PKC reduces the maximal response of TRPM8 to cold and menthol in both HEK293 cells and trigeminal neurons, causing a shift of 2^{o}C in the temperature threshold of activation to lower temperatures. In corneal cold thermoreceptors, PMA reduces both the ongoing activity and the maximal response to cold. Altogether, these results suggest that PKC

acts as a negative modulator of TRPM8 channels, suggesting a relevant role of this kinase in cold sensingin inflammatory conditions.

Disclosures: B.O. Rivera: None. **R. Madrid:** None. **M. Campos:** None. **B. Lavanderos:** None. **M. Pertusa:** None.

Poster

219. Somatosensation: TRP Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 219.06/X5

Topic: D.03. Somatosensation: Pain

Support: SAF2014-54518-C3-1-R

SAF2014-54518-C3-2-R

Title: Monitoring plasticity and regeneration of individual intraepithelial corneal cold nerves in the adult living mouse

Authors: A. ÍÑIGO-PORTUGUÉS[1], *F. BORRAS[2], *L. RINCON-FRUTOS[1], G. EXPOSITO[1], *J. GALLAR[1], C. BELMONTE[1], V. M. MESEGUER[1]
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Abstract: Sensory nerves in the transparent cornea experience continuous remodeling and active regeneration after injury. Due to their accessibility, corneal nerves are an excellent experimental model to visualize *in vivo* and define in detail the dynamics and molecular basis of the spontaneous remodeling of intact axons and the regeneration processes that follow peripheral injury. With this aim, we measured in the cornea of anesthetized TRPM8^{BAC}-EYFP mice the time course and change in length of individual intraepithelial corneal cold sensory nerves (a subbasal leash and its terminal branches, ICCN). We studied remodeling of single ICCNs in intact corneas while regeneration of individual nerves was analyzed after selective ablation of single ICCNs. Individual ICCNs were imaged using a confocal microscope and monitored at different time points over a week and then reconstructed in 3D using Imaris 8.2 software. The rate of length change and number, shape and distribution of branches during remodeling or regeneration were measured repeatedly in a given ICCN along the exploration time. In some experiments, the cornea was fixed at the end of the exploration period and the expression of GAP43 in the previously studied ICCN was determined using immunofluorescence techniques. In 5 out of 10 remodeling ICCNs measured in five mice, the total length increased at a rate of 165 ± 57.5 μm/day. Contrarily, in another five remodeling ICCNs, total length decreased at a rate of -91.7 ± 27.1 μm/day. On another hand, four regenerating ICCNs increased their total length at

an average rate of 65.5 ± 24.6 μm/day in 4 mice while the number, location and shape of the nerve terminals given by these ICCNs changed with time. In other set of experiments, we observed that GAP43 expressed in a fraction of remodeling ICCNs. Our work shows that presumed cold-thermoreceptor ($TRPM8^+$) corneal nerve axons and their terminals in the living animal experience dynamic configuration changes in length, shape and distribution; additionally, a fraction of them express GAP43, indicating the co-existence of nerve endings in different growing states. These observations confirm and extend previous qualitative observations and additionally offers for the first time, an experimental model to follow dynamically the growth and regeneration, at the resolution level of an individual fiber, of peripheral sensory nerves in the adult living mouse.

Disclosures: A. Íñigo-Portugués: None. **F. Borras:** None. **L. Rincon-Frutos:** None. **G. Exposito:** None. **J. Gallar:** None. **C. Belmonte:** None. **V.M. Meseguer:** None.

Poster

219. Somatosensation: TRP Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 219.07/X6

Topic: D.03. Somatosensation: Pain

Title: Tacrolimus, a calcineurin inhibitor, promotes capsaicin-induced colonic pain in mice

Authors: *K. MATSUI, Y. TERADA, M. TSUBOTA, A. KAWABATA
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Abstract: Transient receptor potential vanilloid-1 (TRPV1) is abundantly expressed in C-fiber nociceptors, and participates in visceral nociception including colonic pain. Interestingly, it has been reported that the expression of TRPV1 is upregulated in colonic biopsies from irritable bowel syndrome patients, which correlates with the severity of colonic pain. TRPV1 is sensitized following phosphorylation by protein kinase C or A, but desensitized following dephosphorylation by calcineurin. Recently, we have revealed that tacrolimus, a calcineurin inhibitor, induces a relapse of pancreatitis-related pain that is dependent on TRPV1 activity in mice with cerulein-induced pancreatitis. Here we thus investigated whether tacrolimus facilitates the colonic pain induced by capsaicin, a TRPV1 agonist. Intracolonic administration of capsaicin at 491 nmol/mouse, but not 164 nmol/mouse, caused colonic pain-like nociceptive behavior and abdominal referred hyperalgesia, as assessed by von Frey test, which were abolished by pretreatement with capsazepin, a TRPV1 antagonist. Tacrolimus, when preadministered, significantly augmented the referred hyperalgesia induced by intracolonic capsaicin at 164 nmol/mouse, the subeffective dose. We then performed immunostaining of phosphorylated extracellular signal-regulated kinase (p-ERK) in the spinal dorsal horn, as a prompt marker for excitation of nociceptive neurons. Preadministration of tacrolimus significantly facilitated the

intracolonic capsaicin-induced phosphorylation of ERK in the spinal dorsal horn at T13-L1 and L5-S1 levels to which colonic sensory neurons project; the increased number of p-ERK-positive cells was observed in laminae I-II, V-VI and X. Together, we suggest that the inhibition of calcineurin by tacrolimus promotes TRPV1-dependent colonic nociception most probably by enhancing phosphorylation of TRPV1 in mice.

Disclosures: K. Matsui: None. **Y. Terada:** None. **M. Tsubota:** None. **A. Kawabata:** None.

Poster

219. Somatosensation: TRP Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 219.08/X7

Topic: D.03. Somatosensation: Pain

Title: Effects of TRPV1 long term antagonism on orthodontic force induced pain

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Abstract: The orthodontic treatment is common therapy to improve functional and aesthetic dental issues, but many patients complain about pain during tooth movement. We have reported that the jaw-opening reflex (JOR) excitability is increased in 1-3 days and is decreased in 7 days after orthodontic force application in rats. Because the period of temporal alteration of the JOR excitability is similar with that of orthodontic pain in clinic, this animal model may allow us to investigate the novel approach to treatment of orthodontic pain. At 1 day, application of TRPV1 antagonist and aspirin significantly reduced JOR excitability, however, effect of prolonged administration of these chemicals is still unknown. Therefore, the aim of this study is to investigate the effects of long term administration of TRPV1 antagonists (A-889425 and AMG9810) on orthodontic pain and amount of tooth movement. In this model, anesthetized rats were applied continuous orthodontic force by Ni-Ti coil spring to only right maxillary first molar. Aspirin (100 mg/kg), A-889425 (5.0 μmol/kg) and AMG9810 (10.0 μmol/kg) were repetitively administrated (i.p., 3 times/day) from immediately after orthodontic force application for subsequent 7 days. On 1 (D1 group) or 7 (D7 group) day(s) after orthodontic force application, rats were anesthetized, electrodes was inserted anterior digastric muscle to record EMG activity and the maxillary first molar gingiva to electric stimulation. Passing current (200 μs) was applied to the right then the left maxillary first molar to determine JOR threshold (Th). The maxillary tooth arch of each animal was impressed by silicone impression paste before application of coil spring and after JOR investigation to obtain cast models. The amount of tooth movement was obtained by measuring the cast model with vernier caliper. The right side orthodontic force application for 1 day significantly decreased right side JOR Th, whereas application of aspirin, A-889425 and AMG9810 significantly ($P < 0.05$)

increased the right side JOR Th. On the other hand, increase of right side JOR Th in D7 group (without medication) was inhibited by aspirin, A-889425 and AMG9810. Interestingly, JOR Th intensities were similar between right and left stimulation in each animal. Since cyclooxygenase and TRPV1 are known as mediators of osteoclast differentiation, we examined the effect of aspirin and TRPV1 antagonists on amount of tooth movement. Aspirin and TRPV1 antagonists not significantly but reduced the amount of tooth movement of 7 days. These data suggest that although both NSAIDs and TRPV1 are able to reduce orthodontic pain, clinical use of them might reduce the amount of tooth movement.

Disclosures: **N. Hasegawa:** None. **A. Sasaki:** None. **T. Tsuchiya:** None. **N. Suda:** None. **K. Adachi:** None.

Poster

219. Somatosensation: TRP Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 219.09/X8

Topic: D.03. Somatosensation: Pain

Support: JSPS KAKENHI Grant Number JP 15K11304

Title: Involvement of TRPV4 and local osmolarity in incisional pain in the rat

Authors: *K. KIDO, E. MASAKI, Y. SHINDO, S. TODA
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Abstract: We previously demonstrated that the activation of proteinase-activated receptor 2 (PAR-2) on afferent nerves induced spontaneous pain, mechanical allodynia and heat hyperalgesia, and local administration of PAR-2 antagonist suppressed guarding pain, mechanical and heat hyperalgesia after hind paw incision in rats. Recently, it has been reported that PAR-2 activated transient receptor potential vanilloid 4 (TRPV4) of primary neurons to induce neurogenic inflammation and pain. The TRP channel has been known as a transducer of hyper/hypotonic stimuli. Therefore, we hypothesized that: (1) incision induced the release of tryptase from mast cells or elastase from neutrophils that activate PAR-2; (2) the activation of PAR-2 sensitizes TRPV4; (3) local osmolarity changes in wounds stimulated TRPV4 and increased postoperative pain and inflammation. In this study, we examined the possible contribution of osmolarity changes in incision area and TRPV4 to incisional pain. Using of a hind paw incisional rat model, the effects of a selective TRPV4 antagonist, HC067047, on nociceptive behaviors, edema formation and local osmolarity were measured after incision in vivo. The responses of nociceptors to osmolarity changes were also evaluated using the rat glabrous in vitro skin-tibial nerve preparation. Local administration of HC067047 suppressed guarding pain, heat hyperalgesia and mechanical allodynia after hind paw incision in vivo.

TRPV4 antagonist also reduced paw edema. Osmolarity of incision area was increased after incision (peaked approximately 450 mOsm). In vitro hypertonic solution increased the prevalence of fibers with ongoing activity in afferents from incised versus control skin. Hypertonicity sensitized C-fiber afferent responses to heat; however, this was less evident in afferents adjacent to the incision. HC067047 blocked sensitization of C-fiber afferents to heat by hypertonicity but did not by itself influence ongoing activity or heat sensitivity in C-fibers innervating control or incised skin. The magnitude of mechanical responses was also not affected by hypertonic solution in C-fibers innervating control or incised skin. This study demonstrates that osmolarity are increased in wounds for at least 48 hours after incision. In skin, TRPV4 contributes to hypersensitivity and paw edema after incision, but increased responsiveness of cutaneous nociceptors to hypertonicity was not evident in incised skin.

Disclosures: **K. Kido:** None. **E. Masaki:** None. **Y. Shindo:** None. **S. Toda:** None.

Poster

219. Somatosensation: TRP Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 219.10/X9

Topic: D.03. Somatosensation: Pain

Title: Role of TRPA1 channel in formalin-induced chronic nociception

Authors: *V. A. MARTINEZ-ROJAS[1], J. MURBARTIAN[2]
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Abstract: TRPA1 is a nonselective cation channel expressed by a subset of primary afferent nociceptive neurons where it acts a sensory receptor and its activity contributes to modulate the nociceptive transmission in acute inflammatory pain. However, the effects of this channel in chronic nociception are unknown. The aim of the present investigation was to assess the role of TRPA1 in formalin-induced allodynia and hyperalgesia in the rat. For this, rats were injected with formalin (1%, 50 µL, s.c.) in to dorsal hind paw. Chronic nociception was assessed 6 days after formalin injection by the application of von Frey filaments to the formalin-treated (ipsilateral) and untreated (contralateral) paw. Formalin injection produced acute nociceptive behaviors (1 h) followed by long-lasting evoked secondary allodynia and hyperalgesia in both paws (6 days). Local peripheral or spinal pre-treatment (-10 min) with the selective TRPA1 blocker, A-967079 (1.0-100 µM) prevented in a dose-dependent manner the long-lasting evoked secondary mechanical allodynia and hyperalgesia in both paws. Likewise, local peripheral or spinal post-treatment (6^{th} day after formalin injection) with A-967079 (1.0-100 µM) reversed formalin-induced secondary mechanical allodynia and hyperalgesia. Furthermore, the effect of protons and formaldehyde in the formalin solution was confirmed since the administration of 100 µM of A-967079 in PBS buffered formalin (7.4) abolish the pro-nociceptive effect of formalin.

Moreover, the expression of TRPA1 protein in dorsal root ganglia was increased at 6 days after formalin injection. Our results show that TRPA1 has a relevant function in nociceptive processing and modulation of chronic nociception induced by formalin in rats.
VAM-R, is Conacyt fellow.
Keywords: TRPA1 channels, inflammatory pain, allodynia and hyperalgesia.

Disclosures: V.A. Martinez-Rojas: None. **J. Murbartian:** None.

Poster

219. Somatosensation: TRP Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 219.11/X10

Topic: D.03. Somatosensation: Pain

Support: USAA Foundation Presidential Distinguished Univ Chair in Neuroscience

Title: Role of high omega-6 diet as risk factor for pain through increased TRPV1 activity

Authors: *J. T. BOYD, K. M. HARGREAVES
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Abstract: Chronic pain management is a significant medical problem seen in about one-third of the population and is the number one reason for patients seeking medical care. Knowledge of the mechanisms involved in chronic pain or in the transition from acute to chronic pain remains incomplete. Recent studies have demonstrated that oxidized metabolites of the omega-6 polyunsaturated fatty acids (PUFAs) lead to increased activation of TRPV1, an important ligand-gated ion channel expressed on nociceptive neurons. Since these are essential fatty acids, tissue levels of omega-6 PUFAs are regulated by dietary intake levels; however, the role of dietary lipid intake on pain is not understood.
Aim of Investigation: We hypothesize that increased dietary omega-6 polyunsaturated fatty acids (PUFA) serves as a risk factor for amplified severity and/or chronicity of pain via increased TRPV1 activity in a Complete Freud's Adjuvant (CFA) model of inflammatory pain.
Methods: Mice were placed on isocaloric diets with high, moderate and low levels of omega-6 PUFAs for 15 weeks. Pre and post-diet thermal and mechanical measures were taken to assess change in baseline nociception. Nocifensive behavior in response to 0.1ug capsaicin was measured to determine variation in TRPV1 activity following the 15 week diet. Finally, thermal and mechanical hyperalgesia was assessed following injection of 1:1 CFA or vehicle in the hindpaw of the mice. Data analyzed by GLM including ANOVA and t-test as appropriate.
Results: 1. Baseline thermal paw withdrawal latency (PWL) decreased in the high omega-6 group; 2. Baseline mechanical paw withdrawal threshold (PWT) did not change after diet; 3. Nocifensive behavior time increased incrementally with increased omega-6 levels in the diet 4.

Diet induced a significant thermal, but not mechanical, hyperalgesia after CFA.
Conclusions: Collectively, these novel data suggest that chronic dietary increase of omega-6 PUFAs acts as a risk factor for increased thermal pain response at baseline and in the CFA model of inflammatory pain. The data also suggest TRPV1 activity, via sensitization or upregulation, increases with increasing levels of dietary omega-6 fatty acids.

Disclosures: J.T. Boyd: None. **K.M. Hargreaves:** None.

Poster

219. Somatosensation: TRP Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 219.12/X11

Topic: D.03. Somatosensation: Pain

Title: NSAIDs attenuate TRPA1 and TRPV1 channels activated by their agonists

Authors: *M. G. TSAGARELI, I. NOZADZE, N. TSIKLAURI, G. GURTSKAIA, E. ABZIANIDZE
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Abstract: Transient receptor potential (TRP) cation channels are involved in somatic sensations. Because some non-steroidal anti-inflammatory drugs (NSAIDs) are structural analogs of prostaglandins, and NSAIDs reduce heat nociception and mechanical allodynia, we examined three widely used NSAIDs (diclofenac, ketorolac, and xefocam) on the activation of TRPA1 and TRPV1 channels by their agonists cinnamaldehyde (CA), allyl isothiocyanates AITC, and capsaicin, respectively using thermal paw withdrawal (Hargreaves) and mechanical paw withdrawal (von Frey) tests in male rats. Thermal withdrawal latencies and mechanical thresholds for both hind paws were obtained with 5, 15, 30, 45, 60, and 120 min intraplantar post-injection of CA, AITC, and capsaicin or vehicle. Twenty minutes prior to the start of the experiment, diclofenac, ketorolac or xefocam were pre-injected in the same hindpaw and animals were examined by these two tests. After pretreatment of all three NSAIDs in the ipsilateral (injected) hindpaw that produced a reduced antinociception, CA, AITC, and capsaicin caused significant decreases in latency of the thermal withdrawal reflex compared with vehicle or the contralateral hindpaw. The same findings were observed for the paw withdrawal threshold. In approximately 30 min the effects of CA, AITC, and capsaicin returned to baseline. We suggest that our study indicates a novel mechanism involving the anti-inflammatory and analgesic effects of NSAIDs, which may be involved in direct inactivation or desensitization of TRPA1 and TRPV1 channels and could be used therapeutically for pain treatment. **Acknowledgement**. Supported partially by the grants from RNSF of Georgia (#31/40 and #217076).

Disclosures: **M.G. Tsagareli:** None. **I. Nozadze:** None. **N. Tsiklauri:** None. **G. Gurtskaia:** None. **E. Abzianidze:** None.

Poster

219. Somatosensation: TRP Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 219.13/X12

Topic: D.03. Somatosensation: Pain

Support: Research Basis Formation Supporting Project for Private University S1411041

Title: TRPA1 regulates colonic motility through prostaglandin release from colon fibroblasts in rats

Authors: Y. YANG[1,2], S. WANG[1,3], K. KOBAYASHI[2], Y. KOGURE[1], H. YAMANAKA[2], S. YAMAMOTO[1], K. NOGUCHI[2], *Y. DAI[1,2,3]
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Abstract: The transient receptor potential ankyrin 1 and vanilloid 1 (TRPA1 and TRPV1, respectively) channels were well recognized pain sensors. These channels are previously reported to be predominantly expressed by intrinsic (Daniel et al. Gastroenterology 2011) and/or extrinsic afferents (Brierley et al. Gastroenterology 2009), as well as by enterochromaffin cells (Nozawa et al. PNAS 2009) in gastrointestinal tract. Here, using reverse transcription polymerase chain reaction, in situ hybridization, immunohistochemistry, calcium imaging, enzyme linked immunosorbent assay and recording of intracolonic pressure and visceromotor response, we investigated the expression and function of TRPA1 channels in rat colon and observed a previously unknown link between TRPA1 and colonic motility. TRPA1, but not TRPV1, was detected by non-neuronal cells in sub-epithelial layer in rat colon tract. These cells were vimentin (a fibroblast marker) and cyclooxygenase-1 immunopositive. Intracolonic injection of allyl-isothiocyanate (AITC), but not capsaicin, significantly potentiated colonic motility, however, did not induce obvious visceral pain. The AITC-induced colonic movement was significantly inhibited by either a prostaglandin $EP_{1/2}$ receptor ($EP_{1/2}$ R) antagonist or a selective EP_1 R antagonist, but not EP_3 R or EP_4 R antagonists. Intraperitoneal PGE_2 application significantly increased colonic motility. In addition, AITC stimulation significantly induced Ca^{2+} influx in human colonic fibroblasts (CCD-18Co) in vitro. AITC-induced PGE_2 release from CCD-18Co cells was significantly prevented by HC-030031, a selective TRPA1 antagonist. Taken together, our results demonstrate a previously unknown expression of TRPA1 in sub-epithelial fibroblasts, and indicate that TRPA1 may regulate colonic motility through prostaglandin release from these fibroblasts.

Disclosures: **Y. Yang:** None. **S. Wang:** None. **K. Kobayashi:** None. **Y. Kogure:** None. **H. Yamanaka:** None. **S. Yamamoto:** None. **K. Noguchi:** None. **Y. Dai:** None.

Poster

219. Somatosensation: TRP Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 219.14/X13

Topic: D.03. Somatosensation: Pain

Support: KAKENHI 16718480

KAKENHI 17918363

Title: Noradrenaline suppresses TRPV1 currents by activation of α_2 adrenergic receptors in sensory neurons

Authors: *Y. MATSUSHITA, M. MANABE, N. KITAMURA, I. SHIBUYA
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Abstract: The adrenergic nervous system is known to modulate the pain. Noradrenaline (NA) is one of the major neurotransmitters of the descending antinociceptive system. TRPV1 channels are predominantly expressed in nociceptive sensory neurons and detect noxious stimuli including heat, acid, mechanical pressure, and capsaicin. However, little has been known about functional association between NA and TRPV1 in peripheral sensory nerves. In this study, we have examined effects of NA on TRPV1 activation by capsaicin and investigated underlying mechanisms in rat dosal root ganglion (DRG) neurons. DRG neurons isolated from male Wistar rats were cultured for 3-7 days before use in the whole-cell voltage-clamp recording. DRG neurons were voltage-clamped at -60 mV and inward current responses to capsaicin (1 μM) were recorded. NA inhibited capsaicin-evoked currents dose-dependently. The maximal inhibition (84%) was observed by NA at 10^{-13} M. Yohimbin or propranolol reduced the inhibitory effect of NA, whereas prazosin did not. Clonidine and Isoproterenol, but not phenylephrine, also inhibited the capsaicin currents. Yohimbin and propranolol abolished the inhibitory effects of clonidine or isoproterenol, respectively. Application of the catalytic subunit of protein kinase A or okadaic acid, a protein phosphatase inhibitor, into the intracellular solution reduced the inhibition ratio of capsaicin currents by NA. Either application of GDPβS into the intracellular solution or pretreatment of neurons with pertussis toxin, which inactivates $G_{i/o}$-protein, abolished the inhibition of capsaicin currents by NA. Pain responses to intraplantar injection of capsaicin were reduced by intraplanter injection of clonidine at the same site. These results suggest that α_2 receptors activating $G_{i/o}$ proteins are the strongest candidate involved in the inhibitory effect of NA on TRPV1 activation. This interaction between α_2 adrenergic receptors and TRPV1 on peripheral sensory nerves may contribute to the pain regulation.

Disclosures: **Y. Matsushita:** None. **M. Manabe:** None. **N. Kitamura:** None. **I. Shibuya:** None.

Poster

219. Somatosensation: TRP Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 219.15/X14

Topic: D.03. Somatosensation: Pain

Support: Alexander von Humboldt Foundation

Sectoral Operational Programme Human Resources Development (SOP HRD), financed by the European Social Fund and by the Romanian Government

IZKF at the University of Erlangen-Nürnberg

Title: 7-dehydrocholesterol photosensitizes TRPA1 and TRPA1 - relevant targets for the Smith-Lemli-Opitz syndrome

Authors: C. I. CIOTU[1], A. BABES[2], T. I. KICHKO[3], T. SELESCU[2], S. K. SAUER[4], P. W. REEH[3], *M. J. FISCHER[1]
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Abstract: The Smith Lemli Opitz syndrome is an inherited developmental disorder caused by a loss of function mutation of the enzyme 7-Dehydrocholesterol (7DHC) reductase. This deficit in the last metabolic step in the cholesterol synthesis causes cholesterol deficits, but more importantly an up to 1000-fold increase in 7DHC plasma levels. The syndrome is characterized by intellectual disability, growth retardation, and debilitating hypersensitivity when exposed to sunlight. We investigated the role of two potential targets, the TRPA1 and TRPV1 ion channels, as the molecular link between UVA photosensitization and excess 7DHC. Using ratiometric calcium microfluorimetry, we assessed the photosensitization caused by 7DHC treatment and UVA light exposure on human TRPA1- or TRPV1-transfected HEK293t cells and mouse DRG neurons. 7DHC acutely activated and photosensitized human TRPA1 channels, as indicated by a substantial increase in intracellular calcium in TRPA1-expressing cells. In contrast, we observed a minimal or absent photosensitization in TRPV1-expressing cells, respectively. The activation and photosensitization were dependent on the presence of extracellular calcium and could be significantly reduced by the TRPA1 antagonists A-967079 or TRPV1 antagonist BCTC. The acute effects were concentration-dependent and in the range of clinically relevant 7DHC levels. Preexposure to 7DHC (1-15h) lead to significant and time-dependant photosensitization in the

expression systems. Experiments performed on DRG neurons also highlighted a predominant role for TRPA1, which was reinforced by the use of TRPA1, TRPV1 and double knockout animals and by pharmacological blockade of the receptors, both in acute and preexposure conditions. Reactive oxygen species (ROS) production was detected using the fluorescent ROS sensing dye 2',7'-dichlorodihydrofluorescein diacetate. UVA illumination of 7DHC exposed HEK293t cells generated increases in ROS production rates. Furthermore, 7DHC effects on TRPA1 were antagonized by the antioxidant dithiothreitol. Using the whole-cell patch clamp technique, we recorded significant 7DHC-induced transmembrane currents in human TRPA1-expressing cells, which were completely abolished by A-967079. Further, 7DHC sensitized the tracheal light response in an isolated mouse trachea preparation, leading to a sustained increase in CGRP release, which was used as an index for neuronal activation. The results indicate a role for TRPA1 and TRPV1 in the 7DHC-induced photosensitivity.

Disclosures: C.I. Ciotu: None. **A. Babes:** None. **T.I. Kichko:** None. **T. Selescu:** None. **S.K. Sauer:** None. **P.W. Reeh:** None. **M.J. Fischer:** None.

Poster

219. Somatosensation: TRP Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 219.16/X15

Topic: D.03. Somatosensation: Pain

Support: JSPS KAKENHI 26460709, 17K09045

Title: Mechanical stretch stimulus activates extracellular signal-regulated kinase via TRP channels and P2X receptor in dorsal root ganglion neurons

Authors: *T. SUGIMOTO, J. MATSUYAMA, T. ISHIDA, E. OKUDA-ASHITAKA
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Abstract: Receptors for various stimuli expressed at the terminal of primary afferent nerve fibers are responsible for the reception and transmission of sensory information. The somatosensory ganglion contains a phenotypically diverse population of neurons that are able to respond to thermal, chemical or mechanical stimuli. Several receptors for thermal and chemical stimuli and their signaling pathways have been identified, but the molecular transduction mechanisms mediating mechanical stimuli remain undefined. In this study, we investigated the high-threshold mechanical stretch stimuli-activated Ca^{2+} influx and mitogen-activated protein kinase activation in mouse dorsal root ganglion (DRG) neurons.
DRG cells were isolated from 4-8 week old mice by collagenase and trypsin, and plated onto poly-D-lysine and laminin-coated stretch chambers. After the 3-day culture, mechanical stretch stimuli at stretch rates ranging from 2.5% to 10% were applied to the DRG neurons. The 5% and

7.5% stretch stimuli, which were equivalent to the extension force of the high-threshold mechanical stimulus, increased the intracellular Ca^{2+} concentration in Fura2/AM loaded-DRG neurons. The 5% stretch stimulus induced Ca^{2+} increases both in a monophasic and a biphasic manner, while the 7.5% stretch stimulus induced only a monophasic response. While the T-type voltage-gated Ca^{2+} channel inhibitor mibefradil could efficiently decrease the 5.0% stretch-activated monophasic Ca^{2+} increase, a TRP channel inhibitor (ruthenium red), a P2X receptor antagonist (PPADS), and mibefradil could decrease the biphasic one. The stretch stimulus induced both increased the extracellular signal-regulated kinase (ERK) and Jun-N-terminal kinase (JNK). Phosphorylation of ERK was suppressed by ruthenium red and PPADS, but not mibefradil; and phosphorylation of JNK was not affected by any of these inhibitors and antagonist. Furthermore, a nitric oxide donor (S-nitroso-N-acetylpencicillamine, SNAP) enhanced the intracellular Ca^{2+} concentration and ERK phosphorylation.
These results suggest that the high-threshold mechanical stimulus activated the ERK activation via TRP channel and P2X receptor in the DRG neurons.

Disclosures: **T. Sugimoto:** None. **J. Matsuyama:** None. **T. Ishida:** None. **E. OKuda-Ashitaka:** None.

Poster

219. Somatosensation: TRP Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 219.17/X16

Topic: D.03. Somatosensation: Pain

Title: Potential roles of the fatty acid receptor and its agonists in modulating TRPV1 in primary sensory neurons

Authors: *X. WEN, M.-H. JEONG, S. PARK, T. KANG, J.-S. KANG, H. CHO
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Abstract: The G-protein-coupled receptor 40 (GPR40) and GPR120 are suggested to function as a transmembrane receptor for long-chain free fatty acids and are implicated to play a role in in the resolution of pain and inflammation, respectively. Although transient receptor potential vanilloid subtype-1 (TRPV1), a non-selective cation channel, mediates inflammatory pain, the role of GPR40 and GPR120 in the regulation of TRPV1 has not been fully examined yet. Here we determined the effects of GPR40 and GPR120 on TRPV1 function using isolated dorsal root ganglion (DRG) neurons and HEK293T cells. In mouse DRG neurons, GPR40 and GPR120 are highly expressed and both receptors are co-localized with TRPV1. Capsaicin increased intracellular Ca^{2+} concentration in these cells through activation of TRPV1. Capsaicin-induced Ca^{2+} responses were potently attenuated by pretreatment of these neurons with a GPR40/120 dual agonist (GW9508), but not with GPR40 specific agonists, AM1638 and TAK875. We also

found that a GPR120 specific agonist, compound A has little effect on capsaicin-evoked Ca^{2+} response. GW9508 inhibition of TRPV1 is mediated by GPRs, since GW9508 has no effect on capsaicin-evoked Ca^{2+} response in HEK293T cells expressing only TRPV1. These data imply that the anti-TRPV1 effects of GW9508 require activation of both GPR40 and GPR120 and that GPR40/120 dual agonist might serve as a new class of analgesics for treating inflammatory and neuropathic pain.

Disclosures: X. Wen: None. **M. Jeong:** None. **S. Park:** None. **T. Kang:** None. **J. Kang:** None. **H. Cho:** None.

Poster

219. Somatosensation: TRP Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 219.18/X17

Topic: D.03. Somatosensation: Pain

Title: Identification of an expression determining interaction in a putative transmembranous assembly domain of the TRPV1 channel

Authors: V. GRASSO, M. BERNHARD, K. LANGER, *B. LAUBE
TU Darmstadt, Darmstadt, Germany

Abstract: The cation selective transient receptor potential vanilloid subtype 1 (TRPV1) channel is due to its diversity in function, its importance in pain perception and inflammation the most studied member of the large TRP (transient receptor potential) family. Structurally, TRP channels are tetramers. Each subunit has a cytosolic N- and C-terminus and a transmembrane region with 6 transmembrane helices (TM). TM5, TM6 and the intervening pore loop with pore helix build the pore domain after assembly. The underlying mechanism of assembly is not understood. Research on homo- and heteromeric assembly of TRPV channels led to the conclusion that the transmembrane and cytosolic regions synergistically contribute to the overall affinity and selectivity of channel assembly. In case of TRPV1 the transmembrane region contributes significantly to channel assembly (Hellwig et al. 2005). The identification of the assembly domain (AD) in TRPV1 could therefore enlighten the mechanism of transmembranous assembly in TRP channels. Our screening approach for known sequence motifs (SMs) important for helix dimerization (Li, Wimley, and Hristova 2012) show in connection with a closer inspection of the published structure of TRPV1 (Liao et al. 2013) that only two, ^{546}AMGWT^{550} of TM 4 and ^{590}GFASTA^{594} of TM5, of 44 found SMs lie in an interface between two subunits and can therefore build a putative transmembranous AD. SMs at this interface exist not only in all TRPV but at least also in closely related TRPA and TRPC channels. Moreover, a π-π-interaction between W549 of TM4 and F589 of TM5 is present in this interface of TRPV1. TRPV1 constructs where this π-π-interaction is removed by an alanine double-substitution or

replaced by S- π interactions through single cysteine substitutions were generated. The surface protein biotinylation method shows that all TRPV1 constructs heterologous expressed in *Xenopus laevis* oocytes are significantly reduced in their plasma membrane expression level in comparison to WT. Furthermore, no activation of the double mutant W549A/F589A can be seen after pseudocapsaicin application despite of overexpression in *Xenopus laevis* oocytes. In contrast the single mutants W549C and F589C can be activated by pseudocapsaicin. These first results show that the identified π-π-interaction can be functionally substituted by S- π interactions and alterations of the interface bearing the putative AD lead to a significant reduction in surface expression. Further experiments in which the cytosolic termini of TRPV1 are deleted and SMs are modified are going to enlighten the function of this putative AD found in TRP channels.

Disclosures: V. Grasso: None. **M. Bernhard:** None. **K. Langer:** None. **B. Laube:** None.

Poster

219. Somatosensation: TRP Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 219.19/X18

Topic: D.03. Somatosensation: Pain

Support: Faculty Research Support Program, Marshall University School of Pharmacy

Title: Exploring a structure-based pharmacophore for the transient potential melastatin 8 (TRPM8) ion channel using flexible docking and e-pharmacophore modeling

Authors: *V. B. JOURNIGAN, C. E. HEFFNER, N. BACHTEL
Pharmaceut. Sci. and Res., Marshall Univ., Huntington, WV

Abstract: The transient potential melastatin 8 (TRPM8) ion channel is a target of interest for neuropathic and inflammatory pain, prostate cancer and nicotine addiction. This pervasive, cold-sensing thermoTRP is found in Aδ- and C-fiber primary afferent neurons, a subpopulation of DRG and TG neurons, and non-neuronal tissues. Despite a large number of reported TRPM8 ligands, no structure-based pharmacophore exists to rationally design menthol-based chemical probes or therapeutic small molecules. We hypothesized that published TRPM8 antagonists with structural similarities could reveal both molecular determinants for ligand recognition and putative pharmacophores, via flexible docking into a published TRPM8 homology model of the closed state, e-pharmacophore generation, and validation with reported structure-activity relationship (SAR) data. TRPM8 selective compounds **1**-**2**, 4-(N-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)-N-(4-(trifluoromethoxy)benzyl)sulfamoyl)benzoic acid (**RQ-00203078**), (R)-3-[(1-(4-fluorophenyl)ethyl)(quinolin-3-ylcarbonyl)amino]methylbenzoic acid (**PF-05105679**),(R)-8-(4-(Trifluoromethyl)phenyl)-N-((S)-1,1,1-trifluoropropan-2-yl)-5,6-

dihydro-1,7-naphthyridine-7(8H)-carboxamide (**AMG2850**), and *N*-(3-aminopropyl)-2-[(3-methylphenyl)methoxy]-*N*-(2-thienylmethyl)benzamide hydrochloride (**AMTB**), with affinities ranging from 0.2-181 nM, and *in vivo* activity at TRPM8, were docked into the putative active site of a single monomer using Schrodinger's induced-fit docking protocol. Tyr745, in the S_2 helix, was selected as the active site centroid based on mutagenesis studies implicating its role in endogenous ligand (menthol) binding. Compounds **1-2**, **RQ-00203078**, **PF-05105679**, **AMG2850**, and **AMTB** docked into a hydrophobic pocket of 25 residues within the 711-749 and 813-830 regions of the S_{1-2} and S_{4-5} helices, and form similar interactions with Lys715, Lys719, Phe738, Asn741, Tyr826 and others. The pharmacophoric features of each ligand were detected using e-pharmacophore modeling, and validated with the published SAR. All pharmacophores were then superimposed to reveal (1) four overlapping regions, each independently containing aromatic, hydrophobic, and acidic features; (2) three non-overlapping regions, containing both hydrophobic and aromatic features in close proximity; and (3) three non-overlapping H-bond acceptor groups. These results suggest an initial pharmacophore based on the overlapping regions, and additional pharmacophoric features that could be exploited by rational drug design efforts to yield a more comprehensive understanding of TRPM8 ligand recognition.

Disclosures: V.B. Journigan: None. **C.E. Heffner:** None. **N. Bachtel:** None.

Poster

220. Inflammatory Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 220.01/X19

Topic: D.03. Somatosensation: Pain

Title: Thrombin-dependent inhibition of HMGB1-induced mechanical allodynia by thrombomodulin in mice

Authors: *Y. HAYASHI[1], M. MATSUNAMI[1], R. TSUJITA[1,2], G. HONDA[2], A. KAWABATA[1]
[1]Fac. Pharm., Kindai Univ., Higashi Osaka, Japan; [2]Asahi Kasei Pharma, Tokyo, Japan

Abstract: Thrombomodulin (TM) expressed on the membrane surface of the vascular endothelium is composed of five domains, D1 to D5, and shows anticoagulant activity through production of activated protein C by thrombin bound to the D2. TM is also capable of inactivating high mobility group box 1 (HMGB1), one of damage-associated molecular patterns (DAMPs), i.e., the lectin-like D1 adsorbs HMGB1 and promotes its decomposition by thrombin bound to the D2. Recombinant human soluble TM (TMα) consisting of D1-D3 mimics those activity of TM, and is used as a medicine for treatment of disseminated intravascular coagulation in Japan. In a reduced state, HMGB1 exists as all-thiol HMGB1 (at-HMGB1) containing all three cysteine residues (C23, C45 and C106) in a thiol form, which activates RAGE. In an

oxidized state, at-HMGB1 is transformed into disulfide-HMGB1 (ds-HMGB1) containing a disulfide bond between C23 and C45, which activates TLR4. Given our recent evidence that peripheral at-HMGB1 and ds-HMGB1 promote mechanical nociception via RAGE and TLR4, respectively (J Pharmacol Sci 130, 139, 2016), in the present study, we characterized the effect of TMα on the HMGB1-induced hyperalgesia in mice, particularly in terms of its thrombin-dependence. Recombinant HMGB1 was degraded by thrombin at high and low concentrations in the absence and presence of TMα *in vitro*. Intraplantar (i.pl.) injection of bovine thymus-derived HMGB1 and recombinant at-HMGB1 or ds-HMGB1 evoked long-lasting mechanical allodynia, as assessed by von Frey test. TMα, when preadministered i.pl., prevented the HMGB1-induced allodynia, an effect abolished by i.p. argatroban, an anti-thrombin drug, and enhanced by i.pl. thrombin. Thus, TMα is considered to inhibit the HMGB1-induced pain signals in a thrombin-dependent manner.

Disclosures: Y. Hayashi: None. **M. Matsunami:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Asahi Kasei Pharma. **R. Tsujita:** A. Employment/Salary (full or part-time):; Asahi Kasei Pharma. **G. Honda:** A. Employment/Salary (full or part-time):; Asahi Kasei Pharma. **A. Kawabata:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Asahi Kasei Pharma.

Poster

220. Inflammatory Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 220.02/X20

Topic: D.03. Somatosensation: Pain

Title: Allosteric small molecule antagonists of protease-activated receptor 2 (PAR2) inhibit PAR2 induced rat paw inflammation

Authors: *D. G. BROWN[1], L. SUNDSTROM[2], S. GESCHWINDER[2], A. SNIJDER[2], H. SOUTER[3], D. TROAST[3], C. DUMELIN[3], G. BROWN[4], R. K. Y. CHENG[4], C. FIEZ-VANDAL[4], O. SCHLENKER[4], R. COOKE[4], R. PRIHANDOKO[4], B. TEHAN[4], G. WIGGIN[5], A. ZHUKOV[4], M. CONGREVE[4], B. TEOBALD[4], N. DEKKER[2], Y. JIANG[6], R.-J. LOHMAN[6], D. FAIRLIE[6]
[1]Discovery Sci., Astrazeneca R&D Boston, Waltham, MA; [2]AstraZeneca, Gothenburg, Sweden; [3]X-Chem Inc, Waltham, MA; [4]Heptares Therapeut. Ltd, Welwyn Garden City, United Kingdom; [5]4Heptares Therapeut. Ltd, Welwyn Garden City, United Kingdom; [6]Univ. of Queensland, Brisbane, Australia

Abstract: PAR2 is a G-protein coupled receptor (GPCR) on sensory neurons that is activated during inflammation, leading to hyperphosphorylation of TRP channels, pain and hyperalgesia. PAR2 represents an attractive therapeutic target, but there are very few selective PAR2 full

antagonists in the literature. We employed two screening strategies to identify antagonists, one being a DNA-encoded library screen on PAR2 and the second a fragment screen using a stabilized PAR2 GPCR receptor. From these efforts, we identified two lead series of compounds exemplified by AZ3451 (IC_{50} = 23 nM, 1321N1 cells overexpressing human PAR2, SLGRL activation) and AZ8838 (IC_{50} = 1500 nM, 1321N1 cells overexpressing human PAR2, SLGRL activation). These series demonstrated PAR2 antagonism across a range of human cells by binding at two distinct allosteric sites in the receptor. AZ3451 and AZ8838 were also evaluated in two rat models of PAR2 induced paw oedema (2fLIGRL-NH_2 at 350 µg/paw in 100 µL or trypsin at 20 µg/ paw in 100 µL). At a 10 mg/kg dose, both compounds exhibited a significant reduction of paw swelling in both in vivo models. These results confirm that at least two allosteric sites exist on the PAR2 receptor, and that ligands directed to these sites can antagonize PAR2 activation and signaling both in vitro and in vivo.

Disclosures: **D.G. Brown:** None. **L. Sundstrom:** None. **S. Geschwinder:** None. **A. Snijder:** None. **H. Souter:** None. **D. Troast:** None. **C. Dumelin:** None. **G. Brown:** None. **R.K.Y. Cheng:** None. **C. Fiez-Vandal:** None. **O. Schlenker:** None. **R. Cooke:** None. **R. Prihandoko:** None. **B. Tehan:** None. **G. Wiggin:** None. **A. Zhukov:** None. **M. Congreve:** None. **B. Teobald:** None. **N. Dekker:** None. **Y. Jiang:** None. **R. Lohman:** None. **D. Fairlie:** None.

Poster

220. Inflammatory Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 220.03/X21

Topic: D.03. Somatosensation: Pain

Support: GAUK 138215

LQ1604 BIOCEV-FAR

GACR 15-11138S

LH15279

GACR P304/12/G069

CZ.1.05/1.1.00/02.0109

RVO67985823

Title: Modulation of inhibitory postsynaptic currents at spinal cord excitatory neurons in VGAT-ChR2-eYFP mice studied in different pain models

Authors: *P. ADAMEK[1,2], J. PALECEK[1]
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Abstract: The balance between inhibitory and excitatory neurotransmission is essential for processing and modulation of nociceptive information in the spinal cord dorsal horn. It was suggested before that loss or deficit in fast GABAergic and glycinergic synaptic transmission in the spinal cord may be the underlying mechanism of different pain syndromes. We used optogenetic stimulation of inhibitory dorsal horn neurons to study changes of inhibitory neurotransmission in different models of pain states. The goal was to describe changes in GABAergic and glycinergic transmission at excitatory dorsal horn neurons in a model of paclitaxel-induced neuropathy and peripheral inflammation. Whole-cell patch clamp recordings of spontaneous excitatory and inhibitory postsynaptic currents (sEPSC, sIPSC) and blue light-evoked IPSC from putative excitatory (Channelrhodopsin-2 (ChR2) non-expressing) neurons in spinal cord slices from VGAT-ChR2-eYFP mice (The Jackson Laboratory) were used. In the beginning of each recording, neurons were tested for the presence of ChR2 by a 500 ms long blue light pulse (473 nm) at -70 mV. Inhibitory interneurons with ChR2 expression were characterized by inward response with long plateau phases and excitatory neurons without ChR2 by inward response without the plateau. Only non-ChR2 expressing neurons were used for next recording of sEPSC, sIPSC and light-evoked IPSC (473 nm for 5 ms). IPSCs were recorded at 0 mV holding potential with cesium based ICS solution in the presence of CNQX (10 µM) and AP5 (25 µM). Bicuculine (10 µM) and strychnine (5 µM) were used to differentiate GABAergic and glycinergic component of the response. Both GABAergic and glycinergic IPSCs were studied under the control conditions and in a model of paclitaxel-induced neuropathic pain and peripheral inflammation. Our results show that the glycinergic component represented a majority of the light-evoked currents under the control conditions (47 %) while the GABAergic component was much smaller (13 %). Under the pathological conditions, the ratio between the glycinergic and GABAergic component did not change substantially, while the light-evoked IPSCs amplitude and sIPSC frequency declined and sEPSC frequency increased. A better understanding of the processes leading to modulation of inhibitory neurotransmission under pathological conditions may help to improve analgesic therapy in these pathological states.

Disclosures: **P. Adamek:** None. **J. Palecek:** None.

Poster

220. Inflammatory Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 220.04/X22

Topic: D.03. Somatosensation: Pain

Support: GZ919

973 Program (2015CB554504)

NSFC81373735

Sichuan Provincial Innovative Research Team Program (2015TD0010)

Innovative Research Team at the University of Sichuan Province (16TD0015)

Title: Local P2X3 receptor mediates moxibustion-induced analgesia

Authors: *L. M. HUANG[1], X.-L. SHI[1], C.-Y. ZUO[1], H.-Y. YIN[1], S.-G. YU[2], Y. TANG[1]
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Abstract: The P2X3 receptor as one of the families of ligand-gated ion channels that act through ATP is closely associated with pain and analgesia. It is activated by ATP to transmit those messages of pain with a different role in peripheral and central mechanisms, and then modulates the nociceptive activities. Previous studies demonstrated that the antinociceptive effect of acupuncture was mediated by the expression of P2X3 receptor in dorsal root ganglion, spinal cord and periaqueductal gray. However, whether the localized P2X3 receptor (also means the receptor at the acupuncture point) get involved in the antinociceptive effects of acupuncture remains poorly understood. In this study, we injected complete Freund's adjuvant to induce chronic inflammatory pain in mice, applied moxibustion therapy on Zusanli acupuncture point (ST36) and injected P2X3 receptor antagonist (A317491, 0.25nmol/L, 20ul) into ST36 to explore whether the localized P2X3 receptor involved in the moxibustion-induced analgesia.The results showed that moxibustion is effective in treating chronic pain with reducing thermal hyperalgesia and mechanical allodynia obviously in the presence of P2X3 receptor. On the contrary, the anti-nociceptive effect of moxibustion was reduced when A317491 was injected to block the expression of P2X3 receptor. Thus, in the process of moxibustion analgesia, the localized P2X3 receptor would play an important role in the primary transmission of moxibustion analgesic signal to mediate the anti-nociceptive effect.

Disclosures: L.M. Huang: None. **X. Shi:** None. **C. Zuo:** None. **H. Yin:** None. **S. Yu:** None. **Y. Tang:** None.

Poster

220. Inflammatory Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 220.05/X23

Topic: D.03. Somatosensation: Pain

Support: OCAST HR16-003

Title: Effect of TNBS-induced inflammatory colitis on intestinal epithelial cells and enteric nervous system

Authors: *S. DAS[1], K. E. MILLER[2]
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Abstract: Visceral pain is the hallmark of all the inflammatory bowel diseases (IBD) including inflammatory colitis. Development of chronic visceral pain is result from changes that begin with hypersensitivity of the primary sensory neurons innervating GI tract. Primary sensory neuron especially glutamatergic sensory neurons that innervate the gut release a number of molecules that induce vasodilation, edema and swelling. Therefore, this function of sensory neurons significantly contributes to visceral and peripheral inflammation. Intestinal epithelial cells (IECs) At the center of thisare important components of peripheral neuroinflammation in inflammatory colitis are the intestinal epithelial cells (IECs). This neuroinflammation also leads to hypersensitivity of enteric nervous system (ENS). In our a colitis model of neuroinflammation, we use colon inflammation is induced in Sprague-Dawley rats to induce colitis by intra-colonic infusion of trinitro-benzene-sulphonic acid (TNBS). Our preliminary findings show the upregulation of glutaminase (GLS) protein expression, the enzyme responsible for conversion of glutamine to glutamate, an excitatory neurotransmitter. We have also confirmed that in inflammatory colitis, the mMyenteric ganglia number as well as number of neuron per ganglia is reduced in ENS. At the same time, in mucosal epithelium, the GLS mRNA is being targeted by miR-23b-5p for expression regulation. These effects are abolished in GLS heterozygous ($GLS^{+/-}$) rats where TNBS-induced inflammatory colitis does not increase the GLS expression or the increase in miR23b-5p expression. Our Results from *in vitro* experiments, using enterocytes Caco-2 cells, suggest indicate that when treated with TNBS for shorter time period (45 minutes) produces , the cells are cellular stressed stress, as indicated by showing apoptotic bodies as well asand fusion of mitochondria. This TNBS-induced stress is relieved when the cells are pretreated with 6-diazo-5-oxo-L-norleucine (DON), a GLS inhibitor. Based on these results, GLS expression and regulation appears to be the a major player in epithelial barrier maintenance and pathogenesis in inflammatory colitis.

Disclosures: S. Das: None. **K.E. Miller:** None.

Poster

220. Inflammatory Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 220.06/X24

Topic: D.03. Somatosensation: Pain

Support: NIH Grant DE018661

NIH Grant DE023090

Title: Regulation of static plasma membrane tension and Piezo2 channel activity by Rho-associated protein kinase in DRG neurons

Authors: *H. KANDA, V. VIATCHENKO-KARPINSKI, J. LING, J. GU
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Abstract: Primary afferent neurons can sense their physical environment using mechanically activated (MA) channels that convert mechanical force to electrical signals. Piezo2 channel is a newly identified MA channels expressed on primary afferent neurons of the dorsal root ganglia (DRG) and its activation generates rapidly adapting mechanically activated (RA-MA) currents. We have recently shown that actin filament, a main type of cytoskeleton, plays an important role in regulating Piezo2-mediated RA-MA currents via its impact on static plasma membrane tension in DRG neurons. Since Rho-associated protein kinase (ROCK) is a key regulator of actin organization, in the present study we hypothesized that ROCK also plays a key role in regulating static plasma membrane tension and Piezo2 channel activity in DRG neurons. We used the laser tweezers optical trapping technique to determine static plasma membrane tension of cultured DRG neurons, and examined effects of ROCK activation on static plasma membrane tension of DRG neurons. We further examined RA-MA currents using the whole-cell patch-clamp recording technique and determined effects of ROCK activation on RA-MA currents. The static plasma membrane tension was 52.3 ± 0.8 pN/μm (n = 7) in control DGR neurons and was increased to 123 ± 0.2 pN/μm (n = 7, $P < 0.05$) following the treatment with Narciclasine to activate ROCK via RhoA pathway. The increase was blocked by fasdile, a ROCK inhibitor. Concurrent with the increases of static plasma membrane tension, we found that the activation of ROCK also significantly enhanced RA-MA current amplitude in DRG neurons. Taken together, our findings suggest that ROCK regulates static plasma membrane tension and Piezo2 channel activity in DRG neurons.

Disclosures: H. Kanda: None. **V. Viatchenko-Karpinski:** None. **J. Ling:** None. **J. Gu:** None.

Poster

220. Inflammatory Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 220.07/X25

Topic: D.03. Somatosensation: Pain

Support: Discovery Grant from Natural Sciences and Engineering Research Council of Canada (RFN.356021)

Louise and Alan Edwards Foundation Grant in Pain Research (RFN.68772)

Title: COX2-PGE2-EP4 signaling is involved in repeated restraint stress induced prolongation of sensitization pain evoked by subsequent PGE2 challenge

Authors: *W. MA, L. LI, S. XING
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Abstract: More than 20% of the world population suffer from chronic pain, a serious clinical condition that severely deteriorates the quality of life and imposes heavy financial burden on health care system. Prevalence of prior stress experience is associated with high incidence of chronic pain. It has been believed that stress, particularly repeated stress, induces adaptive neuroplasticity along peripheral and central pain pathways, which facilitates sensitization of nociceptive neurons and predisposes transition from acute to chronic pain. Prostaglandin E2 (PGE2), a well-known pain mediator enriched in injured tissues, is involved in chronic pain. Its EP4 receptor is a major player in mediating nociception and pathological pain. In this study, we examined whether COX2/PGE2/EP4 signaling is involved in stress prolongation of sensitization pain, a rat model for transition from acute to chronic pain. We found that pre-exposure to single restraint stress induced analgesia to subsequent PGE2 challenge. However, pre-exposure to 3 restraint stress sessions over 3 consecutive days not only prolonged sensitization pain evoked by subsequent PGE2 challenge from 1d to 4d, but also increased stress hormone corticosterone (CORT) levels in serum, COX2 levels in paw skin, EP4 and TRPV1 levels in dorsal root ganglion (DRG) and paw skin. Pre-exposure to 3d restraint stress also enhanced baseline release or PGE2/EP4 signaling evoked release of pain-related peptide CGRP in cultured DRG neurons. Pre-exposure to CORT for 3d also prolonged pain evoked by subsequent PGE2 challenge while co-injection of glucocorticoid receptor (GR) antagonist RU486 with repeated restraint stress for 3d prevented prolongation of PGE2 evoked pain. Co-injection of a selective COX2 inhibitor NS-398 or a selective EP4 receptor antagonist L161,982 attenuated repeated restraint stress prolongation of PGE2 evoked pain. In DRG cultures, CORT exposure directly induced an increase in EP4 and TRPV1 protein levels via GR activation. Taken together, these data suggest that repeated restraint stress up-regulates COX2/PGE2/EP4 signaling and other pain mediators in peripheral pain pathway. Enhanced COX2/PGE2/EP4 signaling contributes to stress prolonged sensitization pain and is likely involved in stress predisposed transition from acute to chronic pain. [Supported by Discovery Grant from Natural Sciences and Engineering Research Council of Canada (RFN.356021) and Louise and Alan Edwards Foundation Grant in Pain Research (RFN.68772) to Weiya Ma]

Disclosures: W. Ma: None. **L. Li:** None. **S. Xing:** None.

Poster

220. Inflammatory Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 220.08/X26

Topic: D.03. Somatosensation: Pain

Title: Macrophages and NF-κB signaling mediate peripheral HMGB1-induced mechanical allodynia in mice

Authors: *R. DOMOTO, K. NAKASHIMA, M. TSUBOTA, F. SEKIGUCHI, A. KAWABATA
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Abstract: High mobility group box 1 (HMGB1), a nuclear protein containing 3 cysteine residues (C^{23}, C^{45} and C^{106}), is passively released from necrotic cells and actively secreted by activated macrophages (Mφ), thereby playing a pro-inflammatory role as one of damage-associated molecular patterns (DAMPs). Naïve HMGB1 exists as an all-thiol form (at-HMGB1), and is oxidized into a disulfide form (ds-HMGB1) that has a disulfide bond between C^{23} and C^{45}. The at-HMGB1 and ds-HMGB1 activate the receptor for advanced glycation end products (RAGE) and Toll-like receptor 4 (TLR4), respectively. We have actually shown that intraplantar (i.pl.) administration of at-HMGB1 and ds-HMGB1 produces mechanical allodynia through activation of RAGE and TLR4, respectively, in mice (Yamasoba, Kawabata *et al., J. Phermacol. Sci.*, 130, 139-142, 2016). Given evidence that Mφ-derived HMGB1 may activate Mφ in autocrine and paracrine manners, we investigated the role of Mφ in the mechanical allodynia induced by i.pl. administration of at-HMGB1 or ds-HMGB1 in mice. The mechanical nociceptive threshold in the ipsilateral hindpaw was determined by von Frey test in male ddY mice. Intraplantar injection of at-HMGB1 at 100 ng/paw or ds-HMGB1 at 10 ng/paw caused mechanical allodynia that lasted for more than 5 h. The allodynia caused by ds-HMGB1 was significantly inhibited by ethyl pyruvate (EP), known to inhibit HMGB1 release from Mφ, minocycline, an inhibitor of Mφ/microglia activation, and liposomal clodronate (Lipo-Cld) that depletes Mφ. On the other hand, the at-HMGB1-induced allodynia was partially inhibited by EP, minocycline and lipo-Cld. Pyrrolidine dithiocarbamate (PDTC), an NF-κB inhibitor, strongly inhibited the at-HMGB1-induced allodynia, and tended to suppress the ds-HMGB1-induced allodynia. In conclusion, our data suggest that Mφ and NF-κB signaling predominantly mediate the ds-HMGB1-induced allodynia, and, to some extent, contribute to the at-HMGB1-induced allodynia in mice.

Disclosures: R. Domoto: None. **K. Nakashima:** None. **M. Tsubota:** None. **F. Sekiguchi:** None. **A. Kawabata:** None.

Poster

220. Inflammatory Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 220.09/X27

Topic: D.03. Somatosensation: Pain

Support: NIH Grant R01AT007945

Title: Acute and transient biphasic effects of caffeine on chronic pain in rodent inflammatory joint pain model

Authors: *T. TAKANO[1], T. FUJITA[2]
[1]Ctr. for Oral Biol., [2]Eastman Inst. for Oral Hlth., Univ. Rochester, Rochester, NY

Abstract: Caffeine is widely consumed via a variety of foods and drinks. The most widely known effect of caffeine is central nervous system stimulation, primarily by blocking adenosine receptors in central neurons. However, other cell types also express adenosine receptors. In particular, adenosine A1receptor in immune cells suppresses inflammatory responses, while adenosine A2A/A2B receptor can be proinflammatory. We recently reported that when inflammatory pain was induced in animals acclimated to drinking caffeine-containing water, the animals exhibited lower levels of pain compared to non-caffeine drinking group. Such attenuation of pain was erased when caffeine in drinking water was removed. This observation suggests that caffeine reversibly attenuates pain perception by alternating function of central nervous system. However, it is also possible that caffeine slowed down the development of inflammatory pain, or caffeine acutely attenuates inflammatory activity at the site of the pain, resulting lower pain signal generation at the inflammatory site. Therefore, we tested whether acute administration of caffeine can alternate the established inflammatory chronic pain. Chronic joint pain was induced by intra-articular administrating complete Freund's adjuvant (CFA, 5µL) in a left hind ankle ten days prior to the pain evaluation. CFA caused swelling in the ankle, and the pain was developed in three days, which sustained more than ten days. Mechanosensitivity was measured by von Frey filament applied to left hind paw. Before CFA administration, all animals barely responded to the filament touch (13.9 ± 2.0%, N = 24). Inflammatory response induced by CFA increased mechanosensitivity to 68.8 ± 3.9%. We intraperitoneally administered high and low doses of caffeine (75 and 25 mg/kg, respectively) and vehicle (saline) just before the second mechanosensitivity evaluation. The low dose caffeine acutely enhanced the sensitivity from 72.9 ± 7.0% to 87.5 ± 6.1% (N = 8, $p < 0.05$). On the other hand, 75 mg/kg caffeine decreased the sensitivity from 66.7 ± 6.3% to 29.2 ± 6.9% (N = 8, $p < 0.01$). The effects of caffeine were transient, as the mechanosensitivity was restored after 24 hours. To evaluate whether caffeine can directly act at the site of inflammation to change the pain perception, caffeine (100 µM, 5 µL) was locally administered to the inflammatory ankle joint, which did not

alter the mechanosensitivity (from 68.8 ± 4.9% to 64.6 ±8.6%, N = 8, p > 0.5). Combined, these observations indicate that lower dose of systemic caffeine acutely enhance the pain perception, while high dose of caffeine has antinociceptive property toward inflammatory pain.

Disclosures: T. Takano: None. **T. Fujita:** None.

Poster

220. Inflammatory Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 220.10/X28

Topic: D.03. Somatosensation: Pain

Support: Reynolds Family Spine Laboratory Funds

Title: A potential new contributor to pain processing in the dorsal horn in an animal model of multiple sclerosis

Authors: E. MIRABELLI, V. KHARIV, L. NI, R. F. HEARY, *S. ELKABES
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Abstract: It is well known that some individuals with multiple sclerosis (MS) experience pain even at early disease phase. However, the mechanisms underlying the pain responses in MS are not well understood. Recent studies in our laboratory indicated that plasma membrane calcium ATPase 2 (PMCA2), a calcium extrusion pump which is expressed primarily in neurons, could play an important role in mechanisms of pain processing in the dorsal horn (DH) of the spinal cord (SC). Using genetically modified mice, it was shown that reduced PMCA2 expression in PMCA2-heterozygous mice is associated with increased mechanical pain, even in the absence of any pathological state. Since earlier reports from our laboratory demonstrated that PMCA2 levels are decreased in the inflamed SC of mice at onset of experimental autoimmune encephalomyelitis (EAE), an animal model of multiple sclerosis (MS), we undertook investigations to determine whether mice with EAE manifest heightened pain sensitivity in early disease phase, when only flaccid tail is observed, and whether this corresponds with a reduction in PMCA2 levels, especially in the DH.
Experimental autoimmune encephalomyelitis was induced by inoculation of adult, male and female C57Bl/6 mice with Myelin Oligodendrocyte Glycoprotein$_{35-55}$ (MOG$_{35-55}$) in Complete Freund's Adjuvant (CFA). CFA-inoculated mice were used as controls. Mechanical and thermal sensitivities were assessed utilizing the von Frey filament and the hot plate paw withdrawal tests, respectively.
Female mice affected by EAE, showed a significant, 74% decrease in the paw withdrawal threshold in response to a mechanical stimulus ($p<0.0001$, n=16-22) and a 40% decrease in the paw withdrawal latency in response to a heat stimulus ($p<0.0001$, n=16-22), when compared to

controls. Similarly, there was a 94% decrease ($p<0.0001$, n=13-10) in the paw withdrawal threshold and a 60% decrease in the paw withdrawal latency ($p<0.0001$, n=13-10) in male mice with EAE. These findings indicated increased pain sensitivity at onset of motor symptoms during EAE.
Protein isolated from the DH of the same mice was analyzed by western blotting to determine whether PMCA2 levels were decreased. There was a 35% ($p< 0.001$, n=9-5) and a 29% ($p=0.001$, n=10-11) reduction in PMCA2 levels in the female and male EAE mice, respectively, when compared to controls. In contrast, the levels of two other PMCA isoforms, PMCA3 and PMCA4, remained unaltered. Thus, a selective decrease in PMCA2 in the DH corresponds with decreased pain thresholds when the early neurological deficits are manifested. These studies support further the idea that PMCA2 is a novel target in DH pain processing.

Disclosures: E. Mirabelli: None. **V. Khariv:** None. **L. Ni:** None. **R.F. Heary:** None. **S. Elkabes:** None.

Poster

220. Inflammatory Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 220.11/X29

Topic: D.03. Somatosensation: Pain

Support: NSFC Grant 81450064 to QY.T

NSFC Grant 31671212 to QY.T

NSFC Grant 81471314 to Z.Z

NSFC Grant 81671090 to Z. Z

KC16H0230 to QY.T

14KJA320002 to Z.Z

2012-LG-03 to MX.T

Title: Synthetic peptides inhibit mechanosensitive (MS) ion channels and reduce mechanical pain

Authors: Z. ZHANG[1], S.-X. KE[1], P. DONG[1], M. TANG[3], H. LI[1], X.-R. DU[1], Z.-G. ZHONG[1], *Q. TANG[2,4]
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Med. Univ., Luzhou, China; [4]Jiangsu Province Key Lab. of Anesthesiol, Xuzhou Med. Univ., Xuzhou, China

Abstract: The mechanotoxin 4 (GsMTx-4), isolated from *Grammostola spatulata*, has been widely used to identify mechanosensitive (MS) channels in sensory system. It is composed of 34 amino-acids and has characteristic sturdy structure with six cysteines forming three inhibitor cysteine knots (ICK). GsMTx-4 was recently reported to reduce the hyperalgesia of inflammatory and neuropathic pain of rats in different pain models. Thus, this venom appears to have potential clinical use for treating hyperalgesia. Nevertheless, the cost of synthesizing this peptide is still the major obstacle for drug development. In current studies, we designed and synthetized a variety of short peptides mimetics of GsMTx-4 to test their effects on hyperalgesia. We showed that either intradermal injection of the synthesized mimetics in the rat hindpaw or intraperitoneal injection of these short peptides reversed the mechanical hyperalgesia induced by intradermal injection of inflammatory mediators**.** The dose dependence of some of these mimic is comparable with GsMTx-4. The fact that these peptides did not reverse the mechanical hyperalgesia induced by a thermal injury or the baseline mechanical nociceptive thresholds suggested that the mechanism underlying reduced pain sensitivity may be related to mechanical channels. We further tested the effect of these peptides on blocking SAKcaC channel. The results showed that these mimetics inhibited SAKcaC channel in nM range in a similar way as GsMTx-4 does. Also similarly as GsMTx-4, these peptides did not inhibit the loss-of-mechanosensitive SAKcaC mutant, suggesting that they may work as selective inhibitors to MSCs. Taken together, our present results open up a promising way to reduce the cost to develop MS channel inhibitor drug to treat hyperalgesia.

Disclosures: Z. Zhang: None. **S. Ke:** None. **P. Dong:** None. **M. Tang:** None. **H. Li:** None. **X. Du:** None. **Z. Zhong:** None. **Q. Tang:** None.

Poster

220. Inflammatory Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 220.12/X30

Topic: D.03. Somatosensation: Pain

Support: NIH Grant AR047410

Title: Intra-epidermal nerve fiber reconstruction and quantification in three-dimensions

Authors: *M. B. ANDERSON, K. MILLER
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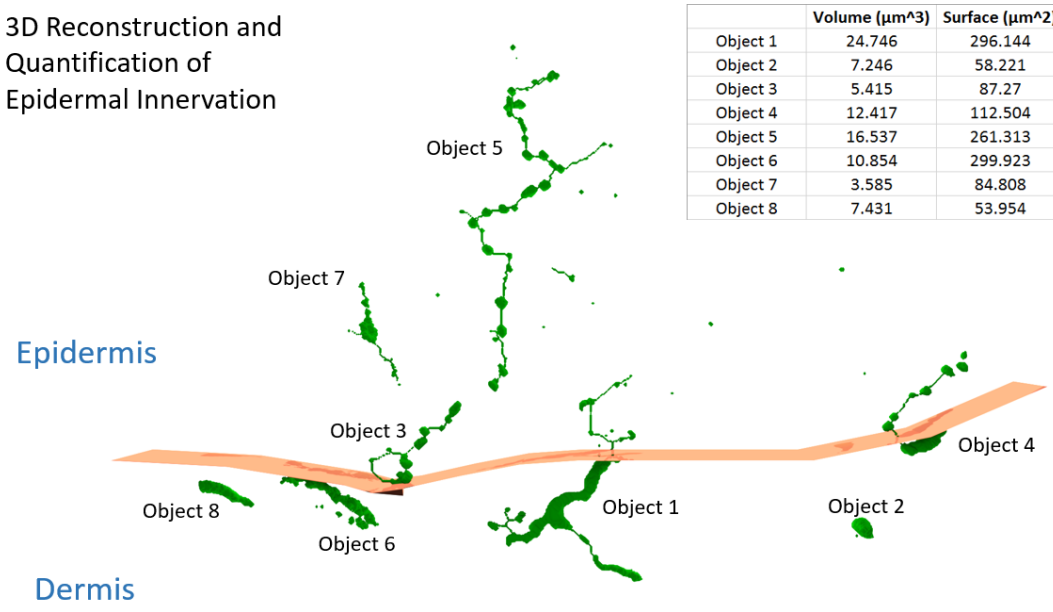
Abstract: Intra-epidermal nerve fibers (IENFs) are the peripheral component of primary sensory neurons and are the anatomical attributes for an organism's ability to sense the environment, i.e., temperature, noxious stimuli. These small, unmyelinated, IENFs are critically important to the survival of an organism. Reduction in the density of these fibers is an indicator of polyneuropathy and IENFs often are clinically evaluated for diagnosis.
Traditional evaluation and quantification of IENFs include: tissue collection, sectioning, labeling with an intra-epidermal nerve marker, and tracing/quantification of two-dimensional (2-D) images. This technique has been the industry standard to quantify the density of intra-epidermal nerves and the limitations have largely been accepted. The challenge has been in the quantification of linear three-dimensional (3-D) structures weaving through the depth (z-plane) of a field-of-view.
Recent advances in tissue clearing (TC), immunohistochemistry optimized for TC, image acquisition, and 3-D quantification have allowed for full 3-D reconstruction and quantification of IENFs from the epidermis of rats. This technique provides the ability to measure volume, surface area, and mean-grey-intensity of immunoreactivity. This procedure also has shown promise to work with non-cleared tissue from thinly sliced, 12 µm, cryostat sections.
The limitation of measuring three-dimensional objects from two-dimensional images has largely been accepted when quantifying the density of intra-epidermal nerve fibers. Our developing IENF protocol unleashes 2-D restraints and provides full 3-D visualization with accurate and whole quantification of IENF complexes.



	Volume (µm^3)	Surface (µm^2)	Mean
Object 1	24.746	296.144	161.947
Object 2	7.246	58.221	182.424
Object 3	5.415	87.27	158.41
Object 4	12.417	112.504	173.092
Object 5	16.537	261.313	158.586
Object 6	10.854	299.923	121.054
Object 7	3.585	84.808	133.167
Object 8	7.431	53.954	178.908

Disclosures: **M.B. Anderson:** None. **K. Miller:** None.

Poster

220. Inflammatory Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 220.13/X31

Topic: D.03. Somatosensation: Pain

Support: CIC UMSNH 26.10

CIC UMSNH 26.10

Title: tramadol may counteract pronociception induced by toluene in rat formalin test

Authors: M. A. TORRES-SANTANA[1], C. CERVANTES-DURAN[2], M. Y. GAUTHEREAU-TORRES[2], *L. F. ORTEGA-VARELA[3]
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Abstract: Toluene is a volatile solvent that can be found in products like thinner, paints and adhesives. Toluene misuse is an important public health problem in Mexico, mainly among street children and teenagers. Pharmacological studies indicate that this solvent produces thermal nociception in mice and rats, but the mechanisms involved are still unclear. In order to find out the participation of toluene on inflammatory nociception in rats after acute or subacute exposure, we used tramadol (an analgesic that includes more than one action mechanism). Female Wistar rats (200-300 g) were placed in a static exposure chamber and exposed to toluene (6000 ppm) or air (control group) during 30 minutes (acute exposure) or 30 minutes twice a day during 7 days (subacute exposure). Other group of rats received tramadol (2.0 mg/kg, p.o.) and then were exposed to toluene or air immediately (acute exposure), and the last one received tramadol (2.0 mg/kg, p.o.) at the eighth day for subacute exposure. After acute or subacute exposure, rats were injected with 50 µl of 1% formalin in the dorsal surface of the right hind paw. This substance causes a typical flinching related behavior, the decrease in the number of flinches reflected as reduction of the area under curve (AUC) is considered as antinociception. We observed that toluene produced a significant increase in AUC compared with rats only exposed to air, in both acute and subacute exposure (607.8 ± 62.26 in toluene group vs. 366.39 ± 31.79 in control group [acute exposure] and 505.0 ± 38.31 in toluene group vs. 351.6 ± 20.2 in control group [subacute exposure]) indicating a pronociceptive effect that was less pronounced after repeated exposure. On the other hand, tramadol showed an antinociceptive effect (AUC = 152.5 ± 8.2 [acute exposure] and 147.5 ± 15.4 [subacute exposure]) that can diminish toluene pronociceptive effect (AUC = 185.8 ± 10.5 [acute exposure] and 179.1 ± 7.2 [subacute exposure]). These results suggest that toluene increases nociception in rat formalin test and repeated toluene exposure decreases its pronociceptive effect; in addition, tramadol may counteract pronociception induced

by toluene. This effect could be mediated through common molecular targets between toluene and tramadol.

Disclosures: **M.A. Torres-Santana:** None. **C. Cervantes-Duran:** None. **M.Y. Gauthereau-Torres:** None. **L.F. Ortega-Varela:** None.

Poster

220. Inflammatory Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 220.14/X32

Topic: D.03. Somatosensation: Pain

Support: NIH Grant 4R01NS081127-04

Title: Effects of selective deletion of Pip5k1c in the sensory ganglia on nociception and inflammatory sensitization

Authors: *L. LOO, M. ZYLKA
Dept. of Cell Biol. and Physiology, Neurosci. Ctr., The Univ. of North Carolina, Chapel Hill, NC

Abstract: Nociceptor sensitization is one of the underlying mechanisms of chronic pain conditions. Pronociceptive factors activate G-protein coupled receptors (GPCRs) and receptor tyrosine kinases (RTKs) on nociceptors and their downstream signaling cascades potentiate the activity and expression of a variety of ion channels and receptors, driving the increase in nociceptor excitability. Inhibiting pronociceptive receptors and kinases attenuates chronic pain in animal models but show modest to no effects in humans. An alternative strategy is to target intermediates downstream of multiple pronociceptive receptors. Phosphatidylinositol 4,5 bisphosphate ($PI(4,5)P_2$ or PIP_2) has an important role in cell signaling and is at the convergence point for many of the aforementioned pronociceptive signaling pathways. Hence, we sought to reduce pronociceptive signaling by inhibiting the lipid kinase that generates PIP_2 in dorsal root ganglion (DRG) neurons. Indeed, lower PIP_2 levels in phosphatidylinositol-4-phosphate 5-kinase type 1 gamma (*Pip5k1c*) haploinsufficient mice lead to a decrease in pain signaling and sensitization. While PIP_2 levels were significantly reduced in the DRGs of *Pip5k1c* haploinsufficient mice, their levels remain unchanged in spinal cord and brain, suggesting that the reduction in pain signaling and sensitization is primarily due to the reduction in PIP_2 levels in the sensory ganglia. We then try to verify whether further depletion of PIP_2 pools via deletion of *Pip5k1c* specifically in sensory neurons is sufficient to decrease initiation and/or maintenance of inflammatory pain. Deletion of *Pip5k1c* in sensory ganglia (Advillin-cre::*Pip5k1c*$^{fl/fl}$) during development led to proprioceptive deficits. To circumvent this developmental dysfunction, we generated 2 lines of tamoxifen-inducible conditional knockouts, Brn3a-cre-ERT2::*Pip5k1c*$^{fl/fl}$

and Advillin-cre-ERT2::*Pip5k1c*$^{fl/fl}$ mice and quantified their basal nociceptive responses and sensitization with the CFA inflammatory model.

Disclosures: L. Loo: None. **M. Zylka:** None.

Poster

220. Inflammatory Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 220.15/X33

Topic: D.03. Somatosensation: Pain

Title: Scaffolded up-regulation of peripheral calcium-permeable ampa receptors

Authors: *Y. ZHANG, N. A. JESKE
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Abstract: Glutamate is the major excitatory neurotransmitter in the nervous system. α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid glutamate receptors (AMPAR) in the spinal dorsal horn are critically involved in nociceptive plasticity associated with inflammatory pain. Furthermore, GluA1-containing, calcium-permeable AMPARs in peripheral nociceptors are implicated in mediating inflammatory mechanical allodynia. However, how inflammation modulates peripheral AMPARs remains largely unknown. Therefore, we aim to investigate the mechanisms of algogen-modulation of GluA1-containing AMPARs in peripheral sensory neurons. Electrophysiology and calcium imaging analyses of cultured dorsal root ganglion (DRG) neurons reveal that bradykinin treatment increases AMPA-mediated currents and $[Ca^{2+}]i$ transients specifically in medium-sized DRG neurons. This potentiation was inhibited by phospholipase C (PLC) and protein kinase C (PKC) inhibitors, and mimicked by PKC activator. Importantly, augmentation of AMPA-mediated responses by bradykinin was abolished in both FITC-A-Kinase Anchoring Protein 79/150 (AKAP) siRNA-treated rat DRG neurons and AKAP knock-out (KO) mouse DRG neurons. These results suggest that AKAP functionally mediates AMPAR up-regulation by bradykinin, supporting the idea that targeting AKAP may serve as an effective strategy for treating chronic inflammatory mechanical allodynia.

Disclosures: Y. Zhang: None. **N.A. Jeske:** None.

Poster

220. Inflammatory Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 220.16/Y1

Topic: D.03. Somatosensation: Pain

Support: Prof. KH René Koczorek Stiftung, Neuried, Germany

Title: Blocking tonic activation of neuronal MR suppresses inflammatory pain by rapid non-genomic effects

Authors: S. A. MOUSA[1], *M. SCHAEFER[2]
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Abstract: Corticosteroids are the most commonly used drugs in the effective relief of pain and inflammation in various type of diseases. There is a growing body of evidence that corticosteroids mainly mediate their anti-inflammatory and immunomodulatory effects through cytosolic receptor activation and subsequent classical genomic pathways. Recently, we provide evidence suggesting rapid non-genomic mineralocorticoid receptor (MR) as well as glucocorticoid receptor (GR) dependent signaling pathways within spinal and peripheral nociceptive neurons. However, evidence for a local endogenous aldosterone and its key processing enzymes is scarce. Here, double immunofluorescence confocal microscopy revealed that MR as well as aldosterone and its processing enzyme predominantly localized in peripheral peptidergic nociceptive C-neurons of dorsal root ganglia (DRG) which were significantly upregulated under inflammatory pain. Moreover, aldosterone and its processing enzymes, which localized on sensory nerve terminals and microglia as well as astrocytes within the dorsal horn of the spinal cord, were significantly upregulated under inflammatory pain. Importantly, i.pl. selective MR antagonist canreonate-K dose-dependently attenuated nociceptive behavior associated with CFA-induced tonic pain by rapid, specific receptor mediated effects confirming a tonic release of the endogenous ligand aldosterone and consequently intrinsic activation of neuronal MR. Taken together, these finding indicate that sensory neurons express MR as well as the endogenous ligand aldosterone and its processing enzymes. Local MR antagonist-induced rapid non-genomic inhibition of pain behavior resulted most likely from the antagonism of the continuous neuronal MR activation through released endogenous ligand aldosterone thus, unraveling a yet unconsidered mechanism of pain relief.

Disclosures: S.A. Mousa: None. **M. Schaefer:** None.

Poster

220. Inflammatory Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 220.17/Y2

Topic: D.03. Somatosensation: Pain

Support: Hungarian Government Grant KTIA_NAP_13–2–2014–0005

Title: Neurons of the superficial spinal dorsal horn that show phosphorylated histone 3 at serine 10 upon tissue injury-associated pain

Authors: A. VARGA[1], M. SIVADO[2], B. GAAL[2], T. BACSKAI[2], E. KOKAI[2], *I. NAGY[3], P. SZUCS[2]
[1]Dept. of Anatomy, Histology and Embryology, MTA-DE-NAP B-Pain Control Res. Group, Univ. of Debrecen, Debrecen, Hungary; [2]Dept. of Anatomy, Histology and Embryology, Univ. of Debrecen, Debrecen, Hungary; [3]Imperial Col. London, London, United Kingdom

Abstract: Transcriptional changes in superficial spinal dorsal horn (SSDH) neurons are essential in the development and maintenance of prolonged pain. Phosphorylation of serine 10 (S10) in histone 3 (H3) was recently proven to occur specifically in a group of rat SSDH neurons following the activation of nociceptive primary sensory neurons by burn injury, capsaicin application or sustained electrical activation of nociceptive primary sensory nerve fibres. It was also proposed that p-S10H3 is a novel marker for nociceptive processing in SSDH neurons with high relevance to transcriptional changes and the development of prolonged pain. In the present study we aim to clarify if these transcriptional changes apply to projection neurons, the major output elements of the SSDH circuitry, or if they are restricted to local interneurons. We combined retrograde labelling of SSDH projection neurons from the lateral parabrachial nucleus and from the periaqueductal grey matter with immunocytochemistry to reveal p-S10H3 in lamina I projection neurons at the cervical and lumbar levels. Our results will shed light on to what extent transcriptional changes effect SSDH circuitry upon tissue-injury associated pain.

Disclosures: **A. Varga:** None. **M. Sivado:** None. **B. Gaal:** None. **T. Bacskai:** None. **E. Kokai:** None. **I. Nagy:** None. **P. Szucs:** None.

Poster

220. Inflammatory Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 220.18/Y3

Topic: D.03. Somatosensation: Pain

Support: NIH grant NS065926

NIH grant NS098826

Title: Calcitonin gene-related peptide promotes pain specifically in females in hyperalgesic priming and neuropathic pain

Authors: *C. A. PAIGE[1], G. PRADHAN[2], P. M. PRADHAN[2], G. DUSSOR[2], T. J. PRICE[3]
[1]Cognition and Neurosci., Univ. of Texas At Dallas, Richardson, TX; [2]Cognition and Neurosci., Univ. of Texas at Dallas, Richardson, TX; [3]Sch. of Behavioral and Brain Sci., UTD, Richardson, TX

Abstract: Several studies have demonstrated male-specific mechanisms for the promotion of neuropathic pain, but few female-specific mechanisms have been identified. In this study we hypothesized that Calcitonin Gene-Related Peptide (CGRP) is necessary for the development and maintenance of hyperalgesic priming in female mice, but not in male mice. In addition, we also hypothesized that CGRP contributes to neuropathic pain in the Spared Nerve Injury (SNI) model only in female mice. To test our hypothesis adult Swiss Webster mice were injected intrathecally (I.T.) with 10μg of olcegepant- a CGRP receptor antagonist- or vehicle and intraplantarly (I.Pl.) with IL-6 (0.1ng) and mechanical withdrawal threshold was measured. Animals were allowed to return to baseline levels of mechanical sensitivity and then injected I.Pl. with PGE_2 (100ng) and mechanical withdrawal thresholds were tested at 3 and 24h to assess priming. This experiment was repeated, but with I.T. injection of olcegepant before the second I.Pl. injection of PGE_2 . In a third set of experiments, we injected olcegepant into mice that had been given a spared nerve injury 14 days prior and measured their mechanical withdrawal threshold post injection. These experiments were then repeated in males and females using $CGRP_{8-37}$ (1μg), a second CGRP receptor antagonist. When given at the time of I.Pl. IL-6 injection, I.T. olcegepant blocked the initial response to IL-6 in female mice, but had no effect in male mice. When I.T. olcegepant was given at the time of PGE_2 injection it again blocked response to PGE_2 in female mice, but not in male mice. In female mice, when olcegepant was given I.T. 14d post SNI surgery, there was a transient reduction in mechanical hypersensitivity only in female mice. $CGRP_{8-37}$ injected I.T. at the time of IL-6 blocked both the response to IL-6 and the development of hyperalgesic priming in females, but had no effect in males. $CGRP_{8-37}$ given at the time of PGE_2 injection in females reversed hyperalgesic priming but again had no effect in males. CGRP8-37 attenuated SNI-induced mechanical hypersensitivity for 24h in

females but did not have an effect in males. Therefore, I.T. delivered CGRP receptor antagonists have pain relieving effects that are only evident in female mice. While more work is warranted to more fully understand this sex-specific mechanism, our findings serve as a further rationale for exploring sex-specific treatments of chronic pain in the clinic.

Disclosures: **C.A. Paige:** None. **G. Pradhan:** None. **P.M. Pradhan:** None. **G. Dussor:** None. **T.J. Price:** None.

Poster

220. Inflammatory Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 220.19/Y4

Topic: D.03. Somatosensation: Pain

Support: DMRDP grant (0130-15-0003-00002)

Title: Modulation of eicosanoid signaling contributes to the anti-nociceptive effect of ABHD6 inhibitor WWL70 in the chronic constriction injury mouse model

Authors: *J. WEN
anatomy, physiology and Genet., Uniformed Services Univ., Frederick, MD

Abstract: Our previous studies have shown that inhibition of the minor endocannabinoid 2-AG hydrolytic enzyme alpha, beta-hydrolase domain 6 (ABHD6) significantly reduces neuroinflammation and exerts neuroprotection in animal models of traumatic brain injury and multiple sclerosis. Selective inhibition of ABHD6 is thought to provide therapeutic benefits without producing cannabimimetic side effects caused by the inhibition of the principle 2-AG hydrolytic enzyme, monoacylglycerol lipase (MAGL). Accumulating evidence suggests that neuroinflammation is a major contributing factor to the pathogenesis of neuropathic pain. In this study we aimed to determine the potential therapeutic effect of a selective ABHD6 inhibitor WWL70 in the management of neuropathic pain. In the murine model of neuropathic pain induced by chronic constriction (CCI) of the sciatic nerve, we found that WWL70 treatment significantly alleviated CCI-induced thermal hyperalgesia and mechanical allodynia in the ipsilateral paw at 3 and 7 days post-injury. Treatment with WWL70 also significantly attenuated the increased inflammatory response characterized by the reduced expression of macrophages and downregulation of TNF-α, IL-6, IL-1β, MCP-1 in the ipsilateral sciatic nerve, DRG and spinal cord dorsal horn of CCI mice. Surprisingly, co-treatment with the cannabinoid receptor antagonists failed to antagonize the effect of WWL70, suggesting that WWL70's anti-nociceptive effect is independent on cannabinoid receptor activation. Using liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS), we found the levels of 2-AG, arachidonic acid (AA) and prostaglandin E_2 (PGE_2) are elevated in the injured sciatic

nerve. Although treatment with WWL70 did not alter the levels of 2-AG and AA, it significantly reduced PGE_2 production. Consistently, WWL70 treatment also reduced the expression of COX-2 and $PGES_2$, two enzymes essential for the production of PGE_2, in the injured sciatic nerve. This result suggested that interference with the eicosanoid signaling pathway contributes, at least in part, to the therapeutic mechanisms of WWL70 on CCI induced neuropathic pain. *This work was supported by DMRDP grant (0130-15-0003-00002)*

Disclosures: J. Wen: None.

Poster

220. Inflammatory Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 220.20/Y5

Topic: D.03. Somatosensation: Pain

Support: GACR 15-11138S

LH15279

GAUK 138215

LQ1604 BIOCEV-FAR

GACR P304/12/G069

CZ.1.05/1.1.00/02.0109

RVO67985823

Title: Peripheral inflammation alters N-arachidonoylphosphatidylethanolamine (20:4-NAPE) induced modulation of nociceptive spinal cord synaptic transmission

Authors: P. ADAMEK[1,2], V. NERANDZIC[1], P. MROZKOVA[1], D. SPICAROVA[1], I. NAGY[3], *J. PALECEK[1]
[1]Inst. of Physiology, Czech Acad. of Sci., Praha, Czech Republic; [2]Fac. of Science, Charles Univ., Prague, Czech Republic; [3]Imperial Col. London, London, United Kingdom

Abstract: Endocannabinoids play an important role in modulation of spinal nociceptive signalling. The cannabinoid receptor 1 (CB1) and the transient receptor potential vanilloid 1 (TRPV1) are both activated by the endocannabinoid anandamide that is a product of biosynthesis from the endogenous lipid precursor N-arachidonoylphosphatidylethanolamine (20:4-NAPE). Here we report the CB1 and TRPV1-mediated effects of 20:4-NAPE application on spinal synaptic transmission in control conditions and after peripheral inflammation. Whole-cell patch

clamp recordings of spontaneous (sEPSCs) and dorsal root stimulation-evoked (eEPSCs) excitatory postsynaptic currents from superficial dorsal horn neurons in rat spinal cord slices were used. Model of peripheral inflammation was induced by 3% carrageenan. Release of anandamide from spinal cord slices after incubation with 20:4-NAPE solution was assessed by mass spectrometry. Our data show that application of 20:4-NAPE increased anandamide concentration in spinal cord slices *in vitro*. 20:4-NAPE (20 μM) also induced sEPSCs frequency and eEPSCs amplitude decrease under control and inflammatory conditions. The inhibitory effect of 20:4-NAPE was sensitive to CB1 antagonist PF514273 (0.2 μM) in both conditions, but to the TRPV1 antagonist SB366791 (10 μM) only after inflammation. After inflammation 20:4-NAPE increased sEPSCs frequency in the presence of PF514273 and this increase was blocked by SB366791. While 20:4-NAPE treatment produced an inhibitory effect on excitatory synaptic transmission in both naive and inflammatory conditions, peripheral inflammation altered the underlying mechanisms. Our data indicate that 20:4-NAPE application induced mainly CB1 receptor mediated inhibitory effects in naive animals while TRPV1-mediated mechanisms were also involved after the inflammation. Increasing anandamide levels for analgesic purposes by applying substrate for its local synthesis may be superior to systemic anandamide application or inhibition of its degradation.

Disclosures: P. Adamek: None. **V. Nerandzic:** None. **P. Mrozkova:** None. **D. Spicarova:** None. **I. Nagy:** None. **J. Palecek:** None.

Poster

220. Inflammatory Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 220.21/Y6

Topic: D.03. Somatosensation: Pain

Title: A pan-Trk inhibitor exerts an analgesic effect through inhibiting peripheral TrkA phosphorylation in a osteoarthritis pain model

Authors: *T. YASUHIRO, A. KAMIYA, S. KATSUMATA, Y. HIROTA
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Abstract: Background and aims:
Peripheral tropomyosin receptor kinase (Trk) A, a specific receptor for nerve growth factor, is a promising target for the management of chronic pain. The importance of this target has been highlighted by anti-nerve growth factor antibodies, which demonstrated significant analgesic effects in clinical trials in patients with osteoarthritis (OA) pain. In this study, we evaluated the analgesic effect of a new pan-Trk inhibitor on OA pain in rat monosodium iodoacetate (MIA)-induced OA model. Moreover, we examined the action of our pan-Trk inhibitor against phosphorylation of Trk in this model.

Methods:
Animal experiments were performed in accordance with Regulations for Animal Experiments of Ono Pharmaceutical Co., Ltd. In rats, osteoarthritis was induced by MIA injection intra-articularly into the knee (3 mg/site). In the experimental groups, the pan-Trk inhibitor (0.1 or 0.3 mg/kg) was orally administered twice a day up to 10 days starting from 14 days after MIA injection. In the control group, tramadol (10 mg/kg) was subcutaneously administered at 24 days after MIA injection. The pain-related behavior was evaluated on Day 24 by the percentage of weight bearing on a hind limb using Linton Incapacitance Tester. The expression of Trk phosphorylation in the dorsal root ganglion and knee joint of the MIA model rat was evaluated by immunohistochemistry using a goat polyclonal antibody against phosphorylated Trk at tyrosine 496.
Results:
The pan-Trk inhibitor dose-dependently inhibited pain-related behavior in the MIA osteoarthritis model. The analgesic effect at 0.3 mg/kg b.i.d. was stronger than that of tramadol at 10 mg/kg. Increased Trk phosphorylation was detected in the dorsal root ganglion and knee joint of 21 days after MIA injection, and our compound inhibited it.
Conclusion:
The pan-Trk inhibitor showed potent analgesic effects in the osteoarthritic pain model more strongly than tramadol. We conclude that the analgesic effect of our compound is attributable to its inhibition of peripheral TrkA phosphorylation.

Disclosures: **T. Yasuhiro:** None. **A. Kamiya:** None. **S. Katsumata:** None. **Y. Hirota:** None.

Poster

220. Inflammatory Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 220.22/Y7

Topic: D.03. Somatosensation: Pain

Support: ARUK Project Grant

Title: Spinal IL6 contributes to central sensitisation and persistent pain hypersensitivity in a model of juvenile idiopathic arthritis

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Abstract: Introduction: Juvenile idiopathic arthritis (JIA) is the most common form of rheumatological disease in childhood. The use of biologics have improved treatment, but joint

inflammatory pain that persists beyond the progress of the disease, remains a major cause of disability. We hypothesise that this pain is maintained by a unique and persistent upregulation of pro-inflammatory cytokines in the spinal cord dorsal horn, not observed in adults. Methods: Postnatal day (P)16 and P40 male Sprague-Dawley rats were obtained from the Biological Services Unit, UCL. Under isoflurane anaesthesia, rats received a single intra-articular injection of complete Freund's adjuvant (CFA, 10µL at P21 and 20µL at P40) or saline (control) into the left ankle joints. Mechanical allodynia was assessed by measuring paw withdrawal thresholds to von Frey hair (vFh) stimulation. Mechanical hyperalgesia was assessed by static weight bearing. *In vivo* single unit extracellular recording of wide dynamic range (WDR) neurons in the spinal dorsal horn was performed to measure neuronal sensitivity in the presence of joint inflammation. The expression of TNFα, IL1β and IL6 in the joint and spinal dorsal horn was quantified with immunoprecipitation. To test the therapeutic potential of targeting spinal IL6, rats received anti-IL6 (3, 10 and 30ng in 10µL PBS) intrathecally on days 7, 8 and 9 after intra-articular injections of CFA, both mechanical and allodynia and hyperalgesia were measured. Result: The duration of active joint swelling, and expression of pro-inflammatory cytokines in the joints were comparable between P21 and P40 rats, but mechanical hyperalgesia was longer lasting in P21 rats. Single unit recordings 2 weeks after CFA injections revealed significant neuronal hypersensitivity in P21 rats, characterised by an increase in spontaneous firing, pinch-evoked firing and expansion of pinch receptive fields. Expression of TNFα and IL1β in the spinal dorsal horn was comparable between P21 and P40 rats, but IL6 remained upregulated at 2 weeks post-CFA in P21 rats. Moreover, local blockade of spinal IL6 transiently alleviated mechanical hyperalgesia in P21 rats. Conclusion: Persistent upregulation of pro-inflammatory cytokines in the spinal dorsal horn contributes to significant neuronal sensitisation and subsequent long-lasting mechanical hyperalgesia, beyond the progress of joint pathology. We identified IL6 as a potential therapeutic target for JIA-pain; expression of spinal IL6 was upregulated 2 weeks after CFA injections, and blockade of spinal IL6 activity was effective in mitigating inflammation-induced hyperalgesia in P21 rats.

Disclosures: **C.H. Kwok:** None. **A. Learoyd:** None. **Y. Ioannou:** None. **M. Fitzgerald:** None.

Poster

220. Inflammatory Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 220.23/Y8

Topic: D.03. Somatosensation: Pain

Support: NIH Grant AR047410

Title: Expression of nerve growth factor in adjuvant-induced arthritis (AIA): A temporal study

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Abstract: Background: Nerve growth factor (NGF) is a molecule, which regulates the maturation of developing sensory neurons in the peripheral nervous system (PNS) and acts as neurotrophin for a subset of nociceptive (pain-producing) sensory neurons. NGF has two known receptors, TrkA and p75NTR. Peripheral inflammation drives peripheral sensitization and modifications in DRG neuronal cell by producing retrograde signals in nociceptive neurons. These signals, e.g., action potentials or nerve growth factor/TrkA, activate or increase transcription of pro-nociceptive molecule, such as glutaminase (GLS), to augment both central and peripheral sensitization. Little is known, however, about the temporal pattern of NGF expression in the skin during inflammation. This study was designed to assess expression of NGF in epidermis during the inflammatory process triggered by AIA to determine the role of NGF in the regulation and development of acute and chronic inflammatory pain. **Methods:** AIA was induced by injection of 150µl of complete Freund's adjuvant into the rat hindpaw. At different time points (6h-12d), rats were euthanized and skin samples were retrieved from the inflamed paw. Utilizing the proteolytic enzyme thermolysin, the epidermis was separated from the dermis. From epidermis sample, immunohistochemistry and western blot were performed to determine NGF protein expression and quantitative real time polymerase chain reaction (qRT-PCR) was used to assess the levels of NGF mRNA. **Results**: In the present study, we confirmed previous reports that the levels of NGF mRNA and protein are upregulated in the presence of peripheral inflammation. NGF showed an early increase during the acute phase of AIA (6-12 hrs), followed by decrease to basal levels. Another upsurge was observed during the chronic phase of AIA (2-4 days) which returned to basal levels by day 12. **Conclusion:** These preliminary studies suggest that the NGF shows a biphasic response in the epidermis following noxious insult and further supports its contribution to the development and regulation of acute and chronic inflammatory pain.

Disclosures: V. Gujar: None. **K.E. Miller:** None.

Poster

220. Inflammatory Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 220.24/Y9

Topic: D.03. Somatosensation: Pain

Support: NIH COBRE Grant P20GM103643

Title: Characterization of pain associated behaviors in a rat model of temporomandibular joint osteoarthritis

Authors: *S. SANNAJUST[1], J. HEATH[1], I. IMBERT[2], T. E. KING[1]
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Abstract: Temporomandibular disorder (TMD) is a musculoskeletal orofacial disorder characterized by pain in the temporomandibular joint (TMJ). Although TMD is a heterogeneous disorder, osteoarthritis (OA) has been found to be present in approximately 16% of the patients and arising in almost 90% of female patients. Pain is the primary complaint associated with loss of function in these patients and is a primary motivation for these patients to seek medical care. We characterized a rat model of TMJ OA in which monosodium iodoacetate (MIA) is injected into the TMJ at a dose previously established to produce cartilage loss. We demonstrated that male rats treated with that MIA injection into the TMJ demonstrated a transient change in meal eating behaviors that resolved by 14 days post-MIA and no change in weight. MIA into the TMJ produced ipsilateral tactile hypersensitivity within 24 hrs followed by infraorbital hypersensitivity 3 days post-injection and contralateral hypersensitivity 7 days post-injection. Forepaw and hindpaw hypersensitivity was observed 7 and 14 days post-MIA injection indicating development of a global hypersensitivity at these later time-points. Administration of systemic duloxetine (30 mg/kg, i.p.) D14 post-MIA reversed the MIA-induced tactile hypersensitivity at the ipsilateral TMJ within 30 min post-injection with tactile hypersensitivity returning 90 min post-duloxetine. In addition, MIA treated rats demonstrated CPP to systemic duloxetine (30 mg/kg, i.p.) indicating that this dose of duloxetine alleviates ongoing pain. These observations indicate that MIA-induced OA of the TMJ produces tactile hypersensitivity and ongoing pain that can be reversed with duloxetine 14 days post-MIA. These results demonstrate that MIA induced OA of the TMJ results in tactile hypersensitivity that spreads across the head and eventually to distal sites such as the hindpaws suggesting development of central sensitization. We further demonstrate that the serotonin-norepinephrine reuptake inhibitor (SNRI) duloxetine blocks both tactile hypersensitivity and ongoing pain in this model of TMJ OA. These observations are consistent with development of advanced osteoarthritis joint pain as observed in the clinical setting. Moreover, our data indicate that treatment with the SNRI duloxetine, used clinically to manage neuropathic pain, alleviates TMJ OA pain.

Disclosures: S. Sannajust: A. Employment/Salary (full or part-time):; University of New England. **J. Heath:** A. Employment/Salary (full or part-time):; University of New England. **I. Imbert:** A. Employment/Salary (full or part-time):; University of New England. **T.E. King:** A. Employment/Salary (full or part-time):; University of New England.

Poster

220. Inflammatory Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 220.25/Y10

Topic: D.03. Somatosensation: Pain

Support: CIHR grant MOP-136903

Louise and Alan Edwards Foundation

Title: Forced walking results in pain-related changes in a rat model of inflammatory arthritis

Authors: *S. LOCKE[1], M. MANNARINO[1], N. YOUSEFPOUR[1], A. RIBEIRO-DA-SILVA[2]
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Abstract: INTRODUCTION: Pain upon movement is a major complaint of arthritis patients and remains poorly managed. Unfortunately, as mechanisms of pain in arthritis are incompletely understood, it is difficult to develop novel efficacious therapies. The Complete Freund's Adjuvant (CFA) intra-articular model of inflammatory arthritis is widely used and results in long-lasting hypersensitivity. However, it remains to be clarified how much ongoing pain or pain in relation to movement is present. Published and preliminary data from our lab using CFA-induced arthritis in the rat ankle joint has shown that early in this model there is an inflammatory infiltration, with later sprouting of sympathetic and peptidergic nociceptive fibres in and around the inflamed joint. These data suggest that temporally distinct mechanisms drive persistent pain behavior, with inflammation driving early pain behavior and neuronal changes driving the later component. During chronic pain, such as in arthritis, pain does not only arise in the periphery, as there is also a contribution of central sensitization. In models of arthritis changes in neuronal activation in the spinal dorsal horn relating to nociception have been shown but this has not yet been investigated in freely moving animals. METHODS: Following intra-articular CFA injection to the ankle joint, behavioural assessment was carried out weekly. Weight bearing assessment and von Frey testing were performed before and after forced exercise (walking on a treadmill). Sham and CFA-treated animals were divided into either forced exercise or non-exercised groups. At 4 weeks post-CFA, 2 hours after forced exercise, animals were sacrificed and processed for immunohistochemistry. Spinal and PBN neuronal activation were assessed using anti-fos antibodies, a marker of neuronal activation. In the joint, anti-CD68 antibodies and toluidine blue staining were used to stain macrophages and mast cells, respectively. Also in the joint, sprouting of sympathetic and peptidergic fibre was assessed with anti-VMAT2 and anti-CGRP, respectively, and synovial fluid was extracted and processed for NGF western blot. RESULTS: Weight bearing showed a greater distribution of weight to the uninjured paw following exercise as compared to the pre-exercise distribution and fos expression in the dorsal horn and PBN was maximal in exercised CFA-treated rats compared to non-exercised CFA-treated animals, with the least fos expression in sham animals. These data suggest that forced walking induces changes in the spinal cord and weight bearing reflective of a pain state.

Disclosures: S. Locke: None. **M. Mannarino:** None. **N. Yousefpour:** None. **A. Ribeiro-da-Silva:** None.

Poster

220. Inflammatory Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 220.26/Y11

Topic: D.04. Somatosensation: Touch

Support: NIH Grant NS040538 to CLS

NIH Grant NS070711 to CLS

NIH Grant NS087716 to KJZ

Research and Education Component of the Advancing a Healthier Wisconsin Endowment at the Medical College of Wisconsin

KJZ is a member of the Medical Science Training Program at MCW which is partially supported by a training grant from NIGMS T32-GM080202

Title: Chemokine receptor 2 (CCR2) mediates mechanical and cold hypersensitivity in sickle cell disease pain

Authors: *K. SADLER[1], K. J. ZAPPIA[1], A. D. WEYER[1], C. O'HARA[1], C. A. HILLERY[2], C. L. STUCKY[1]
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Abstract: Sickle cell disease (SCD) is an inherited blood disorder that affects over 100,000 Americans, mainly those of African and Hispanic descent. During instances of stress, dehydration, and reduced oxygen saturation, SCD patients experience “sickling crises,” intense bouts of acute pain caused by hemoglobin polymerization, red blood cell adhesion, and subsequent vasculature occlusion. As the disease progresses, over 40% of SCD patients also develop persistent, sub-crisis level pain characterized by increased mechanical and/or cold sensitivity. This somatosensory dysregulation severely decreases quality of life and is the leading reason for hospitalization amongst SCD patients. Using a transgenic mouse model of severe SCD (Berk SS), we investigated the contributions of peripheral inflammatory mediators, specifically chemokine ligand 2 (CCL2), to the hypersensitivity associated with SCD.
Increased CCL2 was present in the serum of Berk SS mice suggesting that these animals are in a state of persistent inflammation. The main receptor through which CCL2 exerts activity is chemokine receptor 2 (CCR2); expression of CCR2 mRNA and protein were observed in dorsal root ganglia (DRG) of Berk SS mice. CCR2 involvement in SCD pain was functionally demonstrated by administering the CCR2 antagonist RS 504393 in Berk SS mice. Both the persistent baseline mechanical and cold hypersensitivity observed in these animals were

decreased following RS 504393 treatment. The percentage of cold-sensitive small DRG somata was greater in Berk SS than non-sickle mice, but acute application of RS 504393 did not decrease the number of cold-sensitive neurons in either genotype. These data suggest both a role for non-neuronal CCR2 in SCD cold behavior modulation and the involvement of additional cold-sensitive channels in SCD neuronal cold sensitivity.
Previously, other pro-inflammatory cytokines have been linked to pain modulation through connections with members of the TRP channel family. Because both RS 504393 and A-425619, a potent TRPV1 antagonist, decrease mechanical hypersensitivity in severe SCD mice, we hypothesized that CCR2 and TRPV1 may be working in concert to mediate persistent SCD sensitivity. To this end, we demonstrated that incubation with the CCR2 antagonist decreased the percentage of DRG neurons from SCD mice that were sensitive to capsaicin. Overall these data suggest that peripheral chemokine signaling is contributing to persistent SCD pain through both non-neuronal and TRPV1-dependent neuronal mechanisms.

Disclosures: K. Sadler: None. **K.J. Zappia:** None. **A.D. Weyer:** None. **C. O'Hara:** None. **C.A. Hillery:** None. **C.L. Stucky:** None.

Poster

220. Inflammatory Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 220.27/Y12

Topic: F.10. Food Intake and Energy Balance

Support: IBRO Return Home Fellowship

Title: Peripheral persistent inflammation increases c-fos expression in the basolateral amígdala in the rat

Authors: *J. C. MORALES-MEDINA[1], G. SERRANO-BELLO[2]
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Abstract: Persistent pain reduce the patient quality of life and produce a high social burden. The complete Freund's Adjuvant (CFA) is a model of peripheral inflammation that induce mechanical allodynia and numerous known abnormal physiological processes in the spinal cord however little is known about the supraspinal processes affected. Moreover, c-Fos, a marker of cellular activation, is useful to evaluate how a paradigm increases the activity of cells in a given brain loci. In the present study, we aimed to test the hypothesis that CFA administration will increase c-Fos expression in brain regions involved in the control of pain [anterior cingulate cortex (ACC), basolateral amygdala (BLA), central amygdala (CeA) and rostroventral medulla (RVM)] in the rat. Administration of 50 µL of CFA in the hindpaw induced edema at the third

day post-administration however not all the rats presented mechanical allodynia. Therefore we have three experimental groups: control (treated with saline, C), CFA with allodinia (CFA-A) and CFA without allodinia (CFA-WA). We observed an increase in the expression of c-Fos in the BLA and RVM selectively in the CFA-A group. Thus, these results showed that the BLA and RVM are involved in CFA-induced allodynia in the rat.

Disclosures: J.C. Morales-Medina: None. **G. Serrano-Bello:** None.

Poster

221. Mechanisms of Diabetic Neuropathic Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 221.01/Y13

Topic: D.03. Somatosensation: Pain

Title: The mechanism of pregabalin on pain in streptozotocin-induced diabetic neuropathy model rats

Authors: *Y. SAKURAI, R. TAMANO, M. MATSUO, T. KANOU, K. MINAMI, M. HASEGAWA, T. ASAKI
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Abstract: Pregabalin (PGN) has been widely used as the 1st line drug for neuropathic pain including diabetic painful neuropathy (DNP), however some population of DNP patients often exhibits refractory pain against PGN, which may be due to the heterogeneous pathology various pain mechanisms involve. Streptozotocin (STZ) induced neuropathic pain model is most commonly used as a DNP animal model. Although PGN works on pain of the STZ model 2 weeks after injection (STZ-2w) in many reports, the mechanism of PGN on pain in the DNP has been still under discussion. It was reported that PGN reduced the glutamate release in the spinal cord via blocking Ca^{2+} influx in the sensory neurons, but also activated the descending NA neurons via inhibiting GABA release in the locus coeruleus (LC).
We investigated the mechanism of PGN on pain in the STZ-2w model and partial sciatic nerve ligation (pSNL) model, another neuropathic pain model, focusing on the sensory neuron and the descending NA neuron. Intrathecal (i.t.) injection of PGN reduced the mechanical allodynia by von Frey filaments and mRNA level of α2δ1 subunit, target of PGN, in the dorsal root ganglion was upregulated in the pSNL model but not in the STZ-2w model.
In the STZ-2w model, the intracerebroventricular injection of PGN reduced the mechanical allodynia. The anti-allodynia effect of oral administration of PGN was completely cancelled by the i.t. injection of yohimbine (antagonist against α2 receptor) which could suppress the inhibitory action of NA in the secondary neuron of the spinal cord in the STZ-2w model, but less in the pSNL model. In addition, the number of p-CREB positive cells in the LC, an indicator of NA neuron activation, was reduced in the STZ-2w model, but less in the pSNL model. The oral

administration of PGN increased the number of p-CREB positive cells in both models. These results suggested PGN mainly works on the sensory neuron to exibit the analgesia in the pSNL model, but on the descending NA neuron in the STZ-2w model. The mechanism of PGN may be different depending on the types of neuropathic pain. Moreover, we found the oral administration of PGN did not reduce the mechanical allodynia in STZ model 8 weeks after injection (STZ-8w). The STZ-8w model may exhibit refractory pain against PGN in DNP patients. The impairment of descending NA neuron may be involved in the PGN refractory pain in the DNP.

Disclosures: **Y. Sakurai:** None. **R. Tamano:** None. **M. Matsuo:** None. **T. Kanou:** None. **K. Minami:** None. **M. Hasegawa:** None. **T. Asaki:** None.

Poster

221. Mechanisms of Diabetic Neuropathic Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 221.02/Y14

Topic: D.03. Somatosensation: Pain

Support: Grant NASU (# II - 1- 12) to PVB and NV

Grant NASU (#67/15-H) to PVB

NASU Biotechnology to NV

Title: Diabetes-induced amplification of action potential output of nociceptive DRG neurons by upregulation of somatic T-type Ca^{2+} current

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Abstract: Development of pain symptoms of peripheral diabetic neuropathy (PDN) is associated with upregulation of T-type Ca^{2+} channels in soma of nociceptive DRG neurons. Moreover, a pharmacological or genetic block of these channels in DRG neurons effectively reversed mechanical and thermal hyperalgesia in animal diabetic models indicating that T-channel functioning is causally linked to PDN maintenance. In spite of clear importance of these channels in development and maintenance of PDN no particular mechanisms relating upregulation of T-channels in soma of nociceptive DRG neurons to the pathological pain processing in PDN have been suggested that prevents development of targeted therapies against PDN devoid of side effects. Here we have electrophysiologically identified voltage-gated currents expressed in a narrow class of small DRG neurons, which may contribute to non-thermal nociception at later-stage diabetes, and used it to develop a comprehensive computation

model of these neurons including peripheral and central processes. A reduced somatic part of this model fairly reproduced patterns of activity observed in these DRG neurons in electrophysiological recordings. In this model, under normal conditions, an action potential (AP) evoked in a receptor-zone propagates via the peripheral process, invades the soma and further propagates along the central process. Increasing density of somatic T-type current to a level, observed in these neurons under diabetic conditions, transforms a single AP invading the soma into a burst of multiple APs conducted in the central axon; thus far the peripheral nociceptive input is strongly amplified. This amplification may partially or completely account for mechanical hyperalgesia observed in diabetic rats, in which T-channels are upregulated in the class of nociceptors under study. By further increase of the current density in the soma, the model alternates between single AP-induced and spontaneous bursting that might be a mechanism of spontaneous pain also observed at later stage diabetes. The model also demonstrates somatic amplification of peripheral input in case of shift of steady-state inactivation of T-type current revealed at early stage of STZ-diabetes in small capsaicin-sensitive and medium-sized DRG neurons, suggesting a mechanism for thermal hyperalgesia and tactile allodynia. Altogether, the somatic T-channel-dependent amplification demonstrated in this work may strongly contribute to an enhancement of the primary nociceptive input to spinal dorsal horn neurons underlying abnormal nociception at different stages of diabetes development.

Disclosures: P.V. Belan: None. **M. Matveenko:** None. **N.I. Kononenko:** None. **D. Duzhyy:** None. **N. Voitenko:** None. **S.M. Korogod:** None.

Poster

221. Mechanisms of Diabetic Neuropathic Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 221.03/Y15

Topic: D.03. Somatosensation: Pain

Support: KAKENHI 17K09048

Title: AMPK-regulated neuronal TRPA1 plasma membrane expression in painful diabetic neuropathy

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Abstract: AMP activated protein kinase (AMPK) is a widely expressed intracellular energy sensor that monitors and modulates energy expenditure. Transient receptor potential ankyrin 1 (TRPA1) channel is a widely recognized chemical and thermal sensor that plays vital roles in pain transduction. Here, we discovered a functional link between AMPK and TRPA1 in dorsal root ganglion (DRG) neurons, in which AMPK activation rapidly resulted in downregulation of TRPA1 membrane expression and channel activity within minutes. Treatment with two AMPK activators, metformin or AICAR inhibited TRPA1 activity in DRG neurons by decreasing TRPA1 membrane expression. Metformin showed a dose-dependent inhibition in TRPA1-mediated calcium influx. Conversely, in diabetic db/db mice, AMPK activity was impaired in DRG neurons and this was associated with a concomitant increase in TRPA1 membrane expression and mechanical allodynia. Notably, these molecular and behavioral changes were normalized following treatment with AMPK activators. Moreover, high-glucose exposure decreased activated AMPK levels and increased agonist-evoked TRPA1 currents in cultured DRG neurons, which were prevented upon treatment with AMPK activators. Our results identify AMPK as a previously unknown regulator of TRPA1 channels, and indicate that AMPK modulation of TRPA1 expression could serve as an underlying mechanism of and potential therapeutic molecular target in painful diabetic neuropathy.

Disclosures: S. Wang: None. **K. Kobayashi:** None. **Y. Kogure:** None. **H. Yamanaka:** None. **S. Yamamoto:** None. **H. Yagi:** None. **K. Noguchi:** None. **Y. Dai:** None.

Poster

221. Mechanisms of Diabetic Neuropathic Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 221.04/Y16

Topic: D.03. Somatosensation: Pain

Support: LSU HSC

MD Anderson Cancer Center

Wings for Life

Title: Expression of agrin isoforms in diabetic neuropathic rats

Authors: *J. CUI[1], D. ERASSO[2], G. TENDER[3], G. CHEN[1], F. CULICCHIA[3], S. ABDI[1]
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Abstract: Our previous research revealed that agrin, a heparan sulfate con proteoglycan, plays an important role in regulating neuropathic pain. Agrin gene can be spliced variably at the X, Y,

and Z site, therefore, it can form more than 20 variants with different nucleotide inserts in the X, Y, and Z site. However, it is not clear which agrin isoform plays a role in neuropathic pain. In this project, we used streptozotocin-induced diabetic neuropathic pain rat model and agrin probes that target different inserts to investigate which agrin isoform participated in diabetic neuropathic pain.
STZ was dissolved in 0.05 M citrate buffer at 20 mg/ml. A single STZ intraperitoneal injection of 55 mg/Kg was performed. On the following day, glucose in blood was checked with a glucose meter ACCU-CHEK (Roche, Mannheim, Germany). After STZ IP injection, the rats developed NP within 7-21 days. Dorsal root ganglia were dissected out from allodynic, non-allodynic, and control rats, then the DRG were sectioned and detected with the probes and fluorescence in situ hybridization. Our results suggested that agrin gene (mRNA) with inserts of 0, 12, and 24 nucleotides at the X, Y, and Z site was significantly decreased in the DRG of diabetic neuropathic pain rats, while the gene was not changed in the DRG of diabetic non-neuropathic pain rats. The agrin mRNA (0, 12, 24) decrease was distributed in small, medium, and large size neurons, indicating these neurons in the DRG participated in diabetic neuropathic pain development. The experiments are still going on.

Disclosures: **J. Cui:** None. **D. Erasso:** None. **G. Tender:** None. **G. Chen:** None. **F. Culicchia:** None. **S. Abdi:** None.

Poster

221. Mechanisms of Diabetic Neuropathic Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 221.05/Y17

Topic: D.03. Somatosensation: Pain

Support: CNPq #423977/ 2016-4

CAPES

Title: Evaluation of the potential antinociceptive effect of cannabidiol on neuropathic pain associated with experimental diabetes

Authors: *J. M. CUNHA[1], C. H. A. JESUS[1], D. D. B. REDIVO[1], A. T. GASPARIN[1], K. D. S. GENARO[2], J. A. S. CRIPPA[2], J. M. ZANOVELI[1]
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Abstract: Diabetic neuropathy (DN) affects around 60% of diabetic patients and its most common subtype is the distal symmetrical polyneuropathy. Due to its multifactorial pathogenesis, the pharmacological treatment of DN pain (DNP) includes drugs from different

classes and studies indicate that only a small portion of patients obtains pain relief after these therapeutic approaches. In this sense, the cannabinoids, compounds extracted from *Cannabis sativa*, have shown promising effects in different pathological conditions. Cannabidiol (CBD), the most studied non-psychoactive cannabinoid, seems to affect several targets involved with painful conditions such as DN. Considering the foregoing, this study seeks to investigate the potential antinociceptive effect of CBD in mechanical allodynia in rats with diabetes chemically induced by streptozotocin (STZ). For this, male Wistar rats (180-220 g, n=8-10) were treated intraperitoneally (i.p.) with citrate buffer (10 mM, pH 4.5, vehicle group) or STZ (60mg/kg, DBT- diabetic group). Mechanical threshold was recorded using an electronic Von Frey, prior to administration of STZ (baseline) and 28 days after diabetes induction. To evaluate the acute effect of CBD on mechanical allodynia, DBT animals had their mechanical threshold evaluated 28 days after diabetes induction (before the vehicle or CBD treatment), and hourly (during 4 hours) after treatment i.p. with CBD (0, 0.3, 3 or 30 mg/Kg). To evaluate the sub chronic effect of CBD, DBT animals remained untreated until the 14^{th} day after STZ and then received daily treatment with CBD (0.3 or 3 mg/Kg) for 14 days. Mechanical threshold was reevaluated 21 and 28 days after diabetes induction. To verify the role of CB1 or CB2 cannabinoid receptors in the antinociceptive effect of CBD, rats received i.p. treatment with vehicle, AM251 (1 mg/Kg, CB_1 receptor antagonist) or AM630 (1 mg/Kg, CB_2 antagonist) prior to the CBD injection (3 mg/Kg). It was observed that CBD (0.3 and 3, but not 30 mg/Kg) was able to significantly reverse mechanical allodynia 1 hour after treatment. Only the dose of 3 mg/Kg remained effective 2 hours after treatment. The pre-treatment with cannabinoid receptor antagonists AM251 or AM630 did not affect the antinociceptive effect of CBD (3 mg/Kg). CBD sub chronic treatment (0.3 and 3 mg/Kg) was able to reverse mechanical allodynia established 14 days after STZ injection and the effect was sustained for 2 weeks. Studies are being conducted to evaluate possible mechanisms involved with this anti-allodynic effect of CBD on DNP, which is sustained in a sub chronic treatment schedule, and when acutely, not directly mediated by CB_1 and CB_2 receptors.

Disclosures: **J.M. Cunha:** None. **C.H.A. Jesus:** None. **D.D.B. Redivo:** None. **A.T. Gasparin:** None. **K.D.S. Genaro:** None. **J.A.S. Crippa:** None. **J.M. Zanoveli:** None.

Poster

221. Mechanisms of Diabetic Neuropathic Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 221.06/Y18

Topic: D.03. Somatosensation: Pain

Support: NSERC

CIHR Bridge Fund

University Hospital Foundation

Edmonton Civic Employee Fund

Title: Nile rats as a novel model of protracted type-2 diabetes-induced peripheral sensory neuropathy

Authors: *J. SINGH[1], S. YOUSUF[2], P. SHELEMEY[3], T. JOY[3], H. MACANDILI[3], B. KERR[2], K. JONES[4], Y. SAUVÉ[5], K. BALLANYI[1], C. A. WEBBER[3]
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Abstract: A devastating complication of type-2 diabetes (T2D) is the development of distal peripheral sensory neuropathy which can present as numbness, mechanical allodynia, hyperalgesia, paresthesia or altered temperature sensitivity. These pathological phenotypes are likely due to Aδ- and C-fibers hyperexcitability, loss of intra-epidermal nerve fibers (IENFs) in the footpad. Current animal models have been useful in demonstrating several pathological features of T2D; however, genetic complexity, alteration of the biological system, and rapid T2D progression makes them difficult to select and mimic T2D pathogenesis at preclinical stages. The African Nile grass rat (NGR) is an excellent model for T2D because, like in humans, the onset is metabolic instead of experimental (Yang et al., 2016). Simply feeding male NGRs with a high calorie, low fiber diet (common laboratory rat chow) induces T2D whereas NGRs fed on a high fiber, low fat diet (Hfib) remain healthy. Thus we are establishing the NGR as a novel diet-induced T2D peripheral sensory neuropathy model. Similar to human patients, T2D NGRs have decreased IENFs, decreased nerve conduction velocity and altered sensation. Specifically, chronic T2D leads to hyposensitivity to both painful mechanical (von-Frey test) and heat stimulation (Hargreaves test) compared to controls. At the dorsal root ganglion (DRG), T2D NGRs have increased calcitonin gene-related peptide (CGRP) mRNA and protein levels in the DRG neuronal somas and activation of the surrounding satellite glial cells as demonstrated by increased glial fibrillary acidic protein (GFAP) expression. Furthermore, there was in increase in voltage-gated sodium channel variants Nav 1.7 and Nav 1.9 mRNA and protein levels in T2D NGRs. Single-fiber recordings from T2D NGRs saphenous skin-nerve preparation demonstrate that Aδ- and C-fibres have decreased electrical and mechanical excitation thresholds. These data suggest that, although the epidermis is denervated, dermal nerve terminals are still present and capable of conduction. Early intervention is critical if T2D neuropathy is to be treated. ***The NGR is the first animal model that allows for the study of T2D-induced peripheral sensory neuropathy progression. We will go on to investigate the prediabetic and early diabetic stages to determine when peripheral sensory neuropathy first presents itself.***

Disclosures: J. Singh: None. **S. Yousuf:** None. **P. Shelemey:** None. **T. Joy:** None. **H. Macandili:** None. **B. Kerr:** None. **K. Jones:** None. **Y. Sauvé:** None. **K. Ballanyi:** None. **C.A. Webber:** None.

Poster

221. Mechanisms of Diabetic Neuropathic Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 221.07/Z1

Topic: D.03. Somatosensation: Pain

Support: MOST 106-2321-B-002-017

Title: Visualize nociceptor changes in mice with diabetes neuropathy

Authors: H.-H. CHI, *R.-F. CHEN, C.-T. YEN
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Abstract: Diabetes neuropathy (DN) is one of the most common complications of diabetes mellitus. At least half of all diabetes patients develop some form of neuropathy during their lifetime. The present study used fluorescent imaging approaches to estimate the dynamic change of cutaneous nerve terminals in the peripheral sensory neuropathy in the DN mice model. The protein gene product 9.5 (PGP9.5) is an ubiquitin C-terminal hydrolase expressed in nerve fibers and neurons of both in peripheral and central nervous systems. In addition, PGP9.5 staining also plays as a gold standard measurement approach to investigate the cutaneous innervation which labeled all the myelinated and unmyelinated nerve terminals. Voltage-gated sodium channel 1.8 ($Na_v1.8$) is a subset of sensory neuron population highly expressed in the dorsal root ganglion, small-diameter fibers and involved in the nociceptive pathway. In this study, we use the $Na_v1.8$-cre::tdTomato mice to analysis the free nerve endings under the 3th and 5^{th} toe skin. Cutting the sample into 60 μm slices and co-staining with monoclonal PGP9.5 antibody, results showed that 70% of the $Na_v1.8$ positive terminals colocalized with the PGP9.5 positive terminals. In addition, we also investigate how the nerve terminal changes under the paw skin of the streptozotocin (STZ) induced diabetes model via in vivo two-photon microscopic method. These results indicate that $Na_v1.8$ terminal density may be a useful biomarker for DN.
Keywords: Neuropathic pain; Nociceptor; diabetes neuropathy; two-photon fluorescent microscopy
Supported by a grant from the Ministry of Science and Technology, Taiwan, MOST 106-2321-B-002-017

Disclosures: H. Chi: None. **R. Chen:** None. **C. Yen:** None.

Poster

221. Mechanisms of Diabetic Neuropathic Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 221.08/Z2

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Title: Macrophage migration inhibitory factor affects pain signal pathway in diabetic neuropathy

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Abstract: Diabetic neuropathy (DN) is algogenic complications of diabetes and many diabetes patients suffer from chronic neuropathic pain, overwhelmingly in the feet. A high prevalence of DN has also been observed in individuals with normal glucose tolerance and prediabetes. Recently, it has been suggested that macrophage migration inhibitory factor (MIF) is implicated in the onset of neuropathic pain as well as diabetes. The aim of our study was to determine the expression of MIF in footpad of DN rat, and to assess the contributory role of MIF on the locally hyperglycemic skin lesions by performing knockdown of the MIF gene in keratinocytes. We then investigated altered electrophysiological activity, and determined the expression of MIF in spinal cord of DN rat. DN was made in SD rats by streptozotocin (STZ). Pain threshold was evaluated using von Frey monofilaments. On the comparable experiment time after STZ injection, all the footpads and spinal cords were excised and prepared for following procedures; TUNEL staining, glutathione (GSH) assay, Western blot and immunofluorescence. Extracellular electrophysiological recording was performed on the spinal wide dynamic range (WDR) neurons in DN rats. Additionally, human keratinocytes were treated with methylglyoxal (MG), transfected with MIF/control siRNA, and prepared for qRT-PCR and Western blot. As compared to sham group, pain threshold was significantly reduced in DN group, and GSH was decreased on the footpad skin, simultaneously, cell death was increased. Over-expression of MIF, accompanied by low expression of GLO-I and intraepidermal nerve fibers (IENF), was shown on the footpad lesions of DN. Intriguingly, siRNA-transfected knockdown of the MIF gene in MG-treated keratinocytes increased expression of GLO-I and IENF in comparison with control siRNA-transfected cells, which was decreased by induction of MG. In the DN group, press- and pinch evoked neuronal excitabilities were significantly increased in spinal WDR neurons, and spontaneous activity was increased in the 12^{th} week after STZ treatment. Although stimulations were removed, afterdischarges were also definitely increased. Especially, MIF production was markedly increased in the spinal neurons of DN that we recorded. Likewise, microglia marker Iba-1 was strongly expressed, showing immunofluorescent colocalization with MIF. On the other hand, neurofilaments were reduced in spinal cords of DN. This is to demonstrate MIF expression

on the footpad lesions with diabetes and its potential role in the correlation with GLO-I and IENF, and to implicate MIF acting on microglia and neurons as exacerbator of pain in DN.

Disclosures: S. Noh: None. **Y. Lee:** None.

Poster

221. Mechanisms of Diabetic Neuropathic Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 221.09/Z3

Topic: D.03. Somatosensation: Pain

Support: NSFC-81671086

Title: Spinal matrix metalloproteinase-9 contributes to diabetic neuropathic pain in rodents

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Abstract: Chronic pain accompanied with diabetic neuropathy is a typical form of neuropathic pain in certain patients with diabetes. Preventing and reversing diabetic neuropathic pain (DNP) continues to be a clinical challenge and underlying mechanisms of DNP remain elusive. Studies have shown that matrix metalloproteinase-9/2 (MMP-9/2) play important roles in neuropathic pain after nerve injury and pain enhancement after morphine withdrawal. We hypothesized that DNP might share the similar neural mechanisms with other forms of neuropathic pain, thus MMP-9/2 might play a role in DNP. Here, we report that MMP-9, but not MMP-2, in the spinal cord contributes to maintenance of DNP in rodents. Activity of MMP-9 significantly increased in the spinal cord and the dorsal root ganglion (DRG) in STZ-induced DNP rats. Spinal inhibition of MMP-9 inhibited the established, but failed to prevent the induction of mechanical allodynia and the associated neurochemical alterations in DNP rats. Targeted mutation of MMP-9 in mice suppressed diabetic neuropathy following STZ treatment in mice. Systematic administration of α-lipoic acid suppressed STZ-induced MMP-9 activity in the spinal cord and DRG and attenuated mechanical allodynia. In contrast, inhibition of spinal MMP-2, the other gelatinase, did not attenuate mechanical allodynia in DNP rats. This study reveals that activation of MMP-9, but not MMP-2, is critical to the persistence, but not production of DNP and suggests that MMP-9 may be a potential therapeutic target for relieving DNP.

Disclosures: X. Deng: None. **P. Ma:** None. **M. Wu:** None. **L. Cheng:** None. **X. Song:** None.

Poster

221. Mechanisms of Diabetic Neuropathic Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 221.10/Z4

Topic: D.03. Somatosensation: Pain

Title: GDNF differentially regulates neuronal excitability in DRGs from normal and diabetic mice

Authors: *E. CIGLIERI, F. FERRINI, C. SALIO
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Abstract: Diabetic polyneuropathy (DPN) is among the most common long-term complications of diabetes mellitus, affecting up to 50% of diabetic patients of which 15-25% have chronic neuropathic pain. Although this painful signal has believed to originate in the peripheral nervous system, the precise cellular mechanism of chronic pain associated with DPN is still poorly understood. Evidence has accumulated that abnormal excitability of nociceptive primary sensory neurons in dorsal root ganglia (DRGs) contributes to the pathology. Neurotrophic factors, such as glial-derived neurotrophic factor (GDNF), are key regulators of sensory neurons excitability and their altered levels has been associated to pathological conditions.
Here, we investigated the effect of GDNF in controlling sensory neuron activity in normal and diabetic mice. To mimic type 1 diabetes, four week-old male mice were injected intraperitoneally with streptozotocin (STZ, 150 mg/kg) that selectively kills insulin-producing pancreatic β-cells. DRGs were acutely excised and treated with collagenase (7 mg/mL, 1 hour at 35°C). Whole-cell patch clamp recordings were obtained from visually identified neurons within intact DRGs before and after the administration of GDNF (100 ng/mL).
In current clamp, GDNF induced a depolarizing shift of the firing threshold (from -24 to -18 mV) and delayed the firing onset (from 14 to 66 ms) in control conditions, particularly in small neurons (< 25 μm). Conversely, in diabetic mice GDNF was less effective. Since these findings are consistent with the involvement of voltage-dependent K^+ channels, we next verified this hypothesis in voltage clamp after minimizing Na^+- and Ca^{2+}-mediated currents. By applying a hyperpolarizing step protocol, GDNF induced a significant increase of inward K^+ conductance, causing a change in the slope of the current-voltage relationship. These effects were mostly evoked in small neurons from control mice, while little effect was observed in diabetic conditions. Our data indicate that GDNF exerts an inhibitory control on small DRG neurons through the activation of K^+ conductances and that such control is attenuated in diabetes. Restoring this inhibitory control in sensory neurons from diabetic patients may represent a novel strategies for mitigating the symptoms of painful diabetic neuropathy.

Disclosures: **E. Ciglieri:** None. **F. Ferrini:** None. **C. Salio:** None.

Poster

221. Mechanisms of Diabetic Neuropathic Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 221.11/Z5

Topic: F.10. Food Intake and Energy Balance

Title: Elucidation of various inflammatory pathways in experimental paradigms of streptozotocin induced diabetic neuropathy

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Abstract: Diabetic neuropathy affects more than 50 percent of diabetic patients. Rutin has been demonstrated in number of pharmacological activities including anti-diabetic, anti-oxidant and anti-inflammatory activities. Streptozotocin (STZ, 55 mg/kg) was administered intraperitoneally (i.p.) to overnight fasted rats. Naive and diabetic rats were randomly selected and divided into eight groups of six animals in each group. Rutin (100 and 200 mg/kg,i.p.) and Nimesulide (5 and 10 mg/kg, i.p.). All the behavioural parameters (Measurement of body weight, Mechanical allodynia, Cold allodynia, Mechanical hyperalgesia, Thermal hyperalgesia) were performed on day 0 , 2^{nd} , 4^{th}, $6^{th}$and 8^{th} week. On last day (of 8th week), blood was collected retro-orbitally and mean nerve conduction velocity was assessed. The animals were then sacrificed sciatic nerves were isolated for further biochemical estimations, TNF-alpha and caspase-3 activity estimated by ELISA. Rutin(100 and 200 mg/kg) for 8 weeks significantly protected all the behavioral alterations, oxidative damage and change in mean nerve conduction velocity induced by STZ. Further, combination of Rutin (100 and 200 mg/kg) with Nimesulide (10 mg/kg) significantly reversed all the behavioural, biochemical and changes in nerve conduction velocity as compared to their effect per se in STZ-induced diabetic neuropathy. The present study suggests the protective effect of *Rutin* against STZ-induces diabetic neuropathy. Study further provides an evidence that rutin produces better effect in combination with nimesulide against STZ-induces diabetic neuropathy.

Disclosures: R. Mittal: None. **A. Kumar:** None.

Poster

221. Mechanisms of Diabetic Neuropathic Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 221.12/Z6

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH K08 NS079482

Title: DREADD mediated reversal of small fiber degeneration and neuropathic pain in a mouse model of painful diabetic neuropathy

Authors: *S. HACKELBERG, N. D. JAYARAJ, B. J. BHATTACHARYYA, A. A. BELMADANI, D. REN, C. A. RATHWELL, R. J. MILLER, D. M. MENICHELLA
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Abstract: Neuropathic pain is a devastating complication affecting about 25 % of diabetes patients. It is characterized by hyperactivity of nociceptors in the dorsal root ganglia, leading to the activation of pain pathways in the absence of appropriate stimuli. Neuronal damage is further evidenced by distal small fiber degeneration. Despite the high prevalence of diabetic neuropathy and the accompanying impairment of patient quality of life, there is little knowledge on the mechanisms of neuronal damage and disease progression. As a consequence, treatment is ineffective and limited to symptom mitigation. Pain management frequently involves the use opioids, but these are both ineffective and problematic in long term use.Nociceptor hyperexcitability is thought not only to be a consequence of damage leading to pain symptoms, but also a pivotal part of the insult leading to progression of neuronal degeneration. Thus, the prevention and mitigation of nociceptor hyperexcitability is central both to the prevention of disease progression and symptom management. Previously, we have shown that *d*esigner *r*eceptors *e*xclusively activated by designer drugs (DREADD) inhibit DRG neurons in vitro and prevented mechanical allodynia in in the high fat diet mouse model of type II diabetes.For targeting of nociceptors, transgenic mice for the inhibitory hM4 DREADD and the excitatory hM3 DREADD were crossed with $Na_v1.8$-tdTomato-Cre mice. The population of $Na_v1.8$ DRG consists of C-nociceptors (>90%), as well as low-threshold C-mechanoreceptors and a lower percentage of Aδ nociceptors and Aβ afferents. Here, we show electrophysiological recordings *in vitro* confirming the bidirectional modulation of Na_v.1.8-tdTomato DRG neurons by activation of inhibitory and excitatory DREADD. Moreover, activation of inhibitory DREADD receptors *in vivo* reversed small fiber degeneration and mechanical allodynia after onset of fiber degeneration. In contrast, *in vivo* activation of excitatory DREADD accelerated the onset of small fiber degeneration. This study reveals for the first time a critical role of Nav 1.8 nociceptors hyper-excitability in the pathogenesis of neuropathic pain and small fiber neuropathy in diabetes. Furthermore, these observations will add to our understanding of how changes in nociceptors excitability contribute to the progression of small fiber neuropathy in PDN, which is a critical barrier to progression for effective and disease modifying treatment of this currently intractable and widespread affliction.

Disclosures: S. Hackelberg: None. **N.D. Jayaraj:** None. **B.J. Bhattacharyya:** None. **A.A. Belmadani:** None. **D. Ren:** None. **C.A. Rathwell:** None. **R.J. Miller:** None. **D.M. Menichella:** None.

Poster

222. Cancer Pain and Chemotherapy-Evoked Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 222.01/Z7

Topic: D.03. Somatosensation: Pain

Support: The CH Foundation Grant 241865

the CPRIT Foundation Grant RR14008

The NCI Grant CA155223

TTUHSC School of Medicine Grant 121035

Title: Cannabinoid agonists (cp55,940, acea and am1241) following chronic administration cause changes in the estrus cycle in an optimized chemotherapy-induced neuropathic pain model

Authors: K. DONCKELS[1], H. BLANTON[2], D. MEDINA[1], J. LILLEY[2], I. CASTRO[2], K. PRUITT[2], *J. GUINDON[3]
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Abstract: Cannabis-like compounds have demonstrated antinociceptive properties in various chronic pain models. Synthetic cannabinoid such as CB1 (ACEA), CB2 (AM1241) and CB1/CB2 (CP55,940) agonists can modulate chronic pain perception. Indeed, they have previously been shown to alleviate chemotherapy-induced neuropathic pain. However, the impact of chronic administration of these compounds on the estrus cycle needs to be investigated. The goal of this study is to evaluate the role of these different (ACEA, AM1241 and CP55,940) cannabinoid agonists on the estrus cycle following chronic administration in a chemotherapy-induced neuropathic pain model in C57BL/6J mice. This study is evaluating the effects on the estrus cycle following chronic systemic administration of these different cannabinoid agonists (ACEA, CP55,940 and AM1241) in an optimized chemotherapy-induced neuropathic pain (cisplatin 5 mg/kg intraperitoneal and 4 % sodium bicarbonate subcutaneously weekly) mouse model. We tested the estrus cycle by daily vaginal lavage prior to daily injection with the different synthetic cannabinoids. Further staining of the slides with crystal violet and identification of the estrus cycle under the microscope following cell type identification enable the identification of the stage of the estrus cycle (proestrus, estrus, metestrus and diestrus). Our results suggest a compound-specific effect, which may be influenced by hormonal changes and could be mediated by receptor selectivity. The nonselective CB1/2 agonist CP55,940 shifts the cycle towards metestrus - the infertile stage of the cycle. The CB2 selective agonist AM1241 shifts the cycle towards the fertile, estrous stage of the cycle. The CB1 selective agonist ACEA is

also changing the estrus cycle. Further studies investigating the mechanism behind these compound- or receptor-specific influences on cycle progression is needed to fully appreciate the impact of these behavioral and pharmacokinetic differences on hormonal responses and potential influence on pain perception. A better understanding of the cannabinoid-specific mechanisms responsible for changes in the estrus cycle and possible hormonal role in pain perception are mandatory to advance the development of long lasting, highly efficacious, and personalized pain therapies.

Disclosures: K. Donckels: None. **H. Blanton:** None. **D. Medina:** None. **J. Lilley:** None. **I. Castro:** None. **K. Pruitt:** None. **J. Guindon:** None.

Poster

222. Cancer Pain and Chemotherapy-Evoked Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 222.02/Z8

Topic: D.03. Somatosensation: Pain

Support: IASP EC 2013

CNPq 459410/2014-8

CAPES

FAPDF 1930006682015

Title: Cisplatin modulates PPARγ and TNFα gene expression in a Chemotherapy Induced Peripheral Neuropathy model *In vitro*

Authors: *H. R. DE OLIVEIRA, C. L. LIMA, M. S. COÊLHO, D. B. DUARTE
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Abstract: One of the most common side effects induced by antineoplastic drugs such as cisplatin, vincristine, paclitaxel, bortezomib and thalidomide is neurotoxicity. When peripheral nervous system is affected, toxicity is named Chemotherapy Induced Peripheral Neuropathy (CIPN). CIPN is characterized as dysfunction on peripheral sensory neurons and manifested as sensory loss, paresthesia, dysesthaesia, numbness, tingling and neuropathic pain. Also, chemotherapeutic agents induce inflammatory changes in Dorsal Root Ganglia (DRG), such as microglia activation and release of proinflammatory cytokines. Currently, many strategies to prevent or revert CIPN are under development, including neuroprotection. One of these possibilities could be the Peroxisome Proliferator-Activated Receptor γ (PPARγ) activation, which was already demonstrated to be neuroprotective in inflammatory neurodegenerative diseases, such as Alzheimer's disease. To investigate the PPARγ role in cisplatin-induced

peripheral neuropathy, we first characterized the PPARγ and Tumor Necrosis Factor α (TNFα) mRNA expression in an *in vitro* CIPN model. Thus, adult naïve Wistar rats weighting 250 – 350 g were used to isolate DRG cells. We harvested DRGs and after dissociation the cells were maintained in HAM F12 media with nerve growth factor (250 µg/mL) for 9 days in 12-well plates. On day 8, cells were treated with cisplatin (3, 10 or 30 µM) for 24 hours. To evaluate gene expression, the mRNA was extracted with trizol and quantified in triplicate by RT-qPCR. The mRNA expression level was normalized to expression of β-actin mRNA. 3 µM Cisplatin treatment did not produce mRNA expression change , while 10 µM did not alter TNFα expression, but increase 1.3-fold PPARγ mRNA expression ($p < 0.05$). However, the highest cisplatin concentration used (30 µM) increased 2.5-fold TNFα ($p < 0.05$) and reduced to 0.72-fold PPARγ mRNA expression ($p < 0.05$) compared to control. Here we presented that cisplatin treatment modulates TNFα and PPARγ mRNA expression. Once cisplatin 10 µM increased PPARγ expression and did not alter TNFα expression, PPARγ activation in the beginning of chemotherapeutic treatment could ameliorate CIPN symptoms. When 30 µM of cisplatin was used, TNFα expression increased substantially. Also, the number of cells were decreased. One possible explanation is that 30 µM of cisplatin already induced severe changes in the DRG cell culture and augmented inflammation. We will next evaluate whether PPARγ activation could affect the changes observed with the cisplatin treatment.

Disclosures: H.R. De Oliveira: None. **C.L. Lima:** None. **M.S. Coêlho:** None. **D.B. Duarte:** None.

Poster

222. Cancer Pain and Chemotherapy-Evoked Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 222.03/Z9

Topic: D.03. Somatosensation: Pain

Title: Comparisons of anti-cancer platinum compounds in chemotherapy-induced peripheral neuropathy

Authors: *P. J. SHORTLAND[1], E. GEBREMEDHN[2], J. ALDRICH-WRIGHT[1], D. A. MAHNS[2]
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Abstract: Platinum based compounds such as cisplatin and oxaliplatin are first line drugs used in chemotherapy for cancer patients. However, around a third of patients suffer from chemotherapy-induced peripheral neuropathy, an effect which is dose dependent, interferes with the treatment schedule and often results in treatment termination. Peripheral neuropathic pain, especially cold and tactile hypersensitivity is particularly associated with oxaliplatin treatment

that is evident after the first treatment and gets progressively worse with repeated treatment. The mechanisms underlying these chronic pains remain poorly understood. Unconventional platinum IV anticancer compounds such as 56MESS ([(5,6-dimethyl-1,10 phenanthroline)(1*S*,2*S*-diaminocyclohexane)-platinum(II)] dichloride), have also showed efficacy in cancer cell lines with increased cytotoxic potency at lower dose levels compared to clinically available anti-cancer drugs. However, whether or not this compound produces neuropathic pain-like symptoms *in vivo* has not been investigated. This study compared the effects of a single intraperitoneal injection of oxaliplatin (2.5 mg/kg) versus 56MESS (2.5 mg/Kg or at an IC_{50} concentration of 0.25 mg/Kg) on withdrawal reflexes to mechanical, heat or cold stimuli applied to the lower limb of adult rats. Injections of 2.5 mg/Kg oxaliplatin or 56MESS induced mechanical hypersensitivity that was evident by 3 days, peaked by 6 days and remained unchanged at 12 days post injection. Likewise, animals began to show cold hypersensitivity within 1 day of injection that further progressed over time. Responses to heat stimuli also lowered within 3 days are remained at these levels for the next 9 days. However, treatment with 0.25 mg/kg of 56MESS, a dose which has tumour suppressing activity *in vitro*, did not produce any cold or tactile hypersensitivity. These results suggest that 56MESS may offer potential as an anticancer treatment by improving patient compliance.

Disclosures: P.J. Shortland: None. **E. Gebremedhn:** None. **J. Aldrich-Wright:** None. **D.A. Mahns:** None.

Poster

222. Cancer Pain and Chemotherapy-Evoked Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 222.04/Z10

Topic: D.03. Somatosensation: Pain

Support: The Peggy and Avinash Ahuja Foundation and the Helen Buchanan and Stanley Joseph Seeger Endowment at The University of Texas MD Anderson Cancer Center

Title: Losartan alleviates mechanical hyperalgesia in a rat model of chemotherapy-induced peripheral neuropathy

Authors: *E. KIM[1,2], H. KIM[3], S.-H. H. KIM[3], S. ABDI[3], H.-K. KIM[2]
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Abstract: Chemotherapy-induced peripheral neuropathy (CIPN) is one of important problems in cancer patients and survivors due to adverse impact on quality of life. Present, CIPN is a medically challenge to treat with existing pain drugs used for neuropathic pain, Angiotensin II

has roles in the hypertension and regulation of sensory signaling. The objective of this study is to investigate analgesic effect of losartan, an angiotensin II receptor antagonist, on paclitaxel-induced neuropathic pain (PINP) in rats. PINP rat model was produced by intraperitoneal injections of paclitaxel at a dose of 2mg/kg on days 0, 2, 4 and 6. After fully developed pain, the single dose of losartan was intraperitoneally injected on day 21 after the first paclitaxel injection. In addition, multiple doses of losartan were intraperitoneally injected during days 21-25 for 5 days. Mechanical threshold was measured by using a set of Von Frey filaments. The single and multiple systemic injections of losartan significantly increased the mechanical threshold without adverse effects. We concluded that losartan ameliorated PINP in rats and may became available for new option or add-on therapy for CIPN patients.

Disclosures: E. Kim: None. **H. Kim:** None. **S.H. Kim:** None. **S. Abdi:** None. **H. Kim:** None.

Poster

222. Cancer Pain and Chemotherapy-Evoked Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 222.05/Z11

Topic: D.03. Somatosensation: Pain

Support: R01-CA206028

Title: The α7 nicotinic acetylcholine receptors (nAChRs) regulate the development and maintenance of chemotherapy induced peripheral neuropathy (CIPN) induced by paclitaxel in a mouse model

Authors: *W. TOMA[1], *W. TOMA[1], ***W. TOMA**[1], S. L. KYTE[1], D. BAGDAS[1], J. MEADE[1], G. THAKUR[3], J. BIGBEE[2], D. GEWIRTZ[1], M. I. DAMAJ[1]
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Abstract: One of the major dose-limiting side effects of several anticancer drugs is Chemotherapy-Induce Peripheral Neuropathy (CIPN). While paclitaxel is highly efficacious in the treatment of breast, ovarian, neck, and lung cancer, it can induce CIPN symptoms. The intensity of CIPN symptoms varies among patients, with symptoms including mechanical and cold allodynia, numbness, tingling, and painful burning sensations. These symptoms are so severe that in some cases cancer patients discontinue the use of chemotherapy drugs. Currently, there are no effective treatments to alleviate these symptoms; therefore, there is a dire need to develop a treatment for CIPN. The homomeric α7 nicotinic acetylcholine receptors (nAChRs) subtype belongs to the family of nAChRs. The α7 nAChRs are distributed throughout the pain transmission pathway: centrally (on neuronal cells) and peripherally (on neuronal and non-neuronal cells, such as macrophages). The objective of the present study was to characterize the

regulatory role of α7 nAChRs in the initiation and maintenance of CIPN in α7 Wild Type (WT) and Knockout (KO) mice and to test if R-47, a Selective Silent Agonist of α7 nAChRs would reverse and prevent CIPN induced by paclitaxel. Male and female α7 WT and KO mice were intraperitoneally injected with paclitaxel 1 mg/kg every other day for a total of four injections. For the pharmacological intervention studies, R-47 was acutely administered orally at doses of 1, 5, and 10 mg/kg in the reversal of CIPN, and chronically administered at a dose of 10 mg/kg orally twice daily for the prevention of CIPN. Male C57 BL/6J mice were intraperitoneally injected with paclitaxel 8 mg/kg under the same regimen as previously described. The Von Frey test was used to measure the nociceptive (mechanical threshold) behavior. Results show that α7 KO mice exhibit significant worsening of mechanical threshold (initiation and maintenance) compared to α7 WT mice, which show a transient reduction in the mechanical threshold. In addition, R-47 acutely reverses the mechanical threshold in a dose-dependent manner and chronically prevents the development of CIPN with no signs of tolerance. RT-PCR analysis revealed that α7 nAChRs are significantly upregulated in the Dorsal Root Ganglia (DRG) in WT mice treated with paclitaxel 8 mg/kg regimen. In conclusion, our data suggest that α7 nAChRs play a significant role in the development and recovery of paclitaxel-induced nociceptive behavior in mice. Additionally, the selectivity of R-47 for α7 nAChRs renders it a potential therapy to mitigate and/or prevent CIPN.

Disclosures: **W. Toma:** None. **S.L. Kyte:** None. **D. Bagdas:** None. **J. Meade:** None. **G. Thakur:** None. **J. Bigbee:** None. **D. Gewirtz:** None. **M.I. Damaj:** None.

Poster

222. Cancer Pain and Chemotherapy-Evoked Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 222.06/Z12

Topic: D.03. Somatosensation: Pain

Support: Grants-in-Aid for Scientific Research (KAKENHI) from the Japanese Society 26293019, 25670285 and 26893118

The Research Foundation for Pharmaceutical Sciences

Suzuken Memorial Foundation

The Nakatomi Foundation

Smoking Research Foundation

Title: Direct impairment of Schwann cells by taxanes and platinum derivatives is associated with etiologic mechanisms underlying chemotherapy-induced peripheral neuropathy

Authors: *M. KOYANAGI, S. IMAI, Y. NAKAZATO, M. MATSUMOTO, T. OGIHARA, T. NAKAGAWA, K. MATSUBARA
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Abstract: The direct impairment of peripheral sensory neurons by anti-cancer agents, including taxanes and platinum derivatives, has been considered to be a major cause of chemotherapy-induced peripheral neuropathy (CIPN). However, the precise underlying mechanisms are not fully understood. To address this issue, we focused on major supportive roles of Schwann cells in the maintenance of peripheral nerve systems and evaluated the effects of anti-cancer agents on primary cultured rat Schwann cells. Exposure of primary cultured rat Schwann cells to paclitaxel (0.01 μM), cisplatin (1 μM), or oxaliplatin (3 μM) for 48 h induced cytotoxicity and reduced myelin basic protein expression at concentrations lower than those required to induce neurotoxicity in cultured rat dorsal root ganglion (DRG) neurons. Similarly, these anti-cancer drugs disrupted myelin formation in Schwann cell/DRG neuron co-cultures without affecting nerve axons. Cisplatin and oxaliplatin, but not paclitaxel, caused mitochondrial dysfunction in cultured Schwann cells. By contrast, paclitaxel led to dedifferentiation of primary cultured mature Schwann cells into an immature state, characterized by increased expression of immature and dedifferentiated Schwann cells markers, p75 and galectin-3, respectively. Consistent with *in vitro* findings, repeated injection of paclitaxel (4 mg/kg × 4) elevated expression of p75 and galectin-3 in Schwann cells within the mouse sciatic nerve. These results suggest that taxanes and platinum derivatives impair Schwan cells by inducing dedifferentiation and mitochondrial dysfunction, respectively, thereby triggering the pathogenic mechanisms underlying CIPN in conjunction with their direct impairment in peripheral neurons.

Disclosures: M. Koyanagi: None. **S. Imai:** None. **Y. Nakazato:** None. **M. Matsumoto:** None. **T. Ogihara:** None. **T. Nakagawa:** None. **K. Matsubara:** None.

Poster

222. Cancer Pain and Chemotherapy-Evoked Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 222.07/Z13

Topic: D.03. Somatosensation: Pain

Title: The critical role of $Ca_v3.2$ T-type calcium channels in the peripheral neuropathy induced by bortezomib, a proteasome-inhibiting chemotherapy agent, in mice

Authors: *A. KAWABATA[1], S. TOMITA[1], T. DEGUCHI[1], F. SEKIGUCHI[1], M. TSUBOTA[1], S. YOSHIDA[2]
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Abstract: Bortezomib, a proteasome inhibitor, is used for treatment of multiple myeloma. Chemotherapy-induced peripheral neuropathy (CIPN) is one of the treatment-limiting side effects of bortezomib, and its underlying mechanisms are still open to question. The proteasome system regulates the turnover of a variety of proteins including $Ca_v3.2$ T-type calcium channels (T-channels) that play a pronociceptive role in the primary afferents. Considering recent evidence that the inhibition of ubiquitination and proteosomal degradation of $Ca_v3.2$ by ubiquitin-specific peptidase 5 (USP5) is involved in the increased $Ca_v3.2$ expression (Neuron 83, 1144, 2014), we hypothesized that proteasome inhibition by bortezomib might increase $Ca_v3.2$ protein levels and contribute to the development of neuropathy. We thus created a mouse model for bortezomib-induced peripheral neuropathy and analyzed the possible involvement of $Ca_v3.2$. Repeated i.p. administration of bortezomib (3 times a week) for 2 weeks induced mechanical allodynia in mice. Inhibition of $Ca_v3.2$ by TTA-A2, a T-channel blocker, or by ascorbic acid restored the bortezomib-induced allodynia. Bortezomib treatment significantly increased the levels of $Ca_v3.2$ protein in the dorsal root ganglion (DRG). The gene silencing of $Ca_v3.2$ by intrathecal administration of the antisense oligonucleotides abolished the bortezomib-induced allodynia. In rat DRG-derived ND7/23 cells, 24-h stimulation with bortezomib as well as MG-132, another proteasome inhibitor, augmented $Ca_v3.2$ protein, but not mRNA, levels, and elevated T-channel-dependent currents, as assessed by the whole-cell patch clamp procedure. Our data suggest that proteasome inhibition by bortezomib increases $Ca_v3.2$ protein levels in the primary afferents, leading to peripheral neuropathy.

Disclosures: A. Kawabata: None. **S. Tomita:** None. **T. Deguchi:** None. **F. Sekiguchi:** None. **M. Tsubota:** None. **S. Yoshida:** None.

Poster

222. Cancer Pain and Chemotherapy-Evoked Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 222.08/Z14

Topic: D.03. Somatosensation: Pain

Support: CPRIT

Title: Genetic dissection of chemotherapy induced peripheral neuropathy identifies TrpA1 as a conserved target of anti-cancer drugs in sensory nociceptors

Authors: *E. MONTANO[1], N. BOIKO[1], G. MEDRANO[1], K. M. HARGREAVES[2], J. D. STOCKAND[1], B. A. EATON[1]
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Abstract: Chemotherapy-induced peripheral neuropathy (CIPN), a condition that arises from treatment with various anti-cancer drugs, is characterized by a severe pain syndrome. Currently,

there are no effective treatments for this pain syndrome except for the reduction of anti-cancer drug dose, compromising treatment. Existing data supports the model that the pain associated with CIPN is the result of anti-cancer drugs augmenting the function of the peripheral sensory nociceptors but the cellular mechanisms underlying the effects of anti-cancer drugs on sensory nociceptor function are not well described. To elucidate the underlying cellular and molecular mechanisms associated with CIPN, we created a novel model in *Drosophila* larvae that combines sensory neuron-specific genetic manipulations with behavioral and cellular assays for mechanical and thermal nociception. We find that larvae exposed to acute doses of the chemotherapy drugs develop both mechanical allodynia and thermal hyperalgesia, an effect that is dependent upon the TrpA1 channel. Importantly, this effect appears to be evolutionarily conserved in mice, supporting the significance of these studies to chemotherapy-induced pain syndromes in mammals. Furthermore, we use patch-clamp electrophysiology to demonstrate that exposure of isolated sensory neurons to anti-cancer drugs results in the generation of a TrpA1-dependent inward sodium current capable of depolarizing these neurons to threshold resulting in neuronal firing. These data represent the first demonstration of the effects anti-cancer drugs have on the excitation of *Drosophila* sensory neurons. Based on our preliminary results, we propose the model that activation of TrpA1 is an early and formative event during the pathogenesis of CIPN. This model is supported by the protective effect of *TrpA1* mutations on sensory neuron function in animals exposed to chronic doses of anti-cancer drugs. To provide additional insight into the cellular and molecular mechanisms underlying the pathogenesis of TrpA1-dependent CIPN, a forward genetic screen has been initiated. Results from this genetic screen will be presented.

Disclosures: E. Montano: None. **N. Boiko:** None. **G. Medrano:** None. **K.M. Hargreaves:** None. **J.D. Stockand:** None. **B.A. Eaton:** None.

Poster

222. Cancer Pain and Chemotherapy-Evoked Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 222.09/Z15

Topic: D.03. Somatosensation: Pain

Support: The Peggy and Avinash Ahuja Foundation and the Helen Buchanan and Stanley Joseph Seeger Endowment at The University of Texas MD Anderson Cancer Center.

Title: Tempol decreases inflammatory cytokines and superoxide levels in the dorsal root ganglia in chemotherapy-induced neuropathic pain in rats

Authors: *H. KIM, S.-H. HWANG, E. KIM, S. ABDI
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Abstract: Advances in the treatment of cancer using various types of chemotherapy agents have led to improvement in the survival rate of cancer patients. Unfortunately, pain associated with the chemotherapy treatment including taxanes, vinca alkaloids, platinum complexes, and proteasome inhibitor is a significant side effect which affects the quality of life of the survivals. We previously reported that Tempol, a membrane-permeable free radical scavenger, ameliorates paclitaxel (PAC)-induced neuropathic pain in rats. The purpose of this study was to investigate the effect of Tempol on PAC-induced inflammatory cytokines and superoxide levels in dorsal root ganglia (DRGs). PAC (2 mg/kg on days 0, 2, 4, 6) or vehicle (4% dimethyl sulfoxide and 4% Tween 80 in saline) was intraperitoneally injected in adult male Sprague-Dawley rats. Tempol was intraperitoneally infusion for 7 days starting on day 14 after the first PAC injection and the lumbar DRG was dissected on day 20. For western blot, the L1-6 DRGs were dissected, homogenized in RIPA lysis buffer, separated in SDS polyacrylamide gel and then transferred to polyvinylidene fluoride membrane. For detection, blot was incubated with the primary antibody to phosphorylated NFκB (p-NFκB), IL-1β, monocyte chemoattractant protein (MCP)-1, and GAPDH, respectively and then incubated with the horseradish peroxidase-conjugated secondary antibody. The immunoblots were detected by a chemiluminescence detection system and normalized to GAPDH. For live cell imaging, the L1-6 DRGs were dissected, dissociated, and cultured in Dulbecco's Modified Eagle's Medium. DRG cells were placed in a chambered coverglass, stained with MitoSOX, and then treated with PAC and/or Tempol. Red fluorescent intensity in live cells were measured using confocal microscope. Paclitaxel increased the levels of phosphorylated nuclear factor kB, IL-1β, and MCP-1 in the lumbar dorsal root ganglia; however, tempol decreased these levels. Paclitaxel also increased superoxide levels in a culture of primary dorsal root ganglion cells and tempol decreased these levels. We conclude that Tempol alleviates chemotherapy-induced neuropathic pain in rats by reducing the levels of inflammatory cytokines and free radicals in dorsal root ganglia.

Disclosures: H. Kim: None. **S. Hwang:** None. **E. Kim:** None. **S. Abdi:** None.

Poster

222. Cancer Pain and Chemotherapy-Evoked Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 222.10/Z16

Topic: D.03. Somatosensation: Pain

Support: P30NR011396

Title: Global transcriptomic profile of dorsal root ganglion and physiological correlates of cisplatin-induced peripheral neuropathy reveal differences across inbred mouse strains

Authors: *C. B. LASSITER[1], V. CAROZZI[2], S. LESSANS[3], B. SHALABY[3], P. HEINDEL[3], N. OGGIONI[2], A. CHIORAZZI[3], C. THOMPSON[3], M. A. WAGNER[4], J. E. HOLDEN[4], E. J.

RAHN[5], J. D. SWEATT[6], G. CAVALETTI[2], C. L. RENN[3], S. G. DORSEY[3]
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Abstract: Platinum based antineoplastic therapies, such as cisplatin, are among the oldest and most widely used chemotherapy agents to treat solid tumors. Unfortunately, chemotherapy induced peripheral sensory neuropathy (CIPN) is a common complication from cisplatin treatment. Furthermore, little is known about predictive factors associated with the onset or progression of CIPN. Two inbred strains of mice, A/J and C57BL/6J, with differential sensitivity to CIPN were utilized to assess the contribution of dorsal root ganglion transcriptional profiles after one-week of treatment to the development and persistence of CIPN. Peripheral neuropathy was induced with a bi-weekly treatment of 4 mg/kg of cisplatin. We demonstrated that the A/J strain presents with less severe mechanical hypersensitivity, maintenance of sensory neuron nuclear area, and reduced wide dynamic range neuron activity in the spinal dorsal horn to press and pinch stimuli. Our data are suggestive that the resistance of the A/J strain to the neurotoxic effects of cisplatin is robust, lasting over four weeks. Microarray analyses and RT-qPCR indicated lower expression of major histocompatibility complex transcripts in the A/J after cisplatin treatment, suggesting that antigen presentation in the DRG, likely via satellite glia and/or resident macrophages, may contribute to CIPN. Additionally, lower basal and post-cisplatin expression of Pttg1, Thbs4, Mndal, and other apoptosis regulators may provide resistance to the cytotoxicity of cisplatin in the A/J strain of mice.

Disclosures: C.B. Lassiter: None. **V. Carozzi:** None. **S. Lessans:** None. **B. Shalaby:** None. **P. Heindel:** None. **N. Oggioni:** None. **A. Chiorazzi:** None. **C. Thompson:** None. **M.A. Wagner:** None. **J.E. Holden:** None. **E.J. Rahn:** None. **J.D. Sweatt:** None. **G. Cavaletti:** None. **C.L. Renn:** None. **S.G. Dorsey:** None.

Poster

222. Cancer Pain and Chemotherapy-Evoked Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 222.11/Z17

Topic: D.03. Somatosensation: Pain

Support: Nemus Bioscience

Title: Analgesic effects of cannabidiol and a novel cannabidiol analog in a murine model of cisplatin-induced neuropathy; synergistic effects with sub-analgesic doses of morphine

Authors: *H. M. HARRIS[1], W. GUL[2], M. A. ELSOHLY[2,3], K. J. SUFKA[1,2]
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Abstract: Abstract
This research examined whether a cannabidiol (CBD)-opioid pharmacotherapy could attenuate cisplatin induced tactile allodynia. Mice (C57BL/6) were given 6 doses of 2.3 mg/kg cisplatin IP on alternating days to induce tactile allodynia as quantified using an electric von Frey (eVF). Test groups in Exp. 1 received either vehicle, 0.1 or 2.5 mg/kg morphine, 1.0 or 2.0 cannabidiol or the two drugs in combination. Test groups in Exp. 2 received either vehicle, 0.1 or 2.5 mg/kg morphine, 1.6 or 3.2, 4.8 and 6.4 NB2111 (a long-acting cannabidiol analogue). Drugs were administered IP 45 m before eVF assessment. Cisplatin produced tactile allodynia that was attenuated by 2.5 mg/kg morphine. Both CBD and NB2111 produced dose-dependent attenuation of tactile allodynia. CBD and NB2111 given in combination with sub-analgesic doses of morphine produced attenuation of tactile allodynia equivalent to 2.5 mg/kg morphine. These findings suggest that CBD and NB2111, either alone or in combination with sub-analgesic doses of opioids, may be effective against neuropathy in oncology settings.

Disclosures: H.M. Harris: None. **W. Gul:** None. **M.A. ElSohly:** None. **K.J. Sufka:** None.

Poster

222. Cancer Pain and Chemotherapy-Evoked Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 222.12/Z18

Topic: D.03. Somatosensation: Pain

Support: NIH grant HL135895

Title: Schwann cell-derived exosomes contribute to cisplatin-induced hyperalgesia

Authors: A. H. KIM, *I. KHASABOVA, N. LUONG, J. K. OLSON, D. A. SIMONE
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Abstract: Painful peripheral neuropathy is a common dose-limiting side effect associated with cisplatin treatment. Cisplatin is unable to cross the blood-brain barrier, and its effects are limited to the peripheral nervous system (PNS). In the PNS, Schwann cells are an essential component supporting dorsal root ganglion (DRG) neuron viability, and impairments in Schwann cell biology contribute to cisplatin-induced painful neuropathy. Here, we explored the role of Schwann cell-derived exosomes in the development of cisplatin-induced hyperalgesia. Consistent with our previous reports, daily injection of cisplatin (1 mg/kg, i.p.) for 7 days produced mechanical hyperalgesia in C3H/HeN mice. Mechanical hyperalgesia consistently

developed by 24 h after the fourth injection of cisplatin. To investigate the impact of exosome signaling in the development of cisplatin-induced hyperalgesia, exosomes isolated from the sciatic nerve of cisplatin-treated mice were injected intrathecally into naïve mice for 5 days (6 μg of total protein/5 μl, i.t.). Mechanical hyperalgesia was observed after the second injection of exosomes, supporting the involvement of integrated exosome signaling in hyperalgesia produced by cisplatin. In order to distinguish the contributions of Schwann cell-derived exosomes to the hyperalgesia, cultured Schwann cells were treated with cisplatin (13 μM, 48 h). Isolated exosomes from cisplatin or vehicle- treated Schwann cells were injected into naïve mice for 5 days (6 μg/5 μl, i.t.). Mice injected with exosomes from cisplatin-treated Schwann cells developed hyperalgesia after four injections. Importantly, the hyperalgesic effect was related to the cumulative dose of exosomes. The direct effects of exosomes from cisplatin-treated Schwann cells on DRG neurons were studied *in vitro*. DRG neurons were cultured with exosomes (40 μg/ml) from cisplatin or vehicle -treated Schwann cells. Exosomes from cisplatin-treated cells evoked an increase in expression of FAAH mRNA, an enzyme which hydrolyzes the endocannabinoid anandamide. Collectively, our results indicate that Schwann cells affected by cisplatin contribute to mechanical hyperalgesia and exosomes are an important signaling mediator for glia-neuronal communication.

Disclosures: A.H. Kim: None. **I. Khasabova:** None. **N. Luong:** None. **J.K. Olson:** None. **D.A. Simone:** None.

Poster

222. Cancer Pain and Chemotherapy-Evoked Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 222.13/Z19

Topic: D.03. Somatosensation: Pain

Title: Strain specific gut microbiota in the onset of paclitaxel-induced allodynia in C57BL6 and SV129 mice

Authors: *J. A. CORLETO[1], C. RAMAKRISHNA[2], J. BORNEMAN[3], E. CANTIN[2], D. D. MCKEMY[1]
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Abstract: Administration of pharmaceutics to treat cancers include the use of a multitude of compounds such as alkylating agents, alkaloids, and a subset of antibiotics aimed at limiting the spread and effects of cancer cells. One such chemotherapeutic is the taxane-based molecule paclitaxel, a commonly used drug for breast, ovarian, and pancreatic cancers. The discovery of these compounds has led to an increase in patient survival. However, there is a long list of associated side effects including peripheral neuropathy and gastrointestinal toxicity. The role of

the microbiome has recently been implicated in several health and disease states, where gut microbe dysbiosis was shown to play a pivotal role in immunity, metabolism and brain function . Here, we report the use of two different mouse strains, C57BL6 and SV129, to understand the importance of differing microbiota on paclitaxel-induced neuropathy, finding that C57/Bl6 mice with endogenous microbiota develop mechanical and thermal hyperalgesia, whereas the SV129 strain was resistant to paclitaxel-induced pain. To determine the role of the microbiome in these differences, we performed microbiome swap experiments in germ-free mice of both strains. We found that germ-free C57/Bl6 mice harboring an SV129 microbiome were resistant to paclitaxel-induced pain and, conversely, SV129 germ-free mice harboring C57/Bl6-derived microbiomes exhibited paclitaxel-induced allodynia and hyperalgesia. These results suggest the essential role of gut microbiota in the development of paclitaxel-induced pain in mouse strains and pave the way for future studies to parse out the details behind this interaction.

Disclosures: J.A. Corleto: None. **C. Ramakrishna:** None. **J. Borneman:** None. **E. Cantin:** None. **D.D. McKemy:** None.

Poster

222. Cancer Pain and Chemotherapy-Evoked Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 222.14/Z20

Topic: D.03. Somatosensation: Pain

Support: NCATS P30 CA054174

8UL1TR000149

a grant from Calico Life Sciences LLC

Title: The neuroprotective effects of P7C3-A20 require NAMPT to prevent paclitaxel-induced peripheral neuropathy in rats

Authors: H. R. SMITH, P. M. LOCOCO, J. C. ZAMORA, T. A. CHAVERA, K. A. BERG, *W. P. CLARKE
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Abstract: The microtubule-targeting anticancer drug, paclitaxel (PTX), produces a chemotherapy-induced peripheral neuropathy (CIPN) characterized by severe and persistent neuropathic pain. CIPN can negatively affect both the quality of life and prognosis of cancer patients, as the lack of effective therapies leaves cessation of chemotherapy as the only option. P7C3-A20, an aminopropyl carbazole, inhibits the development of PTX-induced neuropathy in rats. The neuroprotective efficacies of P7C3-A20, and its individual enantiomers, were examined using a randomized, double-blind dose-response study in a rat behavioral model of PTX-induced

peripheral neuropathy, induced by treatment of rats with PTX (11.7 mg/kg/day, i.p.; every other day for 3 injections). Racemic (20 mg/kg), enantiomer specific mixtures of P7C3-A20 (6 or 20 mg/kg, i.p., q.d.) or vehicle were administered daily to male Sprague-Dawley rats over a 14-day period beginning 2 days before PTX treatment. P7C3-A20 dose-dependently attenuated PTX-induced mechanical allodynia and prevented the PTX-induced loss of intraepidermal nerve fiber (IENF) density in paw biopsies. Statistical analysis indicated strong correlations between IENF density and nociceptive threshold to mechanical stimuli. Consistent with previous studies that P7C3-A20 stimulates NAMPT, a critical enzyme in the NAD salvage pathway, treatment with the selective NAMPT inhibitor, FK866, prevented the neuroprotective effect of P7C3-A20 on PTX-induced mechanical allodynia and reduced IENF density. Moreover, co-administration of P7C3-A20 with the NAMPT substrate, nicotinamide (150 mg/kg, s.c., q.d.), increased the neuroprotective efficacy of P7C3-A20 such that an ineffective dose (2.2mg/kg) was as effective as a maximal dose of P7C3-A20 (10 mg/kg/day). P7C3-A20 also increased NAD+ levels in hindpaw biopsies from PTX-treated rats. Tests of the racemates of P7C3-A20 revealed that the S-enantiomer was the active form. Taken together, these data suggest that the protective effects of P7C3-A20 require function of NAMPT. Thus, P7C3-A20 may be an exciting new clinical candidate to prevent peripheral neuropathy.

Disclosures: H.R. Smith: None. **P.M. LoCoco:** None. **J.C. Zamora:** None. **T.A. Chavera:** None. **K.A. Berg:** None. **W.P. Clarke:** None.

Poster

222. Cancer Pain and Chemotherapy-Evoked Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 222.15/Z21

Topic: D.03. Somatosensation: Pain

Support: National Institutes of Health CA200263

the H.E.B. Professorship in Cancer Research

Title: Cytokines production and MAPK signaling downstream to TLR4 contributes to paclitaxel-induced peripheral sensory neuron hyperexcitability *In vitro* culture

Authors: *Y. LI[1], R. Y. NORTH[3], C. A. JOHANSSON, 77030[4], P. M. DOUGHERTY[2]
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Abstract: Cancer is the second leading cause of death in the United States, with lung and breast cancers having the highest mortality rates. Paclitaxel affects the growth and division of cancer

cells by promoting the assembly of extremely stable but dysfunctional microtubules. The major dose-limiting toxicity of paclitaxel treatment is chemotherapy induced peripheral neuropathy (CIPN). The mechanisms underlying CIPN are of great complexity and thus a cohesive and detailed process behind it has yet to be fully elucidated. In vivo studies have elucidated many pieces of the puzzle surrounding CIPN. In this study we seek to provide further evidence for this claim by using an in vitro model of paclitaxel treatment. Cytokines have been identified as one of the crucial participants in the pathophysiology driving CIPN. The focus of this research is targeted on IL-6 and MCP-1, TLR4 signal pathway, MAPK signal pathway. By providing evidence for their role in an in vitro paclitaxel treated primary rat DRG culture model we hope to gain a clearer understanding of the mechanisms behind it as well as provide a platform from which potential therapeutics and further research will be based on. In primary rat DRG culture with incubation of paclitaxel, TLR4 and MyD88 was upregulated at 48h, and the immediate down-stream signal molecules Mitogen-activated protein kinases (MAPK), Extracellular signal related kinase (ERK1/2) and p38 but not c-Jun N terminal kinase (JNK), were upregulated at 2h and 48h after paclitaxel incubation using western blot. This upregulation could be prevented by pretreated with TLR4 antagonist (LPS-RS). IL-6 and MCP-1 was released to culture medium detected by using ELISA and upregulated in cultured cells using western blot after paclitaxel treatment. IL-6 and MCP-1 staining was co-localized to TLR4-positive cells. Whole-cell patch clamp recordings in rat DRG neurons revealed that MCP-1 induced spontaneous action potentials and enhanced the amplitude of membrane potential oscillation.

Disclosures: Y. Li: None. **R.Y. North:** None. **C.A. Johansson:** None. **P.M. Dougherty:** None.

Poster

222. Cancer Pain and Chemotherapy-Evoked Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 222.16/Z22

Topic: D.03. Somatosensation: Pain

Title: PF22688 a pan-Trk inhibitor with analgesic properties in cancer pain

Authors: *J.-C. MARTEL[1], L. DE VRIES[2], F. CACHOUX[3], L. BARDIN[4], I. RAULY-LESTIENNE[5], S. GATTI-MCARTHUR[2]
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Abstract: Several cancers in human lead to bone metastasis producing major pain at advanced stages (Pain 154 Suppl. 1: S54, 2013). The mechanisms of bone cancer pain involves sensory neuron rearrangements with both nociceptive and neuropathic components (Curr Opin Support & Palliat Care 8: 83, 2014) associated to increased secretion of cytokines, including NGF and

BDNF (Neurosci. Lett 557: 52, 2013). Compounds blocking neurotrophins signaling may thus reduce occurrence of bone cancer pain and we developed a medicinal chemistry program aiming at blocking Trk kinase activity. An *in vitro* kinase glo plus-based kinase assay (Promega) was developped in a 96 wells assay plate format to assess the inhibiting properties of compounds on tropomyosin related kinases (Trk) receptors, using the soluble intracellular segment of theses receptors, containing the kinase activity. Under these assay conditions, K252a had IC_{50} = 30 & 74 nM at TrkA & TrkB kinases, respectively. We identified PF22688 having IC_{50} = 45 & 31 nM at these respective kinases. This compound was tested in animal models of acute and chronic inflammatory pain following hindpaw injection of NGF in mice (heat allodynia) or injection of CFA in hindpaw of rat (flinches and von Frey allodynia), and in chronic cancer pain in C3H/HeNCrl mice inoculated with NCTC 2472 osteolytic fibrosarcoma cells. PF22688 (10 mg/kg, ip or 2.5 & 10 mg/kg, po) restored time latency in the NGF-induced hot plate allodynia in mice. In the CFA induced pain, PF22688 (0.16, 2.5 & 10 mg/kg ip) reduced spontaneous CFA induced flinching. In addition, oral PF22688 (2.5 & 10 mg/kg, po) also reduced CFA-induced mechanical allodynia. Finally, in the mice chronic cancer pain model, repeated administration of PF22688 (2.5 mg/kg, ip), given once a day 30 minutes before testing over day 8 to 17 post inoculation, improved use of the affected limb, while also reducing touch-induced flinching. These results are compatible with a potential therapeutic benefit of PF22688 to reduce chronic bone cancer pain.

Disclosures: **J. Martel:** A. Employment/Salary (full or part-time):; Institut de Recherche Pierre Fabre. **L. De Vries:** A. Employment/Salary (full or part-time):; Institut de Recherche Pierre Fabre. **F. Cachoux:** A. Employment/Salary (full or part-time):; Institut de Recherche Pierre Fabre. **L. Bardin:** A. Employment/Salary (full or part-time):; Institut de Recherche Pierre Fabre. **I. Rauly-Lestienne:** A. Employment/Salary (full or part-time):; Institut de Recherche Pierre Fabre. **S. Gatti-McArthur:** A. Employment/Salary (full or part-time):; Institut de Recherche Pierre Fabre.

Poster

222. Cancer Pain and Chemotherapy-Evoked Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 222.17/Z23

Topic: D.03. Somatosensation: Pain

Support: Horizion 2020 Grant No. 642720

Title: The role of osteoclasts in cancer induced bone pain

Authors: *L. DE CLAUSER, S. SANTANA-VARELA, J. WOOD, S. SIKANDAR
Univ. Col. London, London, United Kingdom

Abstract: Although cancer treatment has dramatically improved over the past decade, pain remains a serious problem for most patients, particularly in the case of metastatic cancer to the bone. Cancer induced bone pain (CIBP) differs from neuropathic or inflammatory pain with respect to some neurochemical components and its development is dependent on the tumor microenvironment [1]. The bone resorbing osteoclasts may play a role in mediating CIBP. Animal models of CIBP show increased osteoclast activity and in humans the metastatic potential correlates with the amount of receptor activator of nuclear factor kappa-B ligand (RANKL) produced by cancer cells [2]. RANKL stimulates both the migration of myeloid precursors to bone tissue and their differentiation into mature osteoclasts. Notably, clinically licensed drugs, including bisphosphonates and the RANKL inhibitor denosumab, targeting osteoclasts reduce bone loss and relieve pain in cancer patients [3]. However, it is not fully understood how they contribute to CIBP. The aim of this study was to dissociate the bone microenvironment component of CIBP from other pathways that contribute to the pathophysiology of the disease. Our preliminary results, in line with the literature, show that 12 week old male mice injected intrafemorally with Lewis Lung carcinoma have a decreased limb use and weight bearing of the affected limb. At an anatomic level, a decrease in trabecular bone mineral density is evident in animals with bone cancer, whereas systemically there was no evidence for increased resorption. We investigated the potential direct effects of osteoclast-derived mediators, such as BMP6 and S1P on sensory neurons in cancer bearing animals and in combination wtih retrograde labelling of bone afferents in naïve mice.
To further characterize the involvement of osteoclasts on primary neuron sensitization here we describe the establishment of a novel model of local osteoclast activation through intrafemoral RANKL injection using 12 week old male mice. We investigated the effects of local osteoclast activation on pain-related behavior using standardized behavioral assays. We assessed ongoing skeletal pain with limb use scoring and static weight bearing and stimulus- evoked pain with mechanical and thermal sensitivity. Bone resorption was quantified through micro CT scans and histology.
References:
1. Honore, P. et al. Neuroscience 98, 585-598 (2000).
2. Currie, G. L. et al. Pain 154, 917-926 (2013).
3. Lipton, A. & Balakumaran, A. Expert Rev Clin Pharmacol 5, 359-371 (2012).

Disclosures: L. De Clauser: None. **S. Santana-Varela:** None. **J. Wood:** None. **S. Sikandar:** None.

Poster

222. Cancer Pain and Chemotherapy-Evoked Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 222.18/Z24

Topic: D.03. Somatosensation: Pain

Support: RO1 NS088656

RO1 NS75156

AHA 16SDG29860003

Title: Exosomes derived from cerebral endothelial cells mitigate oxaliplatin-induced peripheral neuropathy

Authors: *Y. ZHANG[1], M. CHOPP[1,2], C. LI[1], X. WANG[1], Z. ZHANG[1]
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Abstract: Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most common complications that affect the process and prognosis of cancer treatment. Currently, there are no effective therapies for CIPN. Exosomes, a subpopulation of extracellular vesicles released by living cells, play pivotal roles in cell-cell communication by transferring their cargo, proteins, lipids and genetic materials, to recipient cells. Based on our previous findings that exosomes derived from cerebral endothelial cells (CEC-exosomes) promote axonal growth of cortical neurons, we tested the hypothesis that CEC-exosomes block oxaliplatin-induced peripheral neuropathy. Using adult dorsal root ganglia (DRG) neurons cultured in microfluidic devices that separate axons from their parent cell bodies, we found that application of oxalipatin (9.1nM) into distal axons significantly suppressed axon extension of DRG neurons (51%±10% vs 100% in control, $p<0.05$ n=3/group). However, CEC-exosomes ($3x10^7$ particles) reversed the inhibitory effect of oxaliplatin on axonal growth (78%±12%, $p<0.05$ vs oxaliplatin, n=3/group). These results indicate that oxaliplatin locally inhibits distal axonal growth and that CEC-exosomes overcome the inhibitory effect of oxaliplatin on DRG neurons. We then performed in vivo experiments in which mice were treated with oxaliplatin (3.0mg/kg, i.p.) daily for two rounds of 5 consecutive days per week with one week rest between two rounds. Mice exhibited a significant sensitivity to thermal allodynia measured by a cold plate test (14±2 vs 10±2 jumps in control mice, $p<0.05$, n=7 mice/group) starting the first week of oxaliplatin treatment. Oxaliplatin also impaired mechanical allodynia measured by the Von Frey test (0.7±0.1 vs 1.0±0.1g in control, $p<0.05$), and reduced the sensory, but not motor, conductive velocity (SCV, 22±3 vs 34±2 m/s in control, $p<0.05$). However, treatment of mice subjected to oxaliplatin with CEC-exosomes ($3x10^{11}$ particles, i.v., 3 times/week, 6 weeks) starting the first week of administration of oxaliplatin completely alleviated thermal (11±2 jumps vs CIPN mice, $p<0.05$) and mechanical allodynia (0.9±0.1g vs CIPN mice, $p<0.05$) and improved SCV (30±3 m/s vs CIPN mice, $p<0.05$). Oxaliplatin also reduced the gene-related peptide (CGRP) neuron size in L3 to L5 DRG (26±2 vs 36±2 μm of average diameter in control mice, $p<0.05$, n=220 neurons/group), whereas CEC-exosome treatment reversed the neuron size reduction (39±2 vs CIPN mice, $p<0.05$). Together, our in vitro and in vivo data demonstrate that CEC-exosomes mitigate oxaliplatin-induced peripheral neuropathy, which provides a novel therapeutic strategy to potentially treat CIPN.

Disclosures: **Y. Zhang:** None. **M. Chopp:** None. **C. Li:** None. **X. Wang:** None. **Z. Zhang:** None.

Poster

223. Barrel Cortex: Tactile Discrimination

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 223.01/Z25

Topic: D.04. Somatosensation: Touch

Support: israel science foundation

Title: Mechanisms underlying perceptual constancy in the whisker somatosensory system

Authors: *R. AZOUZ[1], H. SHARMA[2], *R. AZOUZ[1]
[1]Ben-Gurion Univ., Beer-Sheva, Israel; [2]Physiol. and cell biology, Ben-Gurion Univ. of the Negev, Beer-Sheva, Israel

Abstract: One of the most critical and intriguing questions in the field of sensory perception is how an organism preserve an accurate and stable perception of objects, shapes and textures despite large variations in the details of the interaction between animal and objects. To determine the way in which rodents achieve perceptual constancy in a changing environment, while sensing their environment passively, we monitored head movements of awake behaving rats while approaching objects. We then replayed these movements in anesthetized rats, monitored whiskers' movements across various textures, and concurrently recorded the activity of somatosensory cortical neurons. We found that changing texture distance from the pad, velocity, direction of movement and contact with single and multiple whiskers resulted in a modification of response magnitude, degree of neuronal synchrony and texture selectivity in a layer specific manner. Using ideal observer analysis for neural firing rates and synchrony, we found that stimulus configurations reduces neuronal coding stability, i.e. cortical neurons respond differently to the same textures, whereas it does not change texture discrimination. Moreover, stimulus configurations did not influence texture selectivity index, while modifying texture selectivity. Together, these findings suggest that perceptual constancy will be difficult to maintain during receptive sensing. Alternatively, rodents may maintain perceptual constancy using sensorimotor behavioral strategies.

Disclosures: **H. Sharma:** None. **R. Azouz:** None.

Poster

223. Barrel Cortex: Tactile Discrimination

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 223.02/Z26

Topic: D.04. Somatosensation: Touch

Support: NSF GRFP

Title: A behavioral paradigm that challenges mice to identify objects by complex conjunctions of sensory features

Authors: *R. RABINOVICH[1], C. RODGERS[2], R. M. BRUNO[1]
[1]Neurosci., Columbia Univ., New York, NY; [2]Columbia Univ. Med. Ctr., New York, NY

Abstract: While many neuroscience studies use mouse models to investigate sensation, perception, and cognition, the extent to which mice can perform complex sensory discrimination remains unclear. To address this question, we have developed a tactile object recognition task: one of four objects is presented in the whisker field of head-fixed mice, which are required to discriminate them on the basis of conjunctions of features—shape (concave vs. convex) and texture (smooth vs. rough). Of these four objects, two are rewarded, and two are unrewarded; the defining features of a rewarded object can both also be found on unrewarded objects (but not together on the same unrewarded object). Thus, no single feature alone can provide sufficient information about whether reward will follow a given object, and mice must base their decisions on both features. While the task is designed to assay mouse tactile sensation, mice would frequently exploit other senses, particularly olfaction: completely trimming off whiskers often did not impair behavioral performance. Nonetheless, discrimination was poor in a subset of mice after whisker trimming, indicating that individual mice opt for any of a variety of behavioral strategies. Thus, mice appear to be able to use their whiskers to discriminate conjunctions of shapes and textures.

Disclosures: R. Rabinovich: None. **C. Rodgers:** None. **R.M. Bruno:** None.

Poster

223. Barrel Cortex: Tactile Discrimination

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 223.03/DP05/Z27 (Dynamic Poster)

Topic: D.04. Somatosensation: Touch

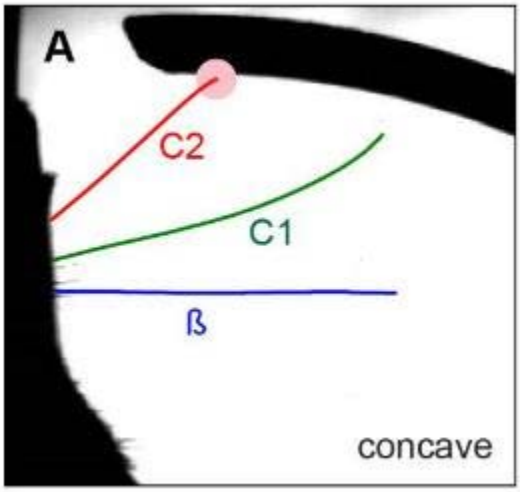
Support: NIH/NINDS R01NS094659

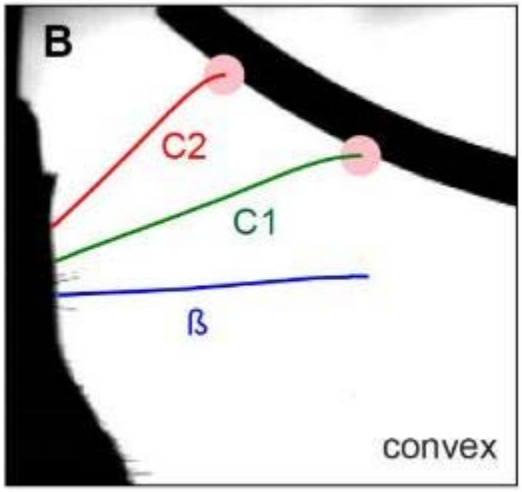
NIH/NINDS F32NS096819

Title: The sensorimotor strategies mediating curvature discrimination by active whisker touch

Authors: *C. RODGERS[1], B. C. PIL[1], R. M. BRUNO[2]
[1]Columbia Univ. Med. Ctr., New York, NY; [2]Neurosci., Columbia Univ., New York, NY

Abstract: Humans and other animals can identify objects by active touch -- coordinated exploratory motion and tactile sensation. For example, we precisely scan our fingertips over objects in order to identify them, integrating tactile and proprioceptive input from each finger into a holistic representation of shape. Similarly, mice adeptly recognize objects by scanning them with their array of whiskers. To identify the behavioral strategies and neural computations that mediate this ability, we have developed a behavioral task for head-fixed mice -- curvature discrimination -- that challenges them to discriminate concave from convex shapes. We can identify the time and location of every whisker contact using high-speed videography. Next, we are statistically characterizing the behavioral strategies mice use to efficiently extract information about object curvature, in order to generate hypotheses about the underlying neural algorithms. Preliminary results suggest that the mice use a two-part "scan, then foveate" strategy: they first whisk broadly to coarsely localize the object, and then target their whisking more precisely to extract more detailed information about shape. Mice typically contact the stimuli in multi-whisker bouts lasting 25-50 ms, producing rich spatiotemporal patterns of contacts across the whisker array. Because the stimuli are presented over a range of positions, it is not possible to unambiguously determine curvature using only information from a single location in space. We have used machine learning algorithms to reveal recurring multi-whisker contact patterns and to decode the curvature of the shape from these patterns. These statistical analyses will reveal the motor control and feature recognition strategies mice employ to infer shape from this complex tactile input. We are presently recording spiking activity from populations of neurons in somatosensory cortex and we next plan to identify how they encode and process these features in order to mediate this behavior.





Disclosures: **C. Rodgers:** None. **B.C. Pil:** None. **R.M. Bruno:** None.

Poster

223. Barrel Cortex: Tactile Discrimination

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 223.04/Z28

Topic: D.04. Somatosensation: Touch

Support: R01 NS069679

F31 NS098670

F32 NS092357

T32 EY013933

Amgen Scholars Program

Title: How mice use whiskers to locate and respond to behaviorally relevant objects

Authors: *G. M. PIERCE[1], A. K. KINNISCHTZKE[1], H. C. MACOMBER[2], B. C. PIL[1], R. M. BRUNO[1]
[1]Neurosci., [2]Biol., Columbia Univ., New York, NY

Abstract: When faced with the large array of objects in our environment, we must selectively respond to the fraction that are most important. How the brain selectively identifies, processes, and responds to these behaviorally relevant stimuli remains unanswered. We seek to answer this question in mice, who can actively move their whiskers onto objects to precisely localize and identify them. Typical behavioral paradigms present mice with one or more objects (e.g. a pole in the whisker field, different textures, etc.) that are completely informative of the correct response (e.g. lick or do not lick). In contrast, we have developed a task in which a “target” pole presented in the upper whisker field indicates the correct response, while a “distractor” pole presented, often simultaneously, in the lower whisker field is irrelevant. We also trained a separate cohort such that the lower pole was the target and the upper pole was the distractor. These two poles are identical in physical characteristics (shape, size, texture, etc.) and differ only in their location and relevance to the animal. Mice learned to associate the presence of the target with the possibility of reward in approximately two weeks. They were unable to perform the task after their whiskers were trimmed, indicating they indeed use the somatosensory system rather than depending on other senses. The head-fixed nature of the task allows us to track whisking motion and whisker contacts onto the objects while animals perform the task. Although mice can perform well on the task when only contacting the target pole, they reliably touched both poles. Mice made more whisker contacts onto the target, even though the target and distractor poles

were located equally close to the face. This finding indicates that mice correctly identified the target as behaviorally relevant and voluntarily sought information about it. We next plan to investigate whether mice use a purely motor strategy, such as angling their whisking, or whether they also use a cognitive strategy, such as spatial attention, to perform this task. This behavior will facilitate the study of how somatosensory circuits incorporate behavioral importance with tactile sensation.

Disclosures: G.M. Pierce: None. **A.K. Kinnischtzke:** None. **H.C. Macomber:** None. **B.C. Pil:** None. **R.M. Bruno:** None.

Poster

223. Barrel Cortex: Tactile Discrimination

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 223.05/Z29

Topic: D.04. Somatosensation: Touch

Support: European Research Council

Human Brain Project

Einstein Stiftung Berlin

Title: Bilateral whisker movement predicts decision-making in mice solving Air-Track plus maze

Authors: *M. A. NASHAAT[1], S. DOMINIAK[2], A. NASR[2], K. SEHARA[2], H. ORABY[2], M. LARKUM[2], R. SACHDEV[2]
[1]Biol. Dept., Neurocure Cluster of Excellence, Humboldt Universi, Berlin, Germany; [2]Biol. Dept., Humboldt Univ. zu Berlin, Berlin, Germany

Abstract: Rodents whisk to detect objects and discriminate between objects. In many species, whiskers also aid in navigation: animals keep whisker contact with walls, or use their whiskers to detect the direction of air or water currents. Here we show that whisking, in particular the movement of single whiskers on each side of the face predicts the behavior of animals trained on a floating “Air-Track” plus maze. The plus maze (28 cm in diameter, with four lanes each 3.5 cm wide, and 10 cm long) floats on an air cushion. Head-fixed mice (n=3) were trained to choose a lane based on a visual stimulus. To obtain a reward, mice moved the maze and rotated it right, left, forward and backward around themselves until they were in the rewarding lane. In the course of the animal’s performance, we examined whether the motion of a colored whisker on each side of the face predicted 1) movement initiation; and 2) direction of movement. The motion of the whiskers was monitored with a 180 Hz color camera system. Whisker tracking was performed offline with a pixy camera. Here we find that mice invariably moved their whiskers

when they walked, with the onset of whisking preceding (by more than 50 ms) the animals' movement. Whisking movement was larger and more consistent when animals were moving forward ina lane as opposed to when they moved backward. Asymmetry in motion of whiskers on two sides of the face was commonplace, but it was especially evident when mice moved the maze backward, exited the lane, and began rotating the maze right or left. The position and motion of whiskers predicted the direction of rotation that the mouse imposed on the maze. Because most behavioral tasks do not use behavioral paradigms where mice move backward for expended periods of time, we also examined the behavior of freely moving mice trained in a similar maze. Our findings show that freely moving animals utilize the same backward movement strategy when backing out of lanes. This work reveals that whisking predicts the dynamics of sensory motor interactions, particularly the onset of walking and decision-making in mice.

Disclosures: **M.A. Nashaat:** None. **S. Dominiak:** None. **A. Nasr:** None. **K. Sehara:** None. **H. Oraby:** None. **M. Larkum:** None. **R. Sachdev:** None.

Poster

223. Barrel Cortex: Tactile Discrimination

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 223.06/Z30

Topic: D.04. Somatosensation: Touch

Support: ERC

Marie Curie

Human Brain Project

DFG

Title: The spatial-temporal dynamics of whisker and whisker pad motion in a touch task

Authors: *S. DOMINIAK, K. SEHARA, M. A. NASHAAT, H. ORABY, M. E. LARKUM, R. N. SACHDEV
Humboldt-Universität zu Berlin, Berlin, Germany

Abstract: Movement is the result of complex interplay of activity in a large number of sensory and motor circuits. The whisker system is a model sensory and motor system, where a set of extrinsic muscles can guide the entire whisker pad, and sling intrinsic muscles around individual whiskers allow the animal to exert fine control over individual whiskers. While rodents have more than 20 vibrissae most studies use reduced models and interrogate circuit activity in relation to single whisker motion. Here we show the complex long lasting dynamics of adjacent

row / arc whiskers and whisker pad, in a contact task. To examine the motion of the pad and whiskers we developed an easy to use 3D optical imaging method that makes use of two orthogonally placed color high-speed cameras (Basler) and a pixy camera for color based tracking of the motion of the whiskers and whisker pad. Head-fixed mice (n=3) were trained to perform a simple auditory go cue triggered movement that brought a whisker into contact with a piezo-film. Contact that exceeded a threshold value was rewarded. Three dimensional tracking of whisker motion revealed consistent changes in movement of whiskers in rostro-caudal and dorsoventral direction: when a whisker made contact with the piezo film, the adjacent row whisker continued to protract and retract for hundreds of milliseconds, and move in a dorsoventral direction in a swooping arc downward. The arc whiskers moved more synchronously in all 3 dimensions even at contact. The motion of the pad was much smaller than the motion of whiskers, but pad motion tracked the motion of an overlying whisker. These results show the complexity and dynamics of motor control in simple whisker triggered tactile tasks.

Disclosures: **S. Dominiak:** None. **K. Sehara:** None. **M.A. Nashaat:** None. **H. Oraby:** None. **M.E. Larkum:** None. **R.N. Sachdev:** None.

Poster

223. Barrel Cortex: Tactile Discrimination

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 223.07/Z31

Topic: D.04. Somatosensation: Touch

Support: DFG Grant LA 3442/3-1

Title: Cell-type specific dendritic activation of layer 5 pyramidal neurons in sensory perception

Authors: *N. TAKAHASHI[1], S. NIERWETBERG[2], M. LARKUM[1]
[1]Humboldt Univ. of Berlin, Berlin, Germany; [2]Charité - Universitätsmedizin Berlin, Berlin, Germany

Abstract: Perceptual detection of sensory stimuli has been shown to depend on calcium currents in apical dendrites of cortical layer 5 (L5) pyramidal neurons in behaving mice (Takahashi et al., *Science,* 2016). Dendritic calcium currents are converted into spike outputs in L5 neurons, which project to various brain regions. Based on their output targets, L5 pyramidal neurons are categorized into two subtypes: cortico-cortical (CC) and cortico-subcortical (CS) neurons, which broadly correspond to L5a and L5b neurons, respectively. Previous studies have revealed distinct morphological and physiological properties between these two subtypes. It is, however, poorly understood how they integrate the information in the dendrites and transmit the outputs to the downstream during the sensory processing. Here, taking advantage of Cre-expressing transgenic

mouse lines, we investigated cell-type specific activation of apical dendrites in a whisker-based tactile detection task. We found that L5 CS neurons (labeled in Sim1-Cre) in the primary somatosensory cortex responded to detected whisker stimuli with increased dendritic calcium activity, while CC neurons (in Tlx3-Cre) showed no change or a slight decrease in dendritic activity, indicating cell-type specific roles in sensory perception. To track the information flow that underlies this distinct dendritic integration, we present preliminary evidence for upstream monosynaptic connectivity of individual subtypes using rabies virus-based tracing methods.

Disclosures: **N. Takahashi:** None. **S. Nierwetberg:** None. **M. Larkum:** None.

Poster

223. Barrel Cortex: Tactile Discrimination

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 223.08/Z32

Topic: D.04. Somatosensation: Touch

Support: Whitehall Foundation BSF-2013033

Title: Representation of object position in somatosensory cortex during object localization

Authors: *J. A. CHEUNG, P. S. MAIRE, J. KIM, E. CHANG-SING, S. A. HIRES
Neurosciences, USC, Los Angeles, CA

Abstract: Our sense of touch is critical for interacting with the world. It allows us to locate objects and create an interactive spatial map. Yet our understanding of how the brain represents basic tactile features, such as object positions, is still in its infancy. Here, we utilize a reward paradigm that incentivizes head-fixed mice to whisk using a single whisker and identify a pole along a continuous range of object positions along an anterior-posterior axis. Our results reveal that mice can discriminate with millimeter precision along this horizontal axis. During active behavior, juxtacellular loose-seal electrophysiological recordings were targeted to L3 and L5b of the barrel column of the single whisker. Excitatory and inhibitory cell types were discriminated through optogenetic-tagging of inhibitory cells. Our preliminary results have identified 18/34 excitatory cells in L5b and 3/14 in L3 that represent tuning to the azimuthal angle of the whisker at touch. 2/12 units recorded outside the barrel column for both L3 and L5b show tuning to whisker angle at touch. Our collection of L5b single units and their preferred firing at specific touch positions tile the sampling space. We further characterize the tuning of these neurons to sensory and motor variables to determine the basis of the object location tuning. These results together reveal a potential neural code for how mice discriminate objects along a horizontal axis in S1, and that L5b stands as an ideal candidate site for integrating tactile and motor information in order to generate a representation of object positions at touch.

Disclosures: **J.A. Cheung:** None. **P.S. Maire:** None. **J. Kim:** None. **E. Chang-Sing:** None. **S.A. Hires:** None.

Poster

223. Barrel Cortex: Tactile Discrimination

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 223.09/AA1

Topic: D.04. Somatosensation: Touch

Support: Wellcome Trust

ERC

BBSRC

MRC

Title: Two-photon all-optical interrogation of mouse barrel cortex during a sensory discrimination task

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Abstract: To identify causal links between sensory stimuli, neural activity, and behaviour it is important to combine behavioural psychophysics with approaches for measuring and manipulating neural activity with cellular resolution. Recent developments in simultaneous 'all-optical' two-photon calcium imaging and optogenetic photostimulation are ideally suited for this type of causal investigation (Packer *et al*, 2015). Importantly, the coupling of a programmable spatial light modulator (SLM) into the photostimulation light path enables neurons to be selectively targeted for photostimulation based on their functional identity – which is not possible using conventional optogenetic strategies. We harnessed this novel technology in combination with a two-alternative forced choice (2AFC) perceptual decision-making task to investigate sensory stimulus encoding in barrel cortex in head-fixed mice. Mice were trained to discriminate brief deflections of the left/right C2 whisker by licking left/right at two lick ports. Varying the left/right deflection amplitude ratio yielded reliable sigmoidal psychometric behaviour. Implantation of a chronic glass imaging window and viral co-expression of a calcium indicator (GCaMP6s) and an optogenetic actuator (C1V1) in layer 2/3 in the C2 barrel permitted all-optical interrogation of neural circuitry during behaviour. During task performance, a small proportion of sampled L2/3 neurons showed responses that were modulated by contralateral stimulus amplitude and behavioural choice. Results from excitatory and inhibitory one-photon optogenetic experiments showed that given ambiguous sensory evidence, increasing/decreasing activity in unilateral barrel cortex optogenetically biases choice towards the

contralateral/ipsilateral stimulus response respectively. We are currently performing two-photon photostimulation experiments to target stimulus and choice-informative neurons specifically during behaviour to explore the mechanisms by which sensory information is encoded in cortical circuits, and how this information may influence behaviour.

Disclosures: O.M. Gauld: None. **A.M. Packer:** None. **L.E. Russell:** None. **M. Hausser:** None.

Poster

223. Barrel Cortex: Tactile Discrimination

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 223.10/AA2

Topic: D.04. Somatosensation: Touch

Support: Wellcome Trust

ERC

BBSRC

MRC

Title: Manipulating behavior with targeted two-photon optogenetic activation of different functional sub-classes of cortical neurons in mouse barrel cortex

Authors: *H. W. DALGLEISH, A. M. PACKER, L. E. RUSSELL, M. HAUSSER
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Abstract: Neocortex is one of the most recently evolved areas of the mammalian brain and is thought to be critically involved in computations underlying complex behaviors. Cortical microcircuits are composed of functionally heterogeneous sub-classes of neurons, even among neurons sharing the same genetic identity. This makes it difficult to investigate how each sub-class contributes to driving behavior. Here we have harnessed the ability to optically interrogate functionally defined neurons at cellular resolution using simultaneous two-photon calcium imaging and optogenetics to examine the contribution of functionally defined neuronal subclasses to behaviour. We developed an operant conditioning paradigm that relies on the targeted activation of specific groups of 70 - 100 neurons in L2/3 barrel cortex to drive reliable behavior in head-fixed mice. This method has several advantages over previous techniques. Firstly, we can read out the functional phenotype of neurons in the population before choosing which sub-class we want to target. Secondly, we can flexibly modulate the identities of neurons that we target on a trial-by-trial basis, allowing us to compare the impact of different sub-classes of neurons within the same animal. Finally, we can read out the activity of the local network

during behavioral training. We have so far used this technique to estimate the minimum number of spikes in a random subset of neurons required to drive reliable behavior. While performance is robust to the dropout of small numbers of neurons in a stimulation pattern, each activated neuron is not equal in its ability to drive behavior. We are currently using a battery of tests to classify neurons based on their sensory responsiveness, coupling to network activity and spontaneous activity levels to elucidate which elements of neuronal identity are privileged in the ability of neurons to drive behavior.

Disclosures: H.W. Dalgleish: None. **A.M. Packer:** None. **L.E. Russell:** None. **M. Hausser:** None.

Poster

223. Barrel Cortex: Tactile Discrimination

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 223.11/AA3

Topic: D.04. Somatosensation: Touch

Support: Medical Research Council grant number MR/P006639/1

Ministerio de Economia y Competitividad grant numbers BFU2011-23049 (co-funded by European Regional Development Fund), BES-2012-052293

Valencia Regional Government grant numbers ACOMP2010/199, PROMETEO/2011/086

University of Sussex internal research development fund

Title: Learning and recognition of tactile temporal sequences by mice and humans

Authors: M. BITZIDOU[1], M. BALE[1], A. PITAS[1,2], *M. MARAVALL[1]
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Abstract: The world around us is replete with stimuli that unfold over time. When we hear an auditory stream like music or speech or scan a texture with our fingertip, physical features in the stimulus are concatenated in a particular order, reflected in patterns of spiking evoked in sensory receptors. To make sense of the stimulus, this temporal patterning must be decoded and recognized by the brain. How this occurs is poorly understood.
To gain insight into temporal sequence discrimination and its underlying mechanisms, we explored the capacity of mice and humans to learn tactile sequences defined by their temporal patterning over hundreds of milliseconds. We developed a task in which a mouse or human had to recognize a continuous modulated noise sequence delivered to the whiskers or fingertips. The

target GO sequence differed from NO-GO sequences only in that the order of their constituent segments was temporally scrambled. We developed variants of the task suitable for combination with electrophysiological and two-photon recording of neuronal population activity. Both mice and humans efficiently performed tactile sequence learning. Mouse performance relied mainly on detecting relative changes in noise amplitude over time, whereas humans appeared to have access to more cues, including the duration of noise modulation segments.
Neurons at the earliest cortical stages of somatosensory processing are sensitive mainly to the current stimulus value, with little integration over time (1,2). Thus, the sites for integration and recognition of temporally patterned stimuli are likely to reside at later stages of cortical processing. This behavior provides an assay for exploring the underlying circuit mechanisms.
1. Pitas, A., Albarracin, A.L., Molano-Mazon, M., and Maravall, M. (2016). Variable Temporal Integration of Stimulus Patterns in the Mouse Barrel Cortex. Cereb Cortex *in press*, https://doi.org/10.1093/cercor/bhw006
2. McGuire, L.M., Telian, G., Laboy-Juarez, K.J., Miyashita, T., Lee, D.J., Smith, K.A., and Feldman, D.E. (2016). Short Time-Scale Sensory Coding in S1 during Discrimination of Whisker Vibrotactile Sequences. PLoS Biol *14*, e1002549.

Disclosures: **M. Bitzidou:** None. **M. Bale:** None. **A. Pitas:** None. **M. Maravall:** None.

Poster

224. Somatosensation: Stimulus Features and Response Properties

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 224.01/AA4

Topic: D.04. Somatosensation: Touch

Title: Demixing the perception of duration and intensity in vibrotactile behavior

Authors: *A. TOSO[1], A. FASSIHIZAKERI[2], F. PULECCHI[3], S. SORELLA[3], M. E. DIAMOND[4]
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Abstract: We investigated how human subjects and rats can flexibly extract both duration and intensity from a single vibrotactile stimulus. In Experiment 1, both rats and humans learned to compare either (i) the relative mean speeds of two sequential vibrations, or else (ii) their relative durations. In Experiment 2, human subjects had to estimate either (i) the duration of a single vibration or (ii) its intensity, by scaling their judgment through a slider. In both experiments, perceived duration depended on stimulus intensity while, symmetrically, perceived intensity depended on stimulus duration.
We developed a behavioral model that explains perceived intensity and duration as a non-linear temporal summation of instantaneous speed:

$$P_{\text{Intensity,Duration}} = k \cdot \sum_{t=1}^{T} sp_t^{\alpha_{I,D}} \cdot e^{\pm \frac{t}{\tau_{I,D}}}$$

Where sp is instantaneous speed, T is stimulus duration, $P_{I,D}$ is the final perceived stimulus intensity and duration, α and τ are free parameteres. The exponents α and τ are task dependent: α would be large and τ small for intensity judgment, while α would be small and τ large for duration judgment. To test our model, we introduced ramping stimuli, where the original vibration was multiplied by a linear sloping function, while conserving its mean speed.
Human and rat subjects judged ramping-up stimuli as longer in duration, but weaker in intensity; the opposite was true for ramping-down stimuli. These results demonstrate that duration and intensity perception are modulated by the integration of vibration speed values following an exponentially growing and decaying function, respectively.
Next, we searched for the neuronal signatures of the duration-intensity confound. Neuronal activity was recorded in behaving rats, during both an intensity and a duration discrimination task, from barrel cortex and premotor cortex. Results are now being analyzed.
Overall our findings support the idea that the representations of stimulus duration and stimulus intensity are intermixed in the brain. While both percepts arise from the accumulation of vibration events, the temporal profile of accumulation changes according to the behavioural task.

Disclosures: **A. Toso:** None. **A. Fassihizakeri:** None. **F. Pulecchi:** None. **S. Sorella:** None. **M.E. Diamond:** None.

Poster

224. Somatosensation: Stimulus Features and Response Properties

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 224.02/AA5

Topic: D.04. Somatosensation: Touch

Support: NIH U01 1U01NS094302-01

Swiss National Science Foundation Early Postdoc Mobility Fellowship

NIH NRSA T90DA032466

NIH U01 1U01MH106027-01

NIH NRSA F31NS089412

NIH R01NS085447

Title: Integration of bilateral tactile stimuli in the somatosensory cortex of the awake mouse

Authors: *A. PALA, B. CHEN, C. J. WHITMIRE, G. B. STANLEY
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Abstract: Humans use both of their hands to obtain and compare information about the nature and spatial location of objects. Primate studies have highlighted the role of the corpus callosum in sensorimotor behaviors involving both sides of the body, as well as the presence of neurons with bilateral receptive fields in both primary (S1) and secondary (S2) somatosensory cortices. However, the principles underlying integration of bilateral sensory signals at the level of individual neurons in S1 and S2 are largely unknown.
Here, we investigated individual neuronal responses to unilateral and bilateral sensory stimuli in whisker S1 and S2 of the awake mouse. Unilateral tactile information reaches neocortex at the level of S1 barrel cortex of the contralateral hemisphere, and to a lesser extent at the level of contralateral S2, which receives most of its sensory signals via axonal projections from S1. Homologous and heterologous callosal connections enable interhemispheric propagation of tactile signals between S1 and S2 of the left and right hemispheres.
We recorded local field potential (LFP) and action potentials from neurons in S1 and S2 using multi-channel laminar silicon probes. We targeted these areas by performing intrinsic optical signal imaging, and then recorded sensory responses evoked by unilateral and bilateral single-whisker stimuli across neocortical layers 2/3 to 6. Preliminary measurements obtained using a galvo-controlled stimulator to deliver precisely timed unilateral and bilateral passive deflections of the whisker revealed the presence of neurons with contralateral, ipsilateral and bilateral receptive fields in both S1 and S2. Further investigations of the laminar and cell-type specificity of the evoked responses in these two cortical areas will contribute towards understanding the neural code for the representation and integration of bilateral sensory information.

Disclosures: **A. Pala:** None. **B. Chen:** None. **C.J. Whitmire:** None. **G.B. Stanley:** None.

Poster

224. Somatosensation: Stimulus Features and Response Properties

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 224.03/AA6

Topic: D.04. Somatosensation: Touch

Support: DFG Forschungsstipendium WA 3862/1-1

U01 - NIH 1U01NS094302-01

NIH R01NS085447

Title: Pushing the perceptual boundary towards optimal performance in a detection task with changing stimulus statistics

Authors: *C. WAIBLINGER, P. Y. BORDEN, M. F. BOLUS, G. B. STANLEY
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Abstract: Psychophysical studies in animal models have become indispensable to study neuronal correlates of perception and decision making processes. In this context, simple behavioral readouts are often considered to provide a direct measure of perceptual sensitivity. However, these readouts might result from a complex interplay of sensory as well as hidden non-sensory variables which can lead to a mis-estimation of perceptual sensitivity, making neurometric-psychometric comparisons difficult. In order to better understand the interplay of sensory and non-sensory variables we used concepts from signal detection theory and trained rats on a standard whisker detection task with changing difficulty levels. Specifically, once expert level was achieved, we systematically varied the task difficulty by changing the statistical distribution of whisker velocities while measuring the animal‘s perceptual threshold and corresponding rate of accumulated reward. Inspection of the psychometric function revealed that subjects were able to consistently shift their decision criterion across experimental blocks to become more sensitive when confronted with weaker stimuli and this effect was reversible when switched back to the original stimulus distribution. Although the measured hit rate increased for whisker velocities that were part of the weaker stimulus distribution, it never reached hypothetical performance levels that would result in reward accumulation matching previous quantities. Hence, we suggest that the partial shift of the psychometric curve reflects the animal’s attempt to compensate for a reduced amount of reward as a result of increased task difficulty but this process is intercepted by perceptual limits and task effort. Our preliminary findings suggests that the high variability in behavioral performance seen in standard psychophysical paradigms such as the detection task used here likely corresponds to the animal’s internal economical model taking into account recent stimulus history and balancing the amount of reward and the amount of effort.

Disclosures: C. Waiblinger: None. **P.Y. Borden:** None. **M.F. Bolus:** None. **G.B. Stanley:** None.

Poster

224. Somatosensation: Stimulus Features and Response Properties

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 224.04/AA7

Topic: D.04. Somatosensation: Touch

Support: NIH 1U01NS094302

NIH R01NS085447

NIH 1U01MH106027

Swiss National Science Foundation (SNSF) Early Postdoc Mobility fellowship

Title: A predictive framework to define the spatial and temporal scale of local cortical state in the awake animal from multi-electrode array recordings in mouse somatosensory cortex

Authors: *A. J. SEDERBERG, A. PALA, G. B. STANLEY
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Abstract: Signatures of global brain states are observed in local measures of ongoing neural activity, such as the substantial low-frequency component of the local field potential (LFP) and intracellular membrane potential in primary sensory areas characteristic of some types of anesthesia, some phases of sleep, and periods of quiet wakefulness. These signatures of state are well-known to affect cortical responsiveness and can account for some amount of trial-by-trial variability in response to controlled sensory stimuli, but a full characterization of the spatial and temporal scales of such local measures of state in the awake animal is lacking. While extracellular recordings from large arrays of electrodes have the potential to reveal these features, there are challenges in identifying the most relevant components of such high-dimensional datasets.

From recordings of the LFP and single-unit spiking activity acquired on 32-channel silicon probes in somatosensory cortex of awake mice, we systematically explore predictive spatial and temporal relationships between recorded signals during spontaneous and sensory-evoked activity, drawing on tools developed for machine learning as well as classical dimensionality reduction methods. We posit that such predictive relationships distill the most relevant elements of the spatially extended measurement of local state.

To begin to explore such relationships, we built a simple, non-dynamical spatial model to reconstruct the LFP at a particular location using the LFP recorded on other channels. As expected, highly accurate predictions (r-squared over 0.95) of a particular channel require predictor channels to be nearby. Preliminary results suggest that this length scale is highly channel location-dependent, possibly reflecting the spatial extent of cortical layers. In a separate set of analyses, we used support vector machine (SVM) classifiers to identify pre-stimulus patterns that are predictive of sensory-evoked response amplitude. Early results show interesting spatial trends: a group of superficial channels could be used to predict evoked response magnitude across the entire array, while a group of deeper-layer channels were predictive only of evoked response size in the deeper channels. Each of these analyses suggest the specific sets of channels that can be combined without loss of predictive power. These results are a step toward a data-driven framework in which to define characteristics of ongoing activity that are predictive of variability in cortical activity in the awake animal.

Disclosures: **A.J. Sederberg:** None. **A. Pala:** None. **G.B. Stanley:** None.

Poster

224. Somatosensation: Stimulus Features and Response Properties

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 224.05/AA8

Topic: D.04. Somatosensation: Touch

Support: Studienstiftung des deutschen Volkes

Title: Neuronal correlates of socio-sexual behavior in the somatosensory cortex of freely interacting rats

Authors: *K. HARTMANN, M. BRECHT
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Abstract: Intraspecific social and sexual behaviors are crucial for the survival in gregarious species such as rats. It is unclear, however, how social information is represented in the rodent forebrain. Since social interactions in rats often involve tactile cues, we wondered how social information is represented in the somatosensory cortex (S1). Earlier work of our group documented prominent responses to mystacial vibrissae mediated facial touch in the barrel cortex. Here, single neurons responded stronger to conspecifics than to objects, and also appeared to discriminate between the sex of the interacting partner and their sexual status (Bobrov et al., 2014). In contrast to our earlier work, in which we restricted social interactions to facial touch, we now aimed at studying neuronal representation of a variety of interactions in completely free social contexts. To this end we combined wireless acquisition of neuronal data with multi-modal surveillance (low speed videography and ultrasonic vocalizations). Our current work focused on the S1 trunk region. We were interested in this cortical representation as the trunk is activated in a variety of socio-sexual behaviors such as huddling, tickling and mounting. We performed extracellular recordings in the trunk region of S1 (male Long Evans rats, n = 3) while they interacted with conspecifics of both sexes. Neuronal responses (99 single units) were studied in relation to 2356 interactions. Of the various behaviors that were characterized (for frequency and duration), the most abundant were anogenital sniffing (20%), facial touch (25%), grooming of conspecific (12%) and sniffing of urine (9%) of all social behaviors. Preliminary neuronal analysis indicates that a large percentage of S1 trunk neurons respond significantly to social interactions. Compared to other responses observed in free behavior the magnitude of the social responses was impressive. Several neurons increased their firing rate 6 to 10 fold during mounting behavior, while being less responsive during all other interactions. In total, 39% of neurons responded when mounting occurred. Sexual behavior seemed to strongly engage neurons somatosensory cortex trunk region. It also appeared that neurons in S1 respond significantly to interactions that do not include direct tactile stimulation of the trunk like sniffing

urine, facial touch and anogenital sniffing. Our findings suggest that neurons somatosensory cortex trunk region integrate social information.

Disclosures: K. Hartmann: None. **M. Brecht:** None.

Poster

224. Somatosensation: Stimulus Features and Response Properties

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 224.06/AA9

Topic: D.04. Somatosensation: Touch

Support: NSF Grant CRCNS-IIS-1208118

NIH Grant R01-NS091439

Title: Whiskers in airflow: Bending, vibrations, and the responses of trigeminal ganglion neurons to sustained airflow in the rat whisker system

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Abstract: The rodent vibrissal (whisker) system is commonly studied in the context of tactile perception and sensorimotor integration. We recently demonstrated that rats also use their whiskers during anemotaxis, i.e., when localizing an airflow source[1]. We have therefore undertaken a series of studies to investigate the mechanical and neural basis for the vibrissal-based sensing of airflow.

In initial work, we demonstrated that whiskers bend primarily in the direction of the airflow, bending magnitude scales with airflow speed, and whiskers vibrate around their new deflected position[2]. In the present work, we quantified these mechanical vibrations and characterized the responses of primary sensory neurons in the trigeminal ganglion (Vg) to a sustained airflow stimulus.

In the first of two experiments, we quantified the three-dimensional (3D) vibrations of whiskers during airflow stimulation using high-speed stereo videography. As expected, we found that as airflow speed increases, the magnitude of whisker vibrations increases. More surprisingly, we found that as airflow speed increases, the average direction of the whisker vibrations changes from parallel to the direction of airflow to perpendicular to the direction of airflow.

In a second experiment, we recorded from Vg neurons in anesthetized rats during presentation of an airflow stimulus at different speeds and from different directions. The average firing rate of Vg neurons increases with airflow speed, and depends on airflow direction. Additionally, we showed that the firing patterns of Vg neurons are related to the intrinsic vibration modes of the

whisker.
Taken together with our earlier studies on whisker bending in response to airflow, the results described here suggest a possible neural representation for both whisker bending and vibration under airflow stimulation.
References:
[1] Yu YSW, Graff MM, Bresee CS, Man YB, Hartmann MJZ. Whiskers aid anemotaxis in rats. *Sci Adv* 2:e1600716(2016).
[2] Yu YSW, Graff MM, Hartmann MJZ. Mechanical responses of rat vibrissae to airflow. *J Exp Biol* 219, 937-948(2016).

Disclosures: Y.S. Yu: None. **N.E. Bush:** None. **M.J.Z. Hartmann:** None.

Poster

224. Somatosensation: Stimulus Features and Response Properties

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 224.07/AA10

Topic: D.04. Somatosensation: Touch

Support: NIH F31-NS092335

NIH R01-NS093585

Title: Encoding of 3D mechanics in primary sensory neurons of the rat vibrissal-trigeminal system

Authors: *N. E. BUSH[1], A. RESULAJ[1], S. A. SOLLA[2,3], M. J. HARTMANN[4,5]
[1]Interdepartmental Neurosci. Program, Northwestern Univ., Evanston, IL; [2]Physiol., Northwestern Univ., Chicago, IL; [3]Physics and Astronomy, [4]Biomed. Engin., [5]Mechanical Engin., Northwestern Univ., Evanston, IL

Abstract: The rodent vibrissal-trigeminal system offers a unique and accessible window into sensorimotor and cortical processing. The responses of whisker-sensitive primary sensory neurons in the trigeminal ganglion (Vg) have traditionally been described in terms of positions and velocities (kinematics). More recent work has brought to light a novel and more nuanced understanding of the sensory inputs into this system. Specifically, it has been shown that Vg neurons more directly represent tactile information in the form of forces and moments (mechanics) rather than the traditional kinematic variables. These findings allow us to understand how the brain represents and encodes information at its earliest stage, before it diverges into parallel processing pathways. One shortcoming of these recent studies is that they have been restricted to two-dimensional (2D) whisker projections based on a top-down camera view. Given that the whisker moves out of the plane significantly, a three-dimensional (3D)

approach is crucial for characterizing the relationship between whisker mechanics, kinematics, and Vg neuron activity. In this study, we used high-speed stereo-videography to create a 3D representation of entire whiskers during passive deflection while simultaneously recording activity from corresponding whisker-responsive Vg neurons. Mechanical models of 3D whisker bending allow us to quantify the full set of forces and moments in 3D. This approach allows us to correlate the responses of several functional types of Vg neurons with the observed and calculated 3D mechanical and kinematic inputs.

Disclosures: **N.E. Bush:** None. **A. Resulaj:** None. **S.A. Solla:** None. **M.J. Hartmann:** None.

Poster

224. Somatosensation: Stimulus Features and Response Properties

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 224.08/AA11

Topic: D.04. Somatosensation: Touch

Support: PROTOTOUCH EU FP7 project 317100

DeTOP EU H2020 project 687905

Title: Human low-threshold mechanoafferent responses to pure changes in friction during sliding motion produced by the StimTac device

Authors: *M. DIONE[1], R. WATKINS[1], E. VEZZOLI[2], B. LEMAIRE-SEMAIL[2], J. WESSBERG[1]
[1]Univ. of Gothenburg, Goeteborg, Sweden; [2]L2EP Univ. Lille1, Villeneuve d'Ascq, France

Abstract: Understanding the neural code characterizing the touch of natural textures is a current challenge, especially in the context of the growing development of nerve-wired limb prostheses that aim at restoring natural sensations in amputee users. When touching natural textures, such as silk or sandpaper, many components interact to give rise to a complex sensory feedback and percept, such as friction, high-frequency vibrations, compliance of the material, etc. In the present study, we used microneurography to record from Aβ-mechanoreceptive afferents in awake human subjects and used a custom-built tactile stimulator device, the StimTac, to study the effects of varying friction on the afferent responses in isolation from other texture properties. The StimTac employs new technology based on unperceived ultrasonic vibration delivered by piezoelectric motors, to reduce the friction between the fingertip and the material on the surface of the device. The device was placed on a force controlled robotic platform to deliver passive stimulation to the participant's skin. Four distinct protocols were used in which we manipulated: (1) the mean vibration amplitude of the device, (2) the mean vibration amplitude with a stepwise return to a base value, (3) the rise time to reach a given amplitude, which affects the sharpness

associated with a change in friction, and (4) a fast alternation between decrease/increase in amplitude to recreate grating-like patterns (in the absence of an actual texture). Single unit afferent responses were recorded from the median nerve in 3 FAI, 1 FAII, 3 SAI and 3 SAIIs. The number of protocols that were tested in each afferent unit depended on the stability of the recording. In protocol 1 & 2, an increase in vibration amplitude of the device resulted in a consistent decrease in lateral tangential force, and a concomitant decrease in the intensity of the response of the afferents. This was true for all afferent classes, but less consistent in units that showed directional sensitivity. In protocol 3, with decreased sharpness of the change in friction, there was an increase in latency to the first spike, whereas the intensity of the response was not consistently affected. In protocol 4, two of the six tested units, 1 FA1 and 1 SA2, effectively followed the frequency of friction modulation, suggesting the possibility to recreate complex sensations based on friction modulation only. This study gives us the means to understand how dynamic and static aspects of the frictional component of surfaces are coded in humans, in isolation of surface texture, hence advancing the understanding of human tactile sensations.

Disclosures: **M. Dione:** None. **R. Watkins:** None. **E. Vezzoli:** None. **B. Lemaire-Semail:** None. **J. Wessberg:** None.

Poster

224. Somatosensation: Stimulus Features and Response Properties

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 224.09/AA12

Topic: D.04. Somatosensation: Touch

Support: NINDS R01NS073119

Title: Computational modeling of mechanotransduction currents in Merkel cell-neurite complexes

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Abstract: Distinct firing properties among touch receptors are influenced by multiple, interworking anatomical structures. Our understanding of the functions and crosstalk of Merkel cells and their associated neurites – the end organs of slowly adapting type I (SAI) afferents – remains incomplete. Piezo2 mechanically activated channels are required both in Merkel cells and in sensory neurons for canonical SAI responses in rodents; however, a central unanswered question is how Piezo2-dependent rapidly inactivating currents give rise to sustained action potential volleys in SAI afferents. The computational model herein synthesizes

mechanotransduction currents originating from Merkel cells and neurites, in context of skin mechanics and neural dynamics. Its goal is to mimic distinct firing patterns from wildtype, epidermal-specific Piezo2 knockout animals, which lack mechanically activated currents in purified Merkel cells, and Atoh1 knockout animals, which completely lack Merkel cells. The developed generator function includes a Merkel-cell mechanism that represents mechanotransduction currents and downstream voltage-activated conductances (slower decay of current) and a neurite mechanism that represents Piezo2 (faster decay of current). To mimic sustained firing in wildtype animals, a longer time constant was needed than the 200 ms observed for mechanically activated membrane depolarizations in rodent Merkel cells. One mechanism that suffices to fit slowly adapting firing patterns is to introduce an ultra-slowly inactivating current in sensory neurons. Thus, we propose that Piezo2-independent mechanisms are present in Merkel cells the intact skin, which would also reconcile differences in firing observed between Piezo2 and Atoh1 knockout animals.

Disclosures: E.A. Lumpkin: None. **G.J. Gerling:** None. **L. Wan:** None. **Y. Wang:** None. **B.U. Hoffman:** None.

Poster

224. Somatosensation: Stimulus Features and Response Properties

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 224.10/AA13

Topic: D.04. Somatosensation: Touch

Support: Prodex, IAP VII/19 DYSCO (BELSPO, Belgian Federal Government)

EU-FP7 Marie Curie Initial Training Network PROTOTOUCH (Grant Agreement no. 317100)

Swedish Research Council grant 3548

Title: Human tactile afferents are sensitive to the onset of active exploration on flat surfaces

Authors: *D. GUEORGUIEV[1,2], M. DIONE[3], R. H. WATKINS[3], A. MOURAUX[1], J.-L. THONNARD[1], J. WESSBERG[3]
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Abstract: The contact forces experienced by our fingers while we manipulate objects or touch surfaces guide our capacity to interact efficiently with the world around us. Recent studies have shown that the contact forces during the onset of the exploratory movement exhibit rich dynamics, which are thought to contribute to the tactile perception of smooth materials. The contribution of the onset of touch to human tactile discrimination has already been shown for

glass and polymethyl methacrylate (PMMA), which have similar friction but differ by their molecular properties since glass is hydrophilic and PMMA is hydrophobic. However, little is known about how the contact forces are encoded by mechanoreceptors during the two initial phases of exploratory movements: (1) the loading phase on the material, during which the finger contact is immobile, and (2) the partial slip phase, during which the outer part of the contact area starts slipping. Our study aims at analysing the activity of the different types of afferents during these two phases.
We recorded from Aβ-mechanoreceptive afferents in awake human subjects using microneurography. Participants were asked to actively explore two flat materials, glass and PMMA, by producing lateral sliding movements with their middle, index or ring finger for 20 seconds. The task was repeated in three speed conditions: slow (2.7 cm/s), fast (10 cm/s) and at a freely decided speed. The activity in seven afferents was recorded from the left median nerve (1 FA1, 2 FA2, 4 SA2). Finger position, the lateral and normal force applied on the textures were also recorded. For all units, at least one condition was completed on one of the two materials. Except for the slow condition, afferent activity was generated at the onset of movement, both during the loading phase and the partial slip phase. For three of the explored units, data was obtained when sliding the finger on the two tested materials (1 FA2, 2 SA2). Only the FA2 unit showed a significantly different temporal activation pattern between the two materials in the fast and the free conditions. The average intensity of firing was similar for both materials but its peak occurred in the loading phase for glass and in the end of the partial slip phase for PMMA. This difference occurred solely for the forward swipe and no material related difference in the afferent activity was observed during the backward movement. These results support the hypothesis that rich skin dynamics at the onset of tactile exploration trigger strong activity in tactile afferents. Because the dynamics of this activity appears to depend on the properties of the explored material, it may contribute to our ability to discriminate smooth materials.

Disclosures: **D. Gueorguiev:** None. **M. Dione:** None. **R.H. Watkins:** None. **A. Mouraux:** None. **J. Thonnard:** None. **J. Wessberg:** None.

Poster

224. Somatosensation: Stimulus Features and Response Properties

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 224.11/AA14

Topic: D.04. Somatosensation: Touch

Title: Dorsal root ganglion neuronal population responses to tactile stimuli in rhesus monkey hand

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Abstract: Manipulation of objects in everyday tasks relies heavily on the availability of somatosensory feedback. Despite intact spinal and supraspinal structures, mechanoreceptors are lost after limb amputation. The dorsal root ganglia (DRG) is an attractive target for recording population activity of peripheral responses because it is composed of cell bodies for all primary afferents, is compact, and is mechanically stable. The purpose of this study was to measure natural firing patterns at the population level to understand how touch is encoded in the DRG. 4x10 and 5x10 penetrating multielectrode arrays were implanted in the C7 and C8 DRG of a Rhesus monkey under anesthesia (isoflurane 1-2%). Cutaneous and proprioceptive units were identified via manual stimulation of the arm and hand, progressing from fingertips, palm, and dorsal surface of the hand to the forearm and upper arm. In total 76 cutaneous units originating in the forearm (19), upper arm (3), palm (15), back of the hand (11), and all of the fingers (28) were identified. Of the units in the fingers, 2, 6, 3, 4, and 13 were from digits 1-5, respectively. These units spanned distal, middle, and proximal regions of the digits. Some units clearly displayed neuronal firing patterns similar to the four main classes of mechanoreceptors, while the dynamics of other neurons were less clear. In addition, units from the C7 array had receptive fields that were primarily located in digits 2 and 3, while units from the C8 array had receptive fields in digits 4 and 5. Once units were identified, the distal joint of the monkey's index finger (D2d) was immobilized to a pedestal. Rotating drums with 10 different textured materials, as well as oriented bars and random dots, were passed over the monkey's finger while neural responses were recorded. This experiment was repeated on the distal regions of digits 4 and 5. The recorded neural activation patterns reflect how sensations of texture are encoded in the DRG. Vibratory stimuli were applied to the palm and middle and proximal regions of digits 2, 4, and 5. Further work is needed to understand how these neural firing patterns can be used to map microstimulation in the DRG for development of a neuroprosthetic device that aims to restore sensation.

Disclosures: **M.F. Liu:** None. **J.E. Winberry:** None. **T.W. Simpson:** None. **B.P. Delhaye:** None. **E.R. Oby:** None. **A.D. Degenhart:** None. **M.A. Urbin:** None. **A.P. Batista:** None. **R.A. Gaunt:** None. **L.E. Fisher:** None. **S.J. Bensmaia:** None. **D.J. Weber:** None.

Poster

224. Somatosensation: Stimulus Features and Response Properties

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 224.12/AA15

Topic: D.04. Somatosensation: Touch

Support: CMRPG3C0464

US Army Research Laboratory CAST 076910227001 and ARL-74A-HR53

Title: Illusory motion reversal in touch

Authors: *Y.-C. HSU[1,2,3,4,5], C.-H. HUNG[6], C.-P. HUNG[7,8,9], C.-I. YEH[2,3,4], Y.-C. PEI[5,6]
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Abstract: The motion correspondence problem occurs when the motion of an object is inferred from the spatial-temporal pattern of sensory inputs. To determine the motion, the human brain must keep track of the identity of a local contour over time. That is, the similarity of elements between two images must be identified before an object's direction of motion can be inferred. In short, it has to determine "what went where" before in the global motion is determined (Dawson, 1991). In touch, psychophysical experiments have shown that the perceived direction is biased toward the direction orthogonal to local edges (Carter et al., 2008). Pei et al. (2010) have found that the majority of direction-selective neurons in S1 are also orientation selective. Further, their preferred direction is orthogonal to their preferred orientation, consistent with the perceptual bias and with the direction-encoding properties of neurons in primary visual cortex. It remains unclear whether somatosensory and visual systems apply the same rule to resolve the ambiguity caused by the correspondence problem. We hypothesized that the tactile correspondence problem is mediated by tuning properties of neurons in the primary somatosensory cortex (S1). In the present study, we studied an archetype of the correspondence problem in which the subject perceives a grating as moving in a direction opposite to its veridical scanning direction, a tactile analogue to the visual wagon-wheel illusion. We presented scanning sinusoid gratings or random dot patterns to the subject's fingerpad with a variety of spatiotemporal parameters, including wavelength (1, 2, 4 mm spacing and random dot balls), speed (20, 40, 80, 160, 320 mm/s) and indentation amplitude (250, 500 μm). Subjects were asked to indicate via mouse click the perceived direction on a circle presented on monitor. A majority of the recruited subjects perceived scanning direction that was opposite to the veridical direction. The illusion was most profound at stimuli presented at the lowest speed (20mm/s), but had no significant effect at other speed or wavelength parameter manipulations. The illusion was observed for gratings but not random dots, indicating edge orientation was necessary to produce this illusion. Also, the indentation depth did not affect the illusion strength. In summary, we report that illusory motion reversal also exists for touch and that S1 cortical neurons that process both direction and orientation may account for this illusion.

Disclosures: **Y. Hsu:** None. **C. Hung:** None. **C. Hung:** None. **C. Yeh:** None. **Y. Pei:** None.

Poster

224. Somatosensation: Stimulus Features and Response Properties

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 224.13/AA16

Topic: D.04. Somatosensation: Touch

Support: Boğaziçi University Research Fund (BAP) no. 10XP1

Title: Effects of morphometric variables and epidermal peeling on the mechanical impedance of rat glabrous skin

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Abstract: We previously showed that human tactile detection thresholds are positively correlated with mechanical resistance of the glabrous skin (Yıldız and Güçlü, 2013; Somatosens. Mot. Res. 30, 37-47). In the current study, we measured several morphometric variables (SCT: stratum corneum thickness, VT: viable epidermal thickness, ET: epidermal thickness, DT: dermal thickness, TT: total skin thickness) and mechanical impedance at two locations (hindpaw digit and sole) of rat glabrous skin. The measurements were repeated also after peeling most of the epidermis by NaBr treatment of the other hindpaw. Ten anesthetized Wistar albino rats were used for the mechanical measurements which were obtained at two sinusoidal stimulation frequencies (40 and 250 Hz). The animals were subsequently perfused for routine histological preparation. 10 μm-thick sections were stained with hematoxylin and eosin. The slides were analyzed under light microscope and by an imaging software. All morphometric variables were significantly higher at the digit compared to the sole (p's<0.001). In the intact skin, stimulation frequency had a significant main effect on the modulus of the impedance (2-way ANOVA, p = 0.018), regardless of the location. The impedance was higher at 250 Hz. No significant effects due to frequency or location were found for the peeled skin. However, the resistance component of the impedance was significantly lower in the peeled skin compared to the intact skin at both frequencies and locations (40 Hz: digit p<0.001, sole p=0.039; 250 Hz: digit p<0.001, sole p=0.005). Moreover, by peeling, the reactance component of the impedance changed to positive values (i.e. more inertia) from negative values (i.e. more springiness) obtained with intact skin. The resistance was somewhat positively correlated with SCT at intact skin (40 Hz: digit p=0.060, sole p<0.001) and with the remaining epidermal thickness at peeled skin (40 Hz: digit p<0.001, sole p<0.001). No correlations were found at 250 Hz. The results suggest that upper layers of the epidermis primarily mediate the resistance component of mechanical impedance, which depends on the anatomical thickness especially at mid-frequencies of the tactile sensitivity range.

Disclosures: C. Gok: None. **B. Guclu:** None.

Poster

224. Somatosensation: Stimulus Features and Response Properties

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 224.14/AA17

Topic: D.04. Somatosensation: Touch

Support: Brain Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT & Future Planning (2016M3C7A1904988)

Title: Simulating temporal spiking patterns of slowly adapting afferents for constant tactile pressing stimuli

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Abstract: Firing activity of slowly adapting (SA) sensory afferents is supposed to encode tactile information regarding skin stretch, compressing and deformation. It implies that we may be able to represent tactile information from the computational modeling of firing activity. Recent studies have proposed a computational model to decode the information of instantaneous forces from the firing rates of SA afferents to time-varying pressure stimuli. Yet, no attempt has been made to build a computational model to describe the firing activity of SA afferents in response to constant pressure stimulation. Since stimulus information remains unchanged in this case, a model should be able to represent a time-varying firing pattern of SA afferents during stimulation. The present study aims to develop such an encoding model representing the firing pattern of SA afferents under various levels of sustained pressure stimulations: 0.1, 1, 10, 50, 100 and 300 mN. Each stimulus was given to the skin of the hindlimb of mice in an ex-vivo experimental setup for 20 s with an inter-stimulus interval of 60 s. Spike data during the stimulations were acquired from 7 SA type-I and 2 SA type-II afferents. As expected, the firing rates of SA afferents was increased sharply after stimulus onset and decreased slowly as the stimulation persisted. Accordingly, the inter-spike interval (ISI) appeared to nonlinearly increase over the stimulation period. We fitted a curve to the ISI sequence using polynomial functions and found that the 5-th order polynomial with quintic and constant terms fitted the best. In addition, the total spike counts of SA type-II afferents during stimulations was increased by increases in the pressure level whereas those of SA type-I afferents was maximum at the pressure level of 50 mN and began to decrease with higher pressure levels. These observations were related to variations of the model coefficients. The leading coefficient of the polynomial model was smallest for the 50-mN pressure in SA type-II afferents whereas it continuously decreased as the pressure level increased. We could also generate an ISI sequence of 20 s to mimic the firing activity of SA afferents for a given pressure level by using the fitted curve as the mean of a

gamma distribution with fixed shape parameter of 2. Using the generated ISI sequence, a synthetic spike train could be readily constructed. It suggests a possibility that a specific level of tactile pressure could be virtually sensed by stimulating SA afferents with a model-based artificially generated spike train. Also, our computational model may help us understand further how the firing pattern of SA afferents encode tactile pressure information.

Disclosures: **J. Park:** None. **S. Jung:** None. **T. Yang:** None. **S. Kim:** None.

Poster

224. Somatosensation: Stimulus Features and Response Properties

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 224.15/AA18

Topic: B.04. Ion Channels

Support: P01NS-057228.

Title: Neural contributions to firing behavior of Ia muscle spindle afferents

Authors: S. N. HOUSLEY[1], *P. NARDELLI[2], T. J. BURKHOLDER[3], T. C. COPE[4]
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Abstract: Recent demonstrations of the presence and systematic distribution of multiple ion channels in the primary endings of muscle spindle Ia afferents suggest their involvement in sculpting the spike trains produced by muscle stretch (Bewick and Banks, 2015; Carrasco et al., 2017). Earlier studies nevertheless attribute the Ia firing profile entirely to viscoelastic properties of the spindle and surrounding tissues (Lippold et al., 1960; Houk et al., 1992; Proske et al., 1993; Nichols and Cope, 2004). The latter assertion is not definitively established, however, and technical challenges preclude direct electrophysiological tests of the non-neuronal vs neuronal contributions to Ia firing patterns. In the present study, we took a different indirect approach to probe the role of neuronal ion channels in producing various features of Ia firing.
In terminal experiments on adult female Wistar rats under isoflurane anesthesia, action potentials were recorded intra-axonally in dorsal roots from single Ia afferents in response to repeated ramp-hold-release stretches of triceps-surae muscles. These firing responses were alternately pre-conditioned by a train of antidromic action potentials induced in one and the same Ia afferent by intra-axonal current injection. The conditioning stimuli were intended to perturb neural encoding without creating any mechanical disturbance. The differential effects of altering antidromic stimulation duration (*ms*), frequency (pps), and time preceding muscle stretch were examined for the effects on stereotypic features of muscle spindle encoding: initial bursting, dynamic response, adaption and static phase firing were examined.
Preliminary results revealed robust and selective effects of conditioning on Ia firing. Pre-

conditioning strongly attenuated both the initial burst at the onset of muscle stretch and static firing during the hold phase. Although, our indirect approach is unable to isolate the contributions of specific neuronal structures, our results provide insight into parameters that underlie neuronal encoding in primary afferents. These findings, in combination with our lab's recent discovery that multiple voltage-gated Na channels are expressed in muscle spindle encoding regions (Carrasco et al., 2017) reopens interest in isolating the neural contribution to stereotypic features of muscle spindle encoding from those solely attributed to a mechanical origin (Lippold et al., 1960; Emonet-Denand and Houk, 1969).

Disclosures: S.N. Housley: None. **P. Nardelli:** None. **T.J. Burkholder:** None. **T.C. Cope:** None.

Poster

225. Auditory and Vestibular Systems: Periphery

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 225.01/AA19

Topic: D.06. Audition

Support: David M. Rubenstein Fund for Hearing Research

F31 DC016538

Title: LIN28B/let-7 gradient is critical for tonotopic specialization of auditory hair cells

Authors: *M. PRAJAPATI[1], *M. PRAJAPATI[1], E. J. GOLDEN[2], A. DOETZLHOFER[1]
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Abstract: The inner ear cochlea is the organ responsible for the detection of sound. Its spiral-shaped sensory epithelium contains mechanosensory hair cells (HCs) that transduce sound waves into neuronal signals. This sensory epithelium is tonotopically organized such that it detects high frequency sounds at the base of the spiral and low frequency sounds at the apex. Features of this tonotopic specialization include graded differences in the size and gene expression of HCs. Little is known of the mechanisms that produce tonotopic specialization in the mammalian cochlea. Here, we investigate if LIN28B/*let-7* signaling instructs this tonotopic specialization. The RNA binding protein LIN28B and the functionally opposing *let-7* miRNAs are known regulators of growth and stemness. We have previously shown that opposing expression gradients of LIN28B and *let-7* in the cochlea regulate the timing of cell cycle exit and HC differentiation. Surprisingly, these gradients persist during the maturation and tonotopic specialization of HCs, with *let-7* highest expressed in basal HCs, and LIN28B expressed highest in apical HCs.

Based on these findings, we hypothesize that the LIN28B/*let-7* gradient informs tonotopic specialization of HCs. To test our hypothesis, we manipulated LIN28B/*let-7* levels in maturing HCs using LIN28B or *let-7g* overexpressing transgenic mice. To determine if these manipulations disrupt frequency-specific HC function, we recorded Auditory Brainstem Responses (ABRs) from these mice. Our hypothesis predicts that LIN28B overexpression will result in a more 'apical' identity of HCs. This would disrupt the function of the basal (high frequency) region of the cochlea. Indeed, ABRs from these mice revealed a severe deficit specifically in high frequency hearing, compared to control littermates. Histological analyses confirmed that these deficits are not due to HC loss. Conversely, overexpression of *let-7g* would cause HCs to have a more 'basal' identity, and a deficit in transduction of low frequency sound. Consistent with this prediction, mice overexpressing *let-7g* during HC maturation show deficits specifically in low frequency hearing, compared to control littermates. These results suggest that the LIN28B/*let-7* pathway plays a critical role in tonotopic specialization, with LIN28B activity conferring a more 'apical' identity to HCs, while *let-7* miRNAs impart a more 'basal' identity. Our findings provide insight into the mechanisms that determine tonotopic identity of HCs. This will benefit efforts in HC regeneration therapies, as generating appropriately specialized HCs along the cochlea will be critical to the perception of meaningful sound.

Disclosures: M. Prajapati: None. **E.J. Golden:** None. **A. Doetzlhofer:** None.

Poster

225. Auditory and Vestibular Systems: Periphery

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 225.02/AA20

Topic: D.06. Audition

Title: The g-secretase inhibitor NXT596 increases auditory hair cells and restores function *In vivo*

Authors: *M. M. POON[1], C. DESPONTS[1], A. DEARIE[1], S. GELLAR[1], K. STEBBINS[1], G. CABRERA[1], K. I. LORRAIN[3], C. LEE[1], J. SEIDERS[1], J. ROPPE[1], C. CHAPMAN[1], J. WALDHAUS[4], J. WICHMANN[5], S. HELLER[4], R. K. JAGASIA[6], P. PRASIT[1], D. LORRAIN[2]
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Abstract: Regeneration of auditory hair cells in the organ of Corti is one promising avenue of hearing restoration following damage. Previous studies have documented the ability of γ-secretase inhibitors (GSI) to block Notch signaling and induce hair cell regeneration by way of support cell transdifferentiation. The majority of these mechanistic studies were done in a neonatal rodent setting using commercially available inhibitors, such as DAPT (*N*-[(3,5-

Difluorophenyl)acetyl]-L-alanyl-2-phenyl]glycine-1,1-dimethylethyl ester) or LY411575 which can be used, but are not optimized, for local *in vivo* delivery to the adult organ of Corti. Here, we characterize a potent, selective γ-secretase inhibitor, NXT596, and demonstrate its ability to inhibit Notch signaling and induce auditory hair cells across mouse and human *in vitro* and *ex vivo* cellular contexts. Moreover, by way of local delivery, we are able to achieve extended drug exposure in the adult mouse cochlea and show modest recovery of function following noise-induced hearing loss at multiple frequencies as assessed by auditory brainstem recording.

Disclosures: The Disclosure Block has exceeded its maximum limit. Please call Tech support at (217) 398-1792 for more information.

Poster

225. Auditory and Vestibular Systems: Periphery

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 225.03/AA21

Topic: D.06. Audition

Title: Comprehensive analysis of N-glycans in the stria vascularis of the rat cochlea

Authors: *Y. NONOMURA[1], S. SAWAMURA[1], T. HIGUCHI[1], F. NIN[1], S. UETSUKA[2], S. OKUDA[1], A. HORII[1], S. TAKAHASHI[1], S. NATSUKA[1], H. HIBINO[1]
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Abstract: Hearing is an essential sensation in animals including human. The cochlea of the inner ear contains an extracellular fluid, endolymph, which exhibits a highly positive potential of +80 mV and a high [K^+] of 150 mM. The electrochemical properties in the endolymph, which are essential for hearing, are maintained by a network of numerous membrane proteins in the stria vascularis. In the stria, we previously detected approximately 1800 kinds of membrane proteins involved in the homeostasis of the endolymph (Eur J Neurosci, 2015).
In general, glycosylation occurs on Asn residue (N-linked) or alternatively on Ser/Thr residue (O-linked) of the proteins. N-linked glycans play pivotal roles in protein folding, trafficking and the modulation of the activities of the membrane proteins. Recent studies have reported the congenital hearing loss caused by the deficiency of the enzymes in N-glycan synthesis. However, little is known about the glycosylation of the proteins in the cochlea. We previously performed the proteomic analysis of the stria and detected 16 enzymes for N-glycan synthesis. In this study, we comprehensively analyzed the profile of the N-linked glycans in the stria vascularis by using a combination of three different HPLCs. We identified 74 N-glycans and illustrated biosynthetic pathway of N-glycans in the stria. These resources will be useful to further understand molecular mechanisms underlying the audition and deafness.

Disclosures: **Y. Nonomura:** None. **S. Sawamura:** None. **T. Higuchi:** None. **F. Nin:** None. **S. Uetsuka:** None. **S. Okuda:** None. **A. Horii:** None. **S. Takahashi:** None. **S. Natsuka:** None. **H. Hibino:** None.

Poster

225. Auditory and Vestibular Systems: Periphery

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 225.04/AA22

Topic: D.06. Audition

Support: AIIMS New Delhi

Title: Stereological estimation of total capillary length in the human stria vascularis

Authors: S. PILLUTLA[1], T. G. JACOB[1], A. THAKAR[2], D. N. BHARDWAJ[3], *T. ROY[4]
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Abstract: Stria Vascularis (SV) is the vascular epithelium in the lateral wall of the cochlea that secretes endolymph into the scala media and helps in generating the endocochlear potential that is essential in the mechanism of hearing. Alteration in the morphology of the SV or loss of its capillaries can occur with ageing, and lead to decreased hearing known as metabolic or chemical presbycusis. There are no studies on ageing changes in the total length of the capillaries in the SV in humans. Therefore, in this study we estimated the total length of the capillaries in human SV using a spaceball probe in four different human cochleae derived from people, who died at ages of 31, 42, 58 and 72 years, after obtaining necessary ethical clearances. In brief, parts of the temporal bones, containing the cochlea were dissected out, fixed with 4% buffered paraformaldehyde (0.1M phosphate buffer, pH 7.4) and decalcified in 10%EDTA solution. Tissues were then dehydrated, embedded in celloidin, sectioned at 40µm and every 10^{th} section was stained with hematoxylin and eosin and used for estimating the total length of the SV capillaries. The SV was identified on the lateral wall of the cochlear duct, extending from the attachment of Reissner's membrane to the spiral prominence. Capillaries were identified by the presence of RBCs and endothelial cells under the 40X objective lens and their total length was estimated using space balls probe (StereoInvestigator, MBF, Vermont, USA). The total volume of SV was also estimated by using the Cavalieri Estimator on the same sections. The total length of the capillaries in each case was as follows: 31y- 322.64 mm, 42y- 281.13 mm; 58y- 258.72 mm; 72y- 199.90 mm. The total volume of the SV in each of these cases was 0.57 mm^3, 0.58 mm^3, 0.51mm^3, 0.50 mm^3, respectively. There was a gradual decrease in the total length of SV capillaries with increasing age; however, the volume of the SV showed no changes with increasing age. Probably, the decreasing total length of the SV capillaries with increasing age

contributes significantly to the phenomenon of presbycusis. This needs to be confirmed further with more numbers in each age group and other techniques to understand the mechanism underlying these changes.

Disclosures: S. Pillutla: None. **T.G. Jacob:** None. **A. Thakar:** None. **D.N. Bhardwaj:** None. **T. Roy:** None.

Poster

225. Auditory and Vestibular Systems: Periphery

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 225.05/AA23

Topic: D.06. Audition

Support: NIH/NIDCD 1R01DC013798 (SMR)

Title: Pulsed infrared stimulation modulates endoplasmic reticulum calcium cycling in spiral ganglion neurons

Authors: *S. RAJGURU[1], S. RINCON[1], J. SINGH[2], E. BARRETT[3], J. BARRETT[3]
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Abstract: Pulsed infrared radiation (pIR) is being investigated as a non-invasive technique for altering activity of excitable cells such as nerve and muscle. pIR stimulation is reported to evoke action potentials in auditory and vestibular neurons, but to decrease activity in some hippocampal neurons. Some effects of IR stimulation might be mediated or modulated by changes in cytosolic (and/or nuclear) [Ca^{2+}]. Here, we have investigated IR-induced [Ca^{2+}] changes in cultured spiral ganglion neurons. Inner ear cells were cultured from p3-5 mice and loaded with fluorescent Ca^{2+}indicators. The Ca^{2+} changes evoked by focused pIR (1863nm, 250pps, 200µs, varied radiant energies) delivered using a 200 or 400 µm optical fiber were measured by tracking fluorescent intensity within cells using a confocal microscope. The images were analyzed with IMAGEJ and MATLAB. Temperature changes induced by pIR were measured using Rhodamine B and a microthermistor. Results show that pIR induces transient increases in cytosolic and nuclear [Ca^{2+}]. Additionally, the [Ca^{2+}] responses were significantly reduced when Ca^{2+} release from the endoplasmic reticulum (ER) was pharmacologically blocked. Major pathways for Ca^{2+} release from ER are ryanodine receptors and inositol tri-phosphate (IP_3) receptors that mediate Ca^{2+}-induced Ca^{2+} release. We present pharmacological evidence that both of these receptors contribute to the IR-induced increase in intracellular [Ca^{2+}] in spiral ganglion neurons. This [Ca^{2+}] increase was produced by thermal changes in response to pIR stimulation. The IR pulses produced a rapid but transient 2-11^{o}C increase in temperature. Neither of these pathways is known to display the temperature-dependence required to mediate

the effects of IR. To identify the temperature-sensitive mechanism mediating the pIR effects on ER, we targeted specific Transient Receptor Potential (TRP) channels that are expressed in ER membranes. Results suggest that the IR-induced increase in cytosolic [Ca^{2+}] in these neurons shares multiple properties resembling those of certain temperature-dependent TRP channels. The photocontrol of intracellular organelles and signaling pathways altering neural activity using INS could lead to new applications in neuroscience.

Disclosures: S. Rajguru: None. **S. Rincon:** None. **J. Singh:** None. **E. Barrett:** None. **J. Barrett:** None.

Poster

225. Auditory and Vestibular Systems: Periphery

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 225.06/AA24

Topic: D.06. Audition

Support: ICMR- 45/19/2012-Ana/BMS

Institutional research grant

Title: Stereological investigation and morphometric classification of spiral ganglion neuron in the human cochlea

Authors: *C. KAUR[1], P. KUMAR[2], T. G. JACOB[2], A. THAKAR[3], D. BHARDWAJ[4], T. C. NAG[2], T. ROY[2]
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Abstract: Spiral ganglion (SG) neurons are continually exposed to noise and additional environmental factors, therefore proper morphological and morphometric evaluation are crucial for aging research. Classically, on the basis of the morphology two types of neuronal cell bodies has been described in the mammalian SG. Majority (95%) of the SG neurons are large type I and the remaining 5-10% are classified as small type II. In the present study seven adult human cadaveric heads were obtained from the forensic science mortuary, with approval from institutional ethics committee. These were accident victims within the age groups 11-30 years old and had no history of hearing loss before death. To estimate neuronal population and their volumes the temporal bones containing the SG were dissected, fixed and decalcified with 10% ethylenediaminetetraacetic acid. Cochleae were serially sectioned (30μm) in the coronal plane. Cryosections were stained with Cresyl Violet using standard protocol. Every seventh section was used for estimation of the total number of neurons (Optical Fractionator). The volume of soma and its nucleus was estimated by (Nucleator) with StereoInvestigator software (Microbrightfield Inc. VT, USA). The mean estimated total number of spiral ganglion neurons (SGNs) was 27,653

± 3199. The mean volume of neurons and their nucleus was 3164 ± 928 $um^3$and 139 ± 39 um^3 respectively. Hierarchical cluster analysis of volumetric data of neurons and their nucleus was used to identify similarities among them. We observed four different populations of SGNs in human inner ear in the age groups 11-30 years. The mean neuronal number in cluster 1, 2, 3 and 4 was 487, 952, 205 and 53 respectively. The mean volume of neurons in cluster 1, 2, 3 and 4 was 3112 ± 1385 um^3, 2488 ± 1409 um^3, 5769 ± 1361 $um^3$and 7487 ± 931 um^3 respectively. The mean volume of neuronal nucleus in cluster 1, 2, 3 and 4 was 193 ± 69 um^3, 92 ± 73 um^3, 188 ± 49 um^3 and 350 ± 55 um^3 respectively. We estimated human SGNs population, volumetric data of neurons along with their nucleus in age groups 11-30 years. The present method of evaluating the neuronal morphology would be valuable for future studies of the spiral ganglion neurons in various physiological including aging and pathological conditions.

Disclosures: C. Kaur: None. **P. Kumar:** None. **T.G. Jacob:** None. **A. Thakar:** None. **D. Bhardwaj:** None. **T.C. Nag:** None. **T. Roy:** None.

Poster

225. Auditory and Vestibular Systems: Periphery

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 225.07/AA25

Topic: D.06. Audition

Title: Eye movement-related eardrum oscillations (EMREOs): A biomarker for visual-auditory spatial integration in the auditory periphery?

Authors: *D. L. MURPHY[1], K. G. GRUTERS[1], D. W. SMITH[2], C. A. SHERA[3], J. M. GROH[1]
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Abstract: Visual and auditory signals that arise from coincident locations in space often fuse to produce a combined visual-auditory percept, such as lip reading cues that facilitate speech comprehension. A critical problem for this process is that the visual and auditory systems employ different methods of determining the locations of stimuli. The visual system uses retinal activation location and the auditory system evaluates interaural timing and intensity differences as well as spectral cues. In species that move their eyes with respect to the head, there is no fixed relationship between these cues, and representations must be adjusted with each change in eye position if the brain is to determine whether a visual and an auditory cues spatially coincide.
• Eye movements have been shown to modulate auditory activity in several brain regions such as the inferior colliculus, auditory cortex, parietal cortex, frontal eye fields, and the superior colliculus, but where eye movement-related signals first contribute to auditory processing is not known. One possibility is the auditory periphery. Outer hair cells, or motile neurons in the cochlea, and the middle ear muscles are under descending control from the brain, providing a possible route of transmission of information about eye movements to the auditory periphery.

• To test this hypothesis, we used a microphone to record movements of the eardrum in human subjects (n=10, 16 ears) performing saccades to visual targets. We found that the eardrums oscillated in conjunction with eye-movements, despite the absence of any delivered sound. These oscillations began at least 10ms before the start of any given saccade. The initial phase and magnitude of these eye-movement related eardrum oscillations (EMREO) was dependent on saccade origin, direction, and length. This relationship suggests it containsthat information the necessary information to facilitate for visual-auditory spatial integration reaches the auditory periphery. EMREOs are a candidate biomarker that may prove useful for assessing the cause of multisensory integration deficits in affected populations., although the exact means by which it does so remains uncertain.

Disclosures: D.L. Murphy: None. **K.G. Gruters:** None. **D.W. Smith:** None. **C.A. Shera:** None. **J.M. Groh:** None.

Poster

225. Auditory and Vestibular Systems: Periphery

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 225.08/AA26

Topic: D.08. Vestibular System

Support: NIH grant DC014368

NASA grant NNX13AL99G

Title: Vestibular afferent discharge in otoferlin-null mice

Authors: *L. F. HOFFMAN[1], T. J. PRINS[1], M. G. PAULIN[2], F. E. SCHWEIZER[1]
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Abstract: Otoferlin is a component of the presynaptic molecular assembly in inner ear hair cells that is critical to the linear relationship between depolarization-induced calcium influx and transmitter exocytosis. Mutations of the otoferlin gene in humans result in a form of hereditary deafness (DFNB9). Within the vestibular epithelia, type I hair cells within the utricular striola of otoferlin-null (*Otof-/-*) mice were shown to be incapable of depolarization-induced exocytosis, while in extrastriola hair cells it appears that the linear relationship between depolarization-induced local calcium and exocytosis is modified. Despite this loss and/or modification of crucial presynaptic mechanisms for stimulus-induced exocytosis, spontaneous discharge in afferent neurons was intact, while vestibular evoked potentials exhibited higher thresholds and lower amplitudes when compared to WT and heterozygous *(Otof+/-)* animals. This model offers the opportunity, therefore, to investigate modifications in the hair cell and afferent local circuit within vestibular epithelia due to partial dysfunction resulting from altered presynaptic

mechanisms. In this investigation we probed the hair cell/afferent circuit through recording spontaneous and evoked discharge characteristics from individual primary afferent neurons projecting to the semicircular canal cristae, and compared these metrics to WT and *Otof+/-* animals. In the data collected thus far we have found little evidence of modifications in spontaneous discharge recorded from afferents in *Otof-/-* compared to WT or *Otof+/-*. Furthermore, in confirmed semicircular canal afferents (e.g. those responding to rotational stimuli) afferent response dynamics from *Otof-/-* preparations were similar to those of WT and *Otof+/-* for stimuli up to 1 Hz. We are exploring the responses to higher stimulus frequencies and velocities. We are currently probing the discharge of afferents that are unresponsive to rotation in *Otof-/-* animals; while such afferents in our preparations could reflect the absence of stimulus-evoked exocytosis in canal afferents, they could also reflect utricular afferents that retain sensory functionality (e.g. project from extrastriolar utricular regions) despite the lack of otoferlin.

Disclosures: L.F. Hoffman: None. **T.J. Prins:** None. **M.G. Paulin:** None. **F.E. Schweizer:** None.

Poster

225. Auditory and Vestibular Systems: Periphery

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 225.09/AA27

Topic: D.08. Vestibular System

Support: 1P03DC015091-01

American Otological Society

Title: Selective modulation of vestibular afferent activity via thermal inhibition of efferents

Authors: *V. RAGHU, R. SALVI, S. MANOHAR, S. G. SADEGHI
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Abstract: Study of vestibular efferent neurons by stimulatory methods in the past, has unearthed important characteristics about afferent - efferent relationship. Nonetheless, the individual functional roles of efferents or the two kinds of afferents (irregular and regular) are largely unknown. Vestibular efferents are believed to be predominantly unmyelinated or thinly myelinated and various reports in the past have shown that such fibers are susceptible to inhibition by heat. Here, we provide evidence that heat inhibits vestibular efferents, resulting in a selective inhibition of irregular afferents. The vestibular nerve was exposed by suctioning part of the cerebellum through a craniotomy in anesthetized CB57BL/6 mice. Single unit extracellular recordings were made from the vestibular nerve near Scarpa’s ganglion and afferents were

divided into regular and irregular firing based on a normalized coefficient of variation of interspike intervals of their resting discharge. We used a temperature-controlled saline perfusion to inundate the 8th nerve from origin to the point of entry into the brainstem. The rate of the temperature change inversely affected the resting rates of irregular afferents, but directly affected that of regular fibers. However, when temperature was sustained (25 to 37 ^{o}C), the firing rates reverted back to the original values or higher values in the inhibited neurons. Next, heat was generated locally by a 460 nm (blue) LED-coupled fiber optic (3-10 s at 10 Hz, 90% duty cycle) over three distinct locations: (1) entrance of vestibular nerve to the brain stem, (2) brain stem midline (i.e., crossing efferent fibers), and (3) near Scarpa's ganglion. LED stimulation in the first two positions resulted in 40-100% decreases in resting rate in 97% of irregular fibers, while most regular afferents (85.7%) showed little to no inhibition. This effect had an onset delay of ~ 500 ms and the firing rate returned to baseline ~10 s after stimulation termination. In contrast, LED stimulation over the ganglion, exerted an excitatory effect on all regular afferents whereas it produced a mixed excitatory/ inhibitory effect on irregulars. Opto-thermal inhibition of irregular afferents could be attained at different temperatures (25-37 ^{o}C) sustained by saline perfusion over the nerve. Our findings are consistent with observed efferent-mediated excitation of irregular afferents. Selective inhibition of irregular afferents by changes in temperature could be used for studying the role of different afferents pathways. We propose that lack of activity of efferents could result in inhibition of irregular afferents and compromise vestibular function and plasticity.

Disclosures: V. Raghu: None. **R. Salvi:** None. **S. Manohar:** None. **S.G. Sadeghi:** None.

Poster

225. Auditory and Vestibular Systems: Periphery

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 225.10/AA28

Topic: D.08. Vestibular System

Support: NIH NIDCD Grant 1R03DC015091-01

Title: Cholinergic and GABAergic modulation of membrane properties of vestibular afferent calyx terminal

Authors: *S. G. SADEGHI, Y. RAMAKRISHNA
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Abstract: Calyx afferent terminals contain voltage sensitive potassium channels that are open at resting membrane potentials. As a result, calyces (at least those in central areas of the neuroepithelium) do not readily depolarize, show little spontaneous activity, and have strong spike frequency adaptation. The efferent vestibular pathway to the periphery could potentially

modulate membrane properties of calyces. However, there is limited information about the properties and function of different efferent neurotransmitters and their receptors. Here, we provide evidence that activation of muscarinic acetylcholine receptors (mAChR) and metabotropic GABA-B receptors increase the speed and sensitivity of calyx responses. Patch clamp recordings were obtained from calyces in central areas of the cristae of the horizontal and superior canals in 14 – 21 day old rats *in vitro*. In voltage clamp, application of mAChR agonist oxotremorine-M decreased voltage sensitive currents in calyces, resulting in a shift of their activation curve to the right. In current clamp, mAChR agonist application converted responses of calyces from a single spike at the beginning of step depolarizations to more sustained firing of up to 20 spikes/s throughout the step. Furthermore, first spike latency and spike generation threshold decreased by ~50%. Application of KCNQ (voltage activated potassium channel) antagonists XE-991 and linopirdine resulted in a comparable effect as the muscarinic agonist, suggesting that the effect of mAChR is mainly mediated through decreased activity of KCNQ channels, consistent with previous studies in the vestibular ganglion. Similarly, application of GABA-B agonist baclofen also decreased voltage sensitive membrane currents and surprisingly, non-inhibitory changes like those observed with mAChR agonist: increased responses to step depolarizations, decreased first spike latencies, and decreased action potential thresholds. In some cases, calyces even showed spontaneous firing after baclofen application. Blocking BK potassium channels by iberiotoxin resulted in partial block of the excitatory GABA-B effect, as suggested by reports in the retina. Together, these findings suggest that cholinergic and GABAergic efferent inputs are required for sensitive and fast responses by calyx terminals and by extension, irregular afferents.

Disclosures: S.G. Sadeghi: None. **Y. Ramakrishna:** None.

Poster

225. Auditory and Vestibular Systems: Periphery

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 225.11/AA29

Topic: D.08. Vestibular System

Support: 01GQ1407 of the German BMBF

1R01DC014368

Title: Spike time regularity of horizontal canal afferent fibers as decisive factor for motion encoding in Xenopus laevis tadpoles

Authors: *K. D. GENSBERGER[1], M. WUEHR[2], L. F. HOFFMAN[3], M. G. PAULIN[4], H. STRAKA[5]
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Abstract: Head motion is transformed by the inner sensory epithelia into neuronal signals and transmitted as discharge by vestibular nerve afferents onto neurons in the hindbrain. Different thresholds, sensitivities and spike time regularity of individual vestibular afferents determine the signal content and the respective contribution during particular motion dynamics. Here, we studied the functional organization of vestibular afferent fibers in *Xenopus laevis* tadpoles at mid-larval stages. Horizontal semicircular canal afferents were extracellularly recorded in semi-intact preparations. Based on resting discharge rate regularity, afferents form a continuum, which for classification purposes can be separated into two groups. The first group of neurons had low resting rates of ~0.8 spikes/s and a more irregular discharge with a CV of ~0.7, whereas the second type had resting rates of up to 15 spikes/s and a more regular firing pattern with a CV of ~0.2. The differential dynamics of responses evoked by sinusoidal rotation at frequencies of 0.1-1 Hz and peak velocities of 6-60°/s corresponded to the distinction into two, likely overlapping, functional groups. During sinusoidal rotation at 0.5 Hz, the first group of afferents displayed brief bursts of activity that were phase-advanced by ~45° re peak head velocity, independent of stimulus magnitude. These units increased their gain over a larger range of stimulus frequencies (0.1-1 Hz) and amplitudes (6-30°/s), however responses were rendered half-rectified by the low resting rates. At frequencies between 2-4 Hz, the responses consisted of 1-3 spikes that were phase-locked within a narrow window of the stimulus cycle. The second group of afferents responded with modulated spike trains during sinusoidal rotation, which were largely in phase with peak head velocity. With increasing frequencies between 0.1-1 Hz, the gain augmented only slightly. At rotation frequencies between 2-4 Hz, these afferents continued to exhibit modulated responses with a relatively robust encoding of head velocity with comparable changes in discharge rates. The two encoding strategies are likely based on spike time regularity as decisive factor. Using bipolar band-limited noise (0-30 Hz) for galvanic vestibular stimulation with amplitudes of 30-100 µA, the prediction is that stochastic resonance modifies spike timing and differentially alters the sensitivity of the more regular and the more irregular afferents for rotational stimuli. This will allow testing if electrical noise influences the motion detection threshold of afferents in a fiber type-specific manner by shifting subthreshold stimuli above their detection level.

Disclosures: K.D. Gensberger: None. **M. Wuehr:** None. **L.F. Hoffman:** None. **M.G. Paulin:** None. **H. Straka:** None.

Poster

225. Auditory and Vestibular Systems: Periphery

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 225.12/AA30

Topic: D.08. Vestibular System

Support: NIH Grant K08DC011540

NIH Grant R01DC012564

Title: Vestibular function analysis in calcium and integrin binding protein 2 (CIB2) mice, a model for Usher syndrome type I gene

Authors: *T. MAKISHIMA[1], A. GIESE[2], N. SHIMIZU[1], B. VANDIVER[3], R. AURICH[3], Z. AHMED[2]
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Abstract: A mutation in the CIB2 gene causes Usher syndrome type 1 characterized by pre-lingual deafness, vestibular ataxia, and pre-adolescent development of visual dysfunction. CIB2 plays a crucial role in maintaining mechanoelectrical transduction in the cochlear hair cells. Our goal was to characterize the vestibular function in a transgenic strain of Cib2 mice (Cib2F915), which contains a mutation that leads to hearing loss in humans. Methods: Vestibular function characteristics of Cib2F915 mice and Cib2 knockout mice were assessed by horizontal vestibular ocular reflex (VOR) and otolith ocular reflex (OOR) in combination with pseudo-off vertical axis rotation. Results were compared among wild type (n=5), Cib2+/- heterozygous (n=6), Cib2 knockout (n=16), Cib2F915 heterozygous (n=10) and Cib2F915 homozygous (n=8) mice at ages 6 months and younger. The temporal bone was observed after Xgal staining and tissue clearing. Resutls: VOR gain and phase was similar in all groups. However, there was a trend in mutants having higher gain. In OOR, vertical eye position and horizontal eye velocity was similar among all genotypes. The vestibular organs and hair cells were intact in all genotypes. Conclusion: Cib2 mutant mice had comparable vestibular function to wild type mice at age < 6M, which was consistent with the normal morphology of the vestibular organs.

Disclosures: T. Makishima: None. **A. Giese:** None. **N. Shimizu:** None. **B. Vandiver:** None. **R. Aurich:** None. **Z. Ahmed:** None.

Poster

225. Auditory and Vestibular Systems: Periphery

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 225.13/AA31

Topic: D.08. Vestibular System

Support: VA Grant 1I01RX001986

NIH Grant DC000011

NIH Grant DC005188

NIH Grant DC015097

Title: Reduced vestibular function following noise exposure in rats

Authors: *C. E. STEWART[1], A. KANICKI[2], D. S. BAUER[2], T. D. JOSHI[2], C. O. HADLEY[2], H. K. HAQUE[2], R. A. ALTSCHULER[2], W. M. KING[2]
[1]Otolaryngology, Kresge Hearing Res. Inst., [2]Dept. of Otolaryngology, Kresge Hearing Res. Inst., Univ. of Michigan, Ann Arbor, MI

Abstract: The vestibular system plays a critical role in detection of head movements and orientation with respect to gravity and is essential for normal postural control. Due to their anatomical proximity to the cochlea, the otolith organs are exposed to sound pressure and are at risk for noise overstimulation. Clinical reports suggest a link between noise exposure and balance problems, but the structural and physiological basis for this linkage is not well understood. The goal of this study is to further our understanding of the effect of noise, in particular low frequency noise, on the peripheral vestibular system by correlating changes in eighth nerve activity, vestibular short latency evoked potentials (VsEPs), with (1) head postural control during normal locomotion and (2) changes to saccular afferent endings following noise exposure.Adult male Sprague-Dawley rats (400-450 g) were exposed to either 120 dB SPL (0.5-4 kHz) noise or sham conditions for six hours on a single day. Auditory function was evaluated by measuring auditory brainstem response (ABR) thresholds before and after noise exposure. Changes in vestibular function were assessed by measuring head postural stability and VsEP baselines before noise or sham exposure, and then comparing these baselines to measurements taken immediately following and up to 21 days after noise or sham exposure. After completing the final measurements, inner ears were collected for dissection, staining, and whole mount confocal microscopy to evaluate noise-induced pathology in afferents that terminate in the sacculus. Low frequency noise exposure produced measurable deficits in control of head posture and decrements in the numbers of stained calyces in the sacculus. Although partial recovery of the VsEP waveform was observed as early as three days post-noise, at three weeks there was still not complete recovery in most animals, consistent with a reduced number of calyceal endings. Reduced head postural stability, however, returned to pre-noise baseline by one week post-noise. These findings are consistent with previous literature, which assumed the VsEP represents activity of irregular calyx only and dimorphic afferents because of their large diameters and synchronous firing behavior in response to kinematic jerks. This finding presents a limitation of the VsEP for evaluation of vestibular dysfunction, since only activity of irregular afferents is assessed. Nevertheless, our data show that a single intense noise exposure causes a transient partial vestibular deficit similar to an auditory transient threshold increase after noise exposure.

Disclosures: C.E. Stewart: None. **A. Kanicki:** None. **D.S. Bauer:** None. **T.D. Joshi:** None. **C.O. Hadley:** None. **H.K. Haque:** None. **R.A. Altschuler:** None. **W.M. King:** None.

Poster

226. Auditory Processing: Neural Coding, Experiment, and Theory

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 226.01/AA32

Topic: D.06. Audition

Support: Wellcome Trust NIH PhD Studentship

Title: High accuracy categorization of macaque monkey identities and call types with convolutional neural networks

Authors: *C. D. MÁRTON[1,2], M. FUKUSHIMA[2,3,4], S. S. SCHULTZ[1], B. B. AVERBECK[2]
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Abstract: The representation of auditory information in the brain is still poorly understood, especially in higher sensory areas. Deep neural networks - themselves loosely inspired by brain architecture - have been shown to predict neural responses in visual cortex, including in high-order areas, and to produce representational structure across image categories similar to that of real neural ensembles in visual cortex (Yamins et. al. (2014), PNAS 111(23):8619-8624; Yamins & DiCarlo (2016), Nat Neurosci 19(3):356-365). In a first step towards examining the representational structure of auditory cortical neurons in macaques, we trained a 2-layer convolutional neural network (CNN) to distinguish among 10 different types of conspecific macaque vocalizations based on mel-scaled spectogram information. A hidden Markov Model (HMM) has previously achieved a classification performance of 75% correct (Averbeck & Romanski (2006), J Neurosci 26(43):11023-11033) on this very same set of 136 vocalizations. Our CNN achieved a classification performance of 87% correct on average (10-fold cross-validation; chance level: 10%), thus representing a ~10% higher performance than an HMM. CNN parameters were optimized for classification performance, and included weight decay and dropout terms to guard against overfitting. Training a CNN with the same configuration to distinguish among 8 different monkey identities based on mel-scaled spectograms of 7285 macaque coo-calls, we achieved a performance of 98% correct on average (10-fold cross-validation; chance level: 12.5%). In comparison, a linear multinomial classifier achieved a 92% correct classification performance averaged across the eight animals based on the modulation power spectrum (MPS) of the calls (Fukushima et. al. (2015), R. Soc. open sci. 2:150432). Taken together, these results show that artificial neural networks can accurately discriminate behaviorally relevant auditory signals based on spectral features - these may prove relevant to real auditory neural networks as well.

Disclosures: **C.D. Márton:** None. **M. Fukushima:** None. **S.S. Schultz:** None. **B.B. Averbeck:** None.

Poster

226. Auditory Processing: Neural Coding, Experiment, and Theory

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 226.02/AA33

Topic: D.06. Audition

Support: NIH 1K99DC015543 - 01A1

NIH NIDCD DC012557

Title: The significance of nominally non-responsive activity in auditory perception and behavior

Authors: *M. INSANALLY[1], I. CARCEA[1], B. F. ALBANNA[2], R. FROEMKE[1]
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Abstract: Spike trains recorded from the cortex of behaving animals can be complex, highly variable from trial-to-trial and therefore challenging to interpret. A fraction of cells exhibit trial-averaged responses with obvious task-related features such as orientation tuning in the visual cortex or pure tone frequency tuning in the auditory cortex. However, a substantial number do not appear to fire in a task-related manner. These cells - including cells in primary sensory cortex - typically comprise >50% of datasets yet are often neglected from analysis. Even cells with classical response profiles lose their stimulus representation during task-engagement without impairing behavior. These results suggest that cells with no discernible trial-averaged responses may play an underappreciated role in sensory processing and cognition. To understand their role, we devised a novel single-trial, spike-timing-based analysis to evaluate whether the activity of single-units recorded from auditory and frontal cortex encode task variables in rats trained on a go/no go frequency recognition task. Our algorithm evaluates the extent to which singe-unit responses encode task variables in time on individual trials (stimulus category and behavioral choice) by using the statistical prevalence of the interspike interval (ISI) on trials of a certain stimulus category (target vs. nontarget) or behavioral category (go vs. no-go). Using this analysis, we have made four discoveries: 1) Nominally non-responsive cells reveal hidden task information. The activity of cells that seem unresponsive (42/77 ACtx cells and 41/57 FR2 cells from six animals had neither significant tone-modulated activity or ramping activity; $p < 0.05$, 5,000 bootstraps) when trial-averaged often encode task-relevant information at levels comparable to responsive cells. 2) Excluding nominally non-responsive cells impairs decoding performance indicating the activity of nominally non-responsive cells is necessary for encoding behavioral variables. 3) Frontal cortex is more informative about task-relevant auditory stimuli than auditory cortex. Auditory cortex reliably responds to pure tones in untrained animals.

However, when tones take on behavioral significance, this information is encoded more accurately in frontal cortex suggesting that this region is critical for extracting task-relevant stimulus information. 4) Frontal cortex benefits most from decoding using small ensembles. Decoding performance in frontal cortex dramatically improves when using small ensembles whereas decoding from auditory cortex increases only marginally suggesting a highly redundant coding scheme in frontal cortex.

Disclosures: M. Insanally: None. **I. Carcea:** None. **B.F. Albanna:** None. **R. Froemke:** None.

Poster

226. Auditory Processing: Neural Coding, Experiment, and Theory

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 226.03/AA34

Topic: D.06. Audition

Support: DARPA TNT Grant

Title: Cortical map plasticity as a function of the duration of vagus nerve stimulation paired with an auditory stimulus

Authors: *E. BUELL[1], K. LOERWALD[3], M. BORLAND[1], C. KELLY[1], J. BUELL[1], M. FRECH[1], E. JENSEN[1], J. KURVARI[1], C. CHANDLER[1], M. P. KILGARD[2]
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Abstract: Repeatedly pairing stimulation of the vagus nerve with a sensory stimulus increases the number of responding cortical neurons. These changes have been observed in the primary auditory cortex (A1) when pairing a pure tone with VNS, as well as in the primary motor cortex when pairing a movement with VNS (Engineer et al., 2011; Porter et al., 2012). Patients with tinnitus have reported long-lasting relief from VNS treatment paired with tones outside their tinnitus frequency. However, no patient has yet reported having no perception of tinnitus as a result of this treatment. Inverted-U functions have been observed after altering the intensity of stimulation given per treatment session. Specifically, significant cortical changes were observed at 0.4-0.8 mA, but not at 1.2 or 1.6 mA (Borland et al., 2015). This function may exist in other parameters of VNS, as well. Although it is clear that VNS drives plasticity, optimal parameters under which this treatment is delivered remain undefined. The purpose of this project is to investigate how the duration of VNS can change the degree of map plasticity. Preliminary data suggests 125 ms of 30 Hz VNS paired with a 9 kHz tone does not yield cortical map changes that differ significantly from naïve animals. Conversely, 500 ms and 2000 ms of 30 Hz VNS significantly increases the number of neurons that respond to frequencies around the paired tone

stimulus. These results indicate the amount of cortical plasticity is dependent on the duration of vagus nerve stimulation.

Disclosures: **E. Buell:** None. **K. Loerwald:** None. **M. Borland:** None. **C. Kelly:** None. **J. Buell:** None. **M. Frech:** None. **E. Jensen:** None. **J. Kurvari:** None. **C. Chandler:** None. **M.P. Kilgard:** None.

Poster

226. Auditory Processing: Neural Coding, Experiment, and Theory

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 226.04/AA35

Topic: D.06. Audition

Title: Long-term activity dynamics of neuronal ensembles in mouse auditory cortex

Authors: *D. F. ASCHAUER[1], B. EPPLER[2], L. EWIG[2], M. KASCHUBE[2], S. RUMPEL[1]
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Abstract: A powerful advantage in the usage of modern imaging methods is the possibility to acquire the activity of large populations of neurons simultaneously. Two-photon calcium imaging in layer 2/3 of auditory cortex revealed that the activity of local neuronal ensembles encode broad sound categories into non-linear population response modes generating a basis set of perceptual categories (Bathellier et al., Neuron 2012; 76, 435-449). Chronic spine imaging studies have demonstrated that the connections between such local neuronal ensembles undergo significant remodeling throughout the lifetime of an animal and even in the absence of specific learning paradigms (Loewenstein et al., J. Neurosci. 2011; 31(26):9481-9488). At the same time, it seems obvious that for successful navigation in the environment, major brain functions such as the perception of sounds have to be highly stable and reliable, while at the same time our brains have evolved to allow for flexible integration of novel experiences to form associations to already known stimuli. How do neuronal circuits of the neocortex integrate these two requirements? Towards this goal, we have recorded the activity of large neuronal populations in the auditory cortex in response to sounds of awake mice over days to weeks. Single time point activity dynamics, such as number of responsive neurons and tuning to pure tone frequencies, were largely indistinguishable from one another indicative of stable baseline experimental conditions without learning. Interestingly, individual neurons showed a remarkable degree of representational flexibility whereby the magnitude of the response was correlated with its stability. This feature is reminiscent of the dynamics of individual spines, where the size of a spine correlates with its stability. Moreover, single time point statistics of neuronal ensemble activity showed, similar to previous studies, a strong clustering of activity patterns into discrete, non-linear response modes. Interestingly, we find high correlations in collective response

patterns from time point to time point with the occasional occurrence of abrupt transitions demonstrating a high degree of non-linearity. We aim to combine our experimental approach with a theoretical model of a neocortical circuit to reveal underlying mechanisms of this interplay between stability and volatility of sensory representations.

Disclosures: D.F. Aschauer: None. **B. Eppler:** None. **L. Ewig:** None. **M. Kaschube:** None. **S. Rumpel:** None.

Poster

226. Auditory Processing: Neural Coding, Experiment, and Theory

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 226.05/AA36

Topic: D.06. Audition

Support: BMBF project “FKZ 01GQ1507”

Title: How does structural volatility affect cortical representations?

Authors: *J.-B. EPPLER[1], D. F. ASCHAUER[2], L. EWIG[1], S. RUMPEL[2], M. KASCHUBE[1]
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Abstract: Even without any explicit learning paradigm, ongoing synaptic changes can be found in auditory cortex (e.g. Loewenstein et al., J. Neurosci. 2011; 31(26):9481-9488). How does this volatility in structural connections affect the functional properties of cortical circuits? We address this question in a model of population activity in mouse auditory cortex, to interpret ongoing parallel experiments employing chronic two-photon calcium imaging in the auditory cortex of awake mice. Previous experiments in mouse auditory cortex have shown that responses to complex sounds typically cluster into a near discrete set of activity patterns (Bathellier et al., Neuron 2012; 76, 435-449). Here we present a generic firing rate model that can reproduce key features of experimental data such as a near log-normal activity distribution and clustering in a parameter regime where recurrent connections are sufficiently heterogeneous and the network is dominated by inhibition. We use this model to study the impact of synaptic turnover on collective response properties. Changes in synaptic strength are assumed to follow a random process matching empirical rules derived for spine size changes observed in mouse auditory cortex (Loewenstein et al., J. Neurosci. 2011; 31(26):9481-9488). The model shows that gradual changes in the circuitry can induce rich dynamics in sensory representations: often, representations remain fairly stable over extended periods of time, interrupted by abrupt and strong transitions that can affect the responses to several stimuli simultaneously. Moreover, the overall degree of stability of stimulus responses depends more sensitively on the rate of change of inhibitory than excitatory connections. The model predicts a several-fold slower rate of change of inhibitory synapses to account for the degree of stability of representations that we

observe in the calcium data. We conclude that even subtle and random ongoing changes in synaptic connections can have a significant and highly nonlinear effect on the stability of sensory representations.

Disclosures: **J. Eppler:** None. **D.F. Aschauer:** None. **L. Ewig:** None. **S. Rumpel:** None. **M. Kaschube:** None.

Poster

226. Auditory Processing: Neural Coding, Experiment, and Theory

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 226.06/BB1

Topic: D.06. Audition

Support: NSF Grant 1515587

NIH Grant DC014765

Title: Reticulothalamic and intrareticular synaptic microarchitectures determine oscillatory and propagative properties of thalamocortical waves

Authors: *J. W. BROWN[1], A. TAHERI[3], R. V. KENYON[3], T. BERGER-WOLF[3], D. A. LLANO[2]
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Abstract: Recent experimental observations and modeling studies support both the existence and potential functional significance of “open-loop” thalamo-reticulo-thalamic synapses, in which neurons from the thalamic reticular nucleus are not reciprocally excited by the thalamocortical neurons they inhibit. We previously demonstrated that simulated open-loop thalamocortical networks are able sustain the propagation of spindle-like waves across the length of the network at a constant velocity. In the present study, we examine how systematically varying 14 synaptic weights within a simulated 9-neuron thalamocortical network alters the oscillatory and propagative properties of the waves the network supports. Utilizing regression algorithms, we demonstrate that specific individual synapses and synaptic clusters, comprising variously open- and closed-loop thalamo-reticulo-thalamic and intrareticular (GABAergic and electrical) microarchitectures within the network, are strongly correlated, both linearly and nonlinearly, with oscillatory and propagative wave dynamics. These findings are related to the thalamocortical physiology underlying both normal and pathological processes and compared to exclusively closed-loop models capable of approximating the same phenomena.

Disclosures: **J.W. Brown:** None. **A. Taheri:** None. **R.V. Kenyon:** None. **T. Berger-Wolf:** None. **D.A. Llano:** None.

Poster

226. Auditory Processing: Neural Coding, Experiment, and Theory

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 226.07/BB2

Topic: D.06. Audition

Support: NIH NIDCD R01DC015527

NIH NIDCD R01DC014479

PA Lions Hearing Research Foundation

NIH NIDCD R03DC013660-01

Burroughs Wellcome Fund Career Award

Human Frontiers in Science Foundation

Title: Auditory fear conditioning drives changes in frequency representation and functional organisation of neuronal populations in auditory cortex

Authors: *K. WOOD[1], R. BETZEL[2], C. F. ANGELONI[1], M. AIZENBERG[1], D. BASSETT[2], M. N. GEFFEN[1]
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Abstract: Everyday auditory behavior depends critically on learning-driven changes in auditory perception that rely on neuronal plasticity within the auditory pathway. Discriminative auditory fear conditioning (DAFC), a form of associative auditory learning, affects the fundamental auditory task of frequency discrimination acuity. Previous work has shown that the auditory cortex (AC) is required for this modulation and that DAFC induces changes in individual frequency tuning of cortical neurons, with the best frequency shifting toward the paired conditioned tone (CS+). However, how learning shapes frequency representation at the level of *neuronal populations* remains unknown. To understand the transformation in tone representation in AC before and after conditioning, we recorded activity of populations of hundreds of neurons simultaneously in AC of awake, head-fixed mice, tracking the same neurons over days, using two-photon imaging of Calcium activity. We then quantified changes in tone frequency-dependent responses and functional connectivity structure of these populations.
We found that over successive days, even prior to learning, tone-evoked responses of individual neurons were variable, with best frequency of neuronal tuning shifting from day to day.

However, when averaged over the neuronal population, the representation of tones within specific frequency bands was preserved. We then used a novel method, based on graph theory, to demonstrate that over the neuronal population, the spontaneous activity exhibited a clustered correlational structure. Specific clusters contained more tone responsive neurons than would be expected by chance suggesting an underlying functional structure.
Following learning, individual neurons exhibited shifts in best frequency both toward and away from CS+ or the unpaired CS-. However, over the neuronal population, there was an increase in activity in response to both CS+ and CS-. These changes in the response amplitude at CS+ and CS- were significantly correlated. After fear conditioning, the cluster structure of the network architecture was preserved.
Our study demonstrates that auditory fear conditioning drives changes in cortical neuronal populations both at local and global level, leading to enhanced representation of both the paired and the unpaired conditioned tones.

Disclosures: K. Wood: None. **R. Betzel:** None. **C.F. Angeloni:** None. **M. Aizenberg:** None. **D. Bassett:** None. **M.N. Geffen:** None.

Poster

226. Auditory Processing: Neural Coding, Experiment, and Theory

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 226.08/BB3

Topic: D.06. Audition

Support: R. Bruce Masterton Endowment

Title: Intrinsic electrophysiological properties shape physiologically relevant firing patterns in the avian cochlear nucleus

Authors: *D. H. BROWN, R. L. HYSON
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Abstract: In the avian brainstem, separate neural pathways encode sound intensity and timing, features important for sound localization. These pathways begin in anatomically segregated cochlear nuclei, the Nucleus Angularis (NA, intensity) and Nucleus Magnocellularis (NM, timing). NM consists of a relatively homogeneous population of neurons and their role in the sound localization circuit is better understood than that of the heterogeneous population of neurons in NA. Each pathway is inhibited by the Superior Olivary Nucleus (SON), which is known to refine timing signals for sound localization in an intensity-dependent manner. Since some NA neurons project to SON, it likely drives this gain control from SON, but it is unknown which neurons in NA innervate SON, how they process auditory information, or what cellular mechanisms underlie this processing. *In vitro*, NA neurons show a variety of physiological

profiles in response to current injection. These can be generally categorized as “Single-Spiking” vs. “Tonic” neurons. *In vivo*, NA neurons show a variety of responses to sound presentation, commonly categorized as “Onset”, “Primary-like” or “Chopper” units. We show that these sound-evoked categories of firing patterns can be generated *in vitro* by applying a current waveform that would be expected by sound-driven synaptic input *in vivo*. Applying these currents to Single-Spiking neurons yielded Onset responses, while applying these same currents to Tonic neurons generated Primary-Like or Chopper responses. The intrinsic physiological characteristics, input resistance and membrane time constant, systematically varied between cells with different temporal responses, suggesting that passive membrane properties are critical in shaping responses to the modeled current. Active membrane processes (ion channels) also play a role in shaping these responses. For example, blockade of low-threshold K+ current with bath application of dendrotoxin produced more persistent firing in Onset response neurons. These data suggest that many of the varying response profiles observed in NA neurons *in vivo* do not require varying input. Rather, variation in the intrinsic properties of the neurons adequately explains the way different NA neurons respond to sound. Preliminary data from NA neurons retrogradely labeled by dye injection in SON suggest that multiple response types ultimately project to SON, suggesting that the descending inhibition is sensitive both to the onset and ongoing levels of the acoustic stimulus.

Disclosures: D.H. Brown: None. **R.L. Hyson:** None.

Poster

226. Auditory Processing: Neural Coding, Experiment, and Theory

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 226.09/BB4

Topic: D.06. Audition

Support: NIH Grant R01NS082179

NSF Grant IOS1354906

CAPES-Brazil Foundation

Title: Decoding neural responses to complex sounds: An evaluation of pattern classification approaches in a secondary auditory region of a songbird

Authors: *M. MACEDO-LIMA[1], ***M. MACEDO-LIMA**[1], *M. MACEDO-LIMA[3], A. A. KRENTZEL[1], D. M. VAHABA[1], D. POLLAK[2], V. LEE[2], L. REMAGE-HEALEY[2]
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Abstract: A fundamental problem in neuroscience is how to decode the information processed by neurons. In the auditory domain, sensory processing depends on precisely timed responses, frequency/amplitude selectivity, noise filtering and desensitization. Songbirds are an attractive model to study auditory information processing because they learn complex vocalizations and because the cortical brain regions involved are well-delineated. A secondary auditory region, the caudomedial nidopallium (NCM), exhibits selectivity toward conspecific songs, adaptation to familiar songs, and is hypothesized to store auditory memories. Learned vocalizations are frequency- and amplitude-modulated, spectrally complex and can convey information about reproductive fitness and identity. Decoding complex auditory stimuli like song from the stimulus-evoked activity of single neurons requires the incorporation of computational approaches. Here, we investigate techniques for decoding neural responses in the zebra finch NCM. We employ pattern classifier algorithms to evaluate the consistency and discrimination of the firing patterns of neurons isolated from extracellular recordings while presenting songs to birds. We compare classifier performance when employing different metrics, such as timing-based, count-based and non-linear measures. To explore robustness, we compare decoding accuracy by sexes, cell types, and recording protocols such as anesthetized vs awake recording conditions. Our preliminary data show that (1) the classifier performs significantly better with timing-based as opposed to count-based metrics in NCM, in contrast to neurons in the sensorimotor nucleus HVC, which perform similarly using both metrics; (2) neurons from males and females yield similar accuracy performance; (3) and narrow-spiking neurons yielded higher accuracy performance than broad-spiking neurons. Ongoing analyses are investigating the performance of non-linear metrics (such as dynamic time warping), as well as whether anesthesia affects performance. This work describes fundamental properties of NCM neurons and the coding metrics for complex stimuli. We suggest that NCM neurons are highly specialized to discriminate auditory information with 10-20 millisecond precision, in favor of timing-based coding.

Disclosures: **M. Macedo-Lima:** None. **A.A. Krentzel:** None. **D.M. Vahaba:** None. **D. Pollak:** None. **V. Lee:** None. **L. Remage-Healey:** None.

Poster

226. Auditory Processing: Neural Coding, Experiment, and Theory

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 226.10/BB5

Topic: D.06. Audition

Title: Sound texture coding in single auditory cortical neurons

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Abstract: Auditory neuroscience has long lacked a compelling "mid-level" sensory representation bridging simple tones or filtered white noise and richly-structured waveforms such as speech, music, or multi-talker scenes. Secondary sensory regions are often insensitive to simpler stimuli, and thus have been characterized by their selectivity and tolerance to complex objects, though perhaps they would also respond to stimuli of intermediate complexity. A recent proposal from mid-level vision suggests that texture representations, which are rich, multi-scale summary statistics (Portilla & Simoncelli, 2000), may be computed even for scenes composed of a single object (Default Processing Model, Rosenholtz, 2014). Therefore, we seek evidence of neural coding of texture statistics in auditory object processing regions, which would support the Default Processing Model of mid-level audition. We conducted multichannel extracellular recordings in wild-caught European starlings (sturnus vulgaris) under urethane anesthesia while playing a battery of real and synthetic ecologically-relevant sound textures. Several regions of auditory cortex were stereotactically targeted, including the primary thalamorecipient field L, as well as secondary areas CM (caudal mesopallium) and NCM (caudo-medial nidopallium). Recording sites were chosen for responsiveness to starling song motifs—the auditory objects that evoke sparse firing in higher-order regions—yet we observed diverse responses to our texture stimuli in neurons throughout auditory cortex. Mean firing rates were higher for avian chorus texture families (sparrow chorus, starling chorus) than for other families of environmental sounds (bubbling water, wind). Crucially, because our synthetic stimuli matched real texture recordings only in the texture statistics (McDermott & Simoncelli, 2011), we argue that these summary statistics are sufficient to drive selective responses in object processing regions. Furthermore, short (800ms) segments of texture stimuli evoked more variable responses, while longer (5s) ones yielded lower firing rates, in line with the differing stationarity of these audio signals. Thus, in addition to objects, ambient sounds such as our texture stimuli are also represented in high-level auditory regions. This indicates that the Default Processing Model may have several advantages for better understanding of high-level auditory processing in complex, natural scenes.

Disclosures: S.S. Cain: None. **T.Q. Gentner:** None.

Poster

226. Auditory Processing: Neural Coding, Experiment, and Theory

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 226.11/BB6

Topic: D.06. Audition

Support: Mind and Life Institute, Varela Grant

Title: fcMRI and EEG evidence for perceptual decoupling in rhythm induced trance

Authors: *M. HOVE[1], A. HABIBI[2], J. STELZER[3], B. R. CAHN[2]
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[3]Universitaetsklinik Tuebingen, Neuroimaging, Tuebingen, Germany

Abstract: Rhythmic drumming has been used for centuries to alter consciousness and induce states of trance. Rhythm-induced trance is commonly practiced in shamanism, humanity's most ancient spiritual and healing tradition. Similar repetitive rhythms are used across cultures, which suggests a common biological basis. Despite similar techniques across cultures and powerful phenomenology, little is known about the mechanisms underlying this form of trance. We examined the neural correlates of rhythm-induced trance in experienced shamanic practitioners. In the first study, we used fMRI to examine the neural patterns associated with trance. Shamanic practitioners (n=15) underwent 8 minute brain scans while they listened to rhythmic drumming and entered a trance state (or remained in non-trance in a control condition). During trance, brain networks displayed notable reconfigurations, including increased connectivity in regions associated with internal thought (the default mode's posterior cingulate cortex) and cognitive control (dorsal anterior cingulate cortex and insula), as well as decreased connectivity within the auditory pathway. This network configuration suggests perceptual decoupling and that the repetitive drumming was gated out to maintain an internally oriented stream of consciousness. In a follow-up EEG/ERP study, we used a similar design to examine auditory gating and network activity while shamanic practitioners (n=18) experienced rhythm-induced trance and a control state. In response to clicks embedded in the drumming, the N100 and P200 ERP components were decreased during Trance; this suggests decreased sensory encoding and elaborative processing during trance. Together this work suggests that repetitive drumming promotes an internally directed state via perceptual decoupling, and explicates why trance is a common way to gain insight across cultures.

Disclosures: M. Hove: None. **A. Habibi:** None. **J. Stelzer:** None. **B.R. Cahn:** None.

Poster

226. Auditory Processing: Neural Coding, Experiment, and Theory

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 226.12/BB7

Topic: D.06. Audition

Support: NIH RO1DC009607

NIH DC-00046

NSF IIS-1350990

Title: Differential organization of the mouse auditory cortex to tone onset and offset revealed using automated image segmentation

Authors: *J. LIU[1], M. R. WHITEWAY[2], D. A. BUTTS[1], P. O. KANOLD[1]
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Abstract: One of the most robust organizational principles of the auditory cortex is its tonotopy. However, how auditory cortices are organized with respect to other properties of sound, such as sound offset, is still elusive. We thus presented 2-second tones to awake adult mice expressing GCaMP6s, and used widefield imaging combined with a new image segmentation technique that allowed unbiased and unsupervised definition of regions of interest. Our results show that offset responses have tonotopic organization, which spatially overlaps with that of onset responses. We identified Dorsal-Posterior (DP) field as one of the regions preferentially activated by tone offset and found that it contributes to off-tonotopy but not on-tonotopy. Moreover, offset responses show higher signal correlation than onset responses over distance, suggesting that offset responses were more spatially diffusive. Our results suggest that there are different cortical encoding schemes for tone onset and offset.

Disclosures: J. Liu: None. **M.R. Whiteway:** None. **D.A. Butts:** None. **P.O. Kanold:** None.

Poster

226. Auditory Processing: Neural Coding, Experiment, and Theory

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 226.13/BB8

Topic: D.06. Audition

Support: NSF Grant

Title: Nonlinear population cortical responses after midbrain stimulation in the auditory colliculo-thalamocortical mouse brain slice

Authors: *B. A. IBRAHIM[1,2], D. A. LLANO[1,2]
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Abstract: The auditory colliculo-thalamocortical mouse brain slice, developed by our laboratory, retains synaptic connectivity between inferior colliculus (IC), medial geniculate body (MGB), and auditory cortex (AC). Such connections in a brain slice preparation enable the detailed examination of the role of the MGB in transmitting signals from the IC to the AC. Using flavoprotein autofluorescence (FA) to measure the connectivity between circuit components, we

recently observed all-or-none cortical FA responses without any change in IC and MGB responses following IC stimulation. The frequency of the missing FA cortical responses increased with decreasing current amplitude and inter-stimulus-interval. In contrast, direct stimulation of MGB or the subcortical white matter produced only linear cortical responses. Bath perfusion of gabazine, $GABA_A$ receptor blocker, was capable of retrieving the missing cortical FA responses. The preliminary data showed that focal injection of gabazine into MGB showed the same effect of the drug to retrieve the missing FA cortical responses and linearize cortical and MGB responses, but it failed to show the same effect when injected into auditory cortex. Current clamp whole cell recording from layer 4 or 2/3 showed similar all-or-none responses to what was described using FA, and voltage-clamp recording did not reveal a source of inhibition responsible for the missing responses. Current and voltage clamp whole cell as well as cell attached paired recording of MGB cells showed that not all MGB cells fire or receive inhibitory inputs following IC stimulation which could indicate population coding within MGB neuronal ensembles. These data suggest that the thalamus may recruit cortical ensembles rather than linearly encoding ascending stimuli, and that GABAergic inhibition may play a role in selecting cortical ensembles for activation.

Disclosures: B.A. Ibrahim: None. **D.A. Llano:** None.

Poster

226. Auditory Processing: Neural Coding, Experiment, and Theory

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 226.14/BB9

Topic: D.06. Audition

Support: NIH Grant U01-NS090569

Title: Spatial organization of functional properties in layer 2/3 of auditory cortex

Authors: *Z. BOWEN[1], D. E. WINKOWSKI[2], W. LOSERT[3], P. O. KANOLD[2]
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Abstract: It has long been appreciated that stimulus properties are topographically organized in sensory cortices. In the auditory cortex (ACX), high-resolution imaging techniques such as 2-photon imaging have demonstrated that while the ACX exhibits a tonotopic organization on large spatial scales, this organization breaks down at the finer scale. For example, the spatial distribution of frequency preferences of individual layer 2/3 (L2/3) neurons is highly heterogeneous in ACX, and individual cells vary in their responses to repeated presentations of the same stimulus. How then does this highly variable spatial distribution of neuronal responses generate a stable auditory percept? To approach this question, we treat these population

responses as a spatial point patterns, a type of data which has been extensively studied in fields outside of neuroscience, from cell biology to cosmology. We employ cluster and point pattern analysis methods such as Minkowski functionals, which consider higher-order spatial interactions, to make inferences about the underlying circuitry. We applied these spatial analysis methods to *in vivo* 2-photon calcium imaging data of ACX in awake mice measuring the activity of neuronal populations in response to sound stimuli (tones). We found that specific tonal stimuli create population responses that are spatially clustered and dispersed at different length scales. Our results suggest that spatially specific subpopulations of ACX neurons exist that are activated by specific sounds. We further quantify these distinct spatial patterns through principal component analysis and hierarchical clustering of Minkowski functionals, providing insight into the functional spatial processes that exist in ACX stimulus encoding. Additionally, we extend the study to investigate spatiotemporal firing patterns known as neuronal avalanches, and how they propagate in space. The spatial properties of neuronal population responses will thus be quantified at a range of temporal scales.

Disclosures: Z. Bowen: None. **D.E. Winkowski:** None. **W. Losert:** None. **P.O. Kanold:** None.

Poster

226. Auditory Processing: Neural Coding, Experiment, and Theory

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 226.15/BB10

Topic: D.06. Audition

Support: Spinoza grant

Title: Linguistic information of distracting speech modulates selective neural entrainment to target speech

Authors: *B. DAI[1,2], A. KÖSEM[1,2], J. M. MCQUEEN[2,1], O. JENSEN[3], P. HAGOORT[1,2]
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Abstract: In a multi-talker scene, the comprehension of target speech can be degraded due to interference from background sounds. Selective neural entrainment to target speech is hypothesized to solve this problem. However, efficient target speech comprehension is influenced by the properties of the interfering signal. In particular, it can be more strongly impaired in the presence of intelligible speech as compared to non-intelligible sounds. In this magnetoencephalography study, we investigated how competing linguistic information modulates neural entrainment to target speech.An A-B-A training paradigm was used to

manipulate the linguistic component of the distractor without changing its acoustic component. Participants performed a dichotic listening task (A) before and after training on understanding the interfering distractor, which was noise-vocoded speech (B). We predicted that intelligible noise-vocoded speech would have a stronger masking effect after training than before, when it's poorly understood. Specifically, (1) neural entrainment to target speech would become harder; (2) the involved language networks would need more engagement to ignore the distractor.In line with our predictions, we observed a stronger masking effect of the interfering signal after training (when it became more intelligible). In general, entrainment to the target speech was stronger than to the distractor. However, the strength of the entrainment was modulated by training. After training, we found a reduction of target speech-brain coherence (1-8 Hz), accompanied with an enhancement of interfering speech-brain coherence (5-9 Hz), in temporal areas of the ipsilateral hemisphere. Furthermore, alpha power (8-12 Hz) decreased over central sensors after training, which likely reflected the incremental requirement of engagement when the distractor became more difficult to ignore. These results provide insights about how the brain deals with multi-signal scenes, where the ignored signal is not in fact ignored, but instead partly processed at higher linguistic levels.

Disclosures: **B. Dai:** None. **A. Kösem:** None. **J.M. McQueen:** None. **O. Jensen:** None. **P. Hagoort:** None.

Poster

226. Auditory Processing: Neural Coding, Experiment, and Theory

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 226.16/BB11

Topic: D.06. Audition

Support: National Institute of Health, NIDCD, DC014279

Title: Predicting the neural responses to speech in human auditory cortex using deep neural network models

Authors: *H. AKBARI[1,2], B. KHALIGHINEJAD[1,2], J. L. HERRERO[3], A. D. MEHTA[4], N. MESGARANI[1,2]
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Abstract: Recently, interest has grown in characterizing the response properties of sensory neurons under natural stimulus conditions. The majority of previous studies have used linear models to relate the acoustic features of sound to neural responses. However, linear models

cannot capture the inherent non-linearity of the responses in the brain. We investigated the utility of deep neural network models to predict neural responses to speech in human auditory cortex. The neural responses were recorded from the transverse and the superior temporal gyrus of patients undergoing surgery for the treatment of epilepsy as they listened to continuous speech. Deep neural networks (DNNs) have shown great promise in capturing non-linear relationships. Thus, we trained a DNN with a non-linearity in each layer using the time-frequency representation of the stimulus as the input and the envelope of the high-gamma activity of the neural responses as the output of the model. First, we started with a one-node one-layer fully connected network, which is equivalent to the commonly used spectrotemporal receptive field (STRF). We then proceeded by progressively adding nodes and layers to study the effect of deepness and complexity of the model on the accuracy of predictions. In addition, we explored the effect of network architecture such as convolutional (CNN) and recurrent (RNN) neural networks.

To compare the prediction of networks (STRFs, DNNs, RNN, and CNNs), we obtained the difference between the predicted responses of the DNNs and the STRF model and determined the response features that were better predicted by the nonlinear models. We also analyzed the network to figure out the properties of the functions that are applied to the stimulus. In comparison to the STRFs, the predicted responses from the neural networks had a higher correlation with the original responses. On average, using DNNs improved the correlation by 5%, and the CNNs by 25%. We found that a combination of DNNs and CNNs can provide a 35% improvement, which suggests that more complicated networks are needed to model the neural encoding of speech. We further analyzed the properties of the functions learned by the networks to shed light on the computational role of the nonlinear transformations that are applied to the sound features as they travel throughout the auditory pathway.

Disclosures: **H. Akbari:** A. Employment/Salary (full or part-time):; Department of Electrical Engineering, Columbia University, New York, NY. **B. Khalighinejad:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Department of Electrical Engineering, Columbia University, New York, NY. **J.L. Herrero:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Feinstein Institute for Medical Research, 350 Community Dr., Manhasset,. **A.D. Mehta:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Laboratory of Human Brain Mapping, Feinstein Institute for Medical Research; Department of Neurosurgery, Hofstra Northwell School of Medicine, Manhasset, NY. **N. Mesgarani:** 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.; Department of Electrical Engineering, Columbia University, New York, NY 10027, USA, Mortimer B. Zuckerman Mind Brain Behavior Institute, Columbia University, New York, NY.

Poster

226. Auditory Processing: Neural Coding, Experiment, and Theory

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 226.17/BB12

Topic: D.06. Audition

Support: JSPS 15K12069

Title: Amplification of auditory brainstem response by simultaneous infrared laser stimulation to cochlea

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Abstract: Infrared laser stimulation is a novel method for neural stimulation. Neural response from the infrared laser stems from optical absorption of water, which causes instantaneous temperature rise. Ion channels on nerve cell are sensitive to heat, and the action potential can derive from the sensitivity. Previous studies reported that stimulating cochlear nerves by infrared laser caused an optically-evoked brainstem response (OBR) resembling auditory brainstem response (ABR). The purpose of this study was to investigate whether the ABR was able to be amplified by presenting infrared laser simultaneously with sounds. Mongolian gerbil (Meriones unguiculatus) was used as subject. For acoustic stimulus, a loudspeaker was placed 10 cm away from the subject; for optical stimulus, optic fiber was placed in the ear canal to irradiate infrared laser to cochlear nerves. Neural responses were recorded from the round window of the cochlea. In the first experiment, stimulus was presented unimodally, either acoustic or optic. Acoustic stimulation was click sound and changed their sound pressure level between 10 to 80 dB pe SPL. Optic stimulation was pulse infrared laser (wave length 1871 nm) and changed their radiant exposure between 3.5 to 27.6 μJ. As results, obtained stimulus-response curve showed that 30 μV was threefold for the OBR in our experimental setting, and subthreshold stimulus level for the second experiment was determined. In the second experiment, we presented optic and acoustic stimulation simultaneously. Optic stimulation was pulse laser and the radiant exposure was 7.0 to 10.3 μJ. Acoustic stimulation was subthreshold 40 dB pe SPL tone pip, and changed their frequency between 1000 to 20000 Hz. As result, the ABR amplitude increased and exceeded threshold only when tone pip of 3000, 4000 or 5000 Hz was presented with acoustic stimulus. The largest amplitude was recorded by combining infrared laser with 4000 Hz tone pip. These results suggest that infrared laser can amplify ABR responses and the laser could stimulate selective portion of cochlear nerves corresponding 4000 Hz. The result shows the possibility of applying infrared laser to hearing aid because noninvasive stimulation is able to amplify ABR responses.

Disclosures: **K. Horinouchi:** None. **Y. Tamai:** None. **S. Hiryu:** None. **K.I. Kobayashi:** None.

Poster

226. Auditory Processing: Neural Coding, Experiment, and Theory

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 226.18/BB13

Topic: D.06. Audition

Support: NIDCD R01DC014503

Title: Current focusing improves auditory cortical responses to intracochlear electrical stimulation in awake primate

Authors: *K. LIM, K. HAGEMAN, C. DELLA SANTINA, X. WANG
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Abstract: Electrical stimulation of the cochlear nerve via a cochlear implant (CI) is successful in restoring auditory sensation to individuals with profound hearing loss. Despite successes, CI users still face limitations in such situations as music appreciation and hearing in a noisy environment. How CI devices engage the brain at the single neuron level has remained largely unknown, in particular in the primate brain. To this end, our lab has established a non-human primate CI model using the common marmosets (*Callithrix Jacchus).* Using a preparation in which one ear was deafened and implanted with an intracochlear electrode array and the other ear remains intact, our recent studies have shown that conventional intracochlear electrical stimulation (ICES) strategies using monopolar (MP) and bipolar (BP) configurations were inefficient in activating many neurons in primary auditory cortex (A1). In some cases, MP stimulation was found to suppress the spontaneous activity of A1 neurons. Further analysis revealed that a particular group of A1 neurons narrowly tuned to both frequency and sound level, termed the "O-shaped" neurons, were poorly driven by the ICES due to its broad cochlear excitation patterns (Johnson et al 2016). Current focusing techniques have been proposed to sharpen the electrical field generated within the cochlea, and have been proven successful in reducing current spread in neurophysiological studies (George et al 2014; Snyder et al 2008; Bierer et al 2002; Kral et al 1998). In the present study, we tested the hypothesis that current focusing can improve the efficiency of ICES in activating A1 neurons. Our data showed that current focusing techniques using tripolar (TP) and partial tripolar (pTP) configurations indeed increased A1 neurons' responsiveness to ICES in comparison to MP stimulation. In particular, many O-shaped neurons that could not be driven by MP stimulation were responsive to TP and pTP stimulation. Furthermore, using forward masking and channel spread paradigms, it was revealed that the current spread was in fact lower for the TP than the MP configuration. Together, these findings suggest a promising potential of applying current focusing technique in engaging A1 neurons, especially those highly selective to frequency and sound level. These

neurons are likely to play a role in perceptual behaviors requiring fine frequency and level discrimination, such as music appreciation and speech recognition in noise.

Disclosures: K. Lim: None. **K. Hageman:** None. **C. Della Santina:** None. **X. Wang:** None.

Poster

226. Auditory Processing: Neural Coding, Experiment, and Theory

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 226.19/BB14

Topic: D.06. Audition

Support: NIH Grant DC014279

Pew Biomedical Scholars Program

Title: Reconstructing speech from human auditory cortex using deep neural network models

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Abstract: We examined the accuracy of the reconstructed speech spectrograms from neural responses recorded invasively in human auditory cortex. The neural responses were recorded from the transverse temporal gyrus and the superior temporal gyrus of patients undergoing surgery for the treatment of epilepsy as they listened to continuous speech. The envelope of high-gamma activity (80-150 Hz) was then used as the input to the models. We compared the reconstructed spectrograms estimated with two different models: a linear regression model and a deep neural network. Compared with linear regression model, the reconstructed spectrograms from the deep neural network achieved a higher average correlation with the original spectrograms. In addition, the reconstructed spectrograms from the neural network better preserved the average acoustic features of phonemes. We further investigated how changing the number of hidden layers in the network and the network architecture affect the reconstruction accuracy and found a better performance with deeper networks, particularly in the reconstruction of spectrotemporal modulation content of speech. These findings reveal the efficacy of deep neural network models in decoding speech signals from neural responses and provide a method for improving the performance of brain computer interfaces with prosthetic applications.

Disclosures: L.K. Long: None. **H. Akbari:** None. **B. Khalighinejad:** None. **J.L. Herrero:** None. **A.D. Mehta:** None. **N. Mesgarani:** None.

Poster

226. Auditory Processing: Neural Coding, Experiment, and Theory

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 226.20/BB15

Topic: D.06. Audition

Support: NIH R01 Grant DC006212

FWO Grant G.0A11.13

FWO Grant G.091214N

FWO Grant G0B2917N

FWO PhD fellowship

FWO postdoctoral fellowship

MSCA fellowship

Title: *In vivo* sharp electrode and whole-cell recordings from octopus cells in the gerbil ventral cochlear nucleus

Authors: *H.-W. LU[1], T. P. FRANKEN[1], M. SAYLES[1], B. FONTAINE[1], P. H. SMITH[2], P. X. JORIS[1]
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Abstract: Octopus cells in the mammalian cochlear nucleus are considered important for encoding complex sounds. Their dendrites sample auditory nerve inputs across a wide frequency range, and they show remarkable temporal properties. With extremely fast membrane time constant and low input resistance, these cells are hypothesized to be coincidence detectors, firing action potentials only when a large number of auditory inputs are activated over a submillisecond timescale. Despite much speculation from in vitro and in silico findings, the role of octopus cells in sound encoding and their presumed operation as coincidence detectors remain unclear. In particular, there is a near absence of intracellular data for responses to sound. We used sharp and patch-clamp pipettes containing neurobiotin or biocytin to intracellularly record from, and morphologically identify, octopus cells in anaesthetized adult gerbils. In the absence of acoustic stimulation, octopus cells receive high rates of subthreshold spontaneous excitatory events, mostly less than 5 mV. Inhibitory hyperpolarizing events were barely detectable. Cells were broadly tuned to frequency and tended to have high thresholds. Remarkably, octopus cells could fire action potentials in-sync with click trains up to 400 Hz for at least 10 seconds. The amplitudes of action potentials decreased with increasing click frequency, from > 20 mV at 10Hz

to ~ 10 mV at 400 Hz. Membrane potentials were also well-driven and rate-tuned in response to sinusoidal amplitude modulation. Unexpectedly, in response to high frequency (> 4kHz) pure tones, octopus cells responded not only with one large action potential at the onset, but also showed numerous large EPSPs (> 7 mV) with rise time < 1 ms throughout the tone duration. Given that octopus cells receive small subthreshold EPSPs from each auditory nerve fiber in vitro (Golding et al 1995), these large EPSPs suggest that there is near synchronous activation of multiple auditory nerve fibers even during sustained pure tone stimulation. In conclusion, our intracellular data confirm that octopus cells act as broadband transient detectors, but raise questions regarding the coincidence process underlying their responses.

Disclosures: **H. Lu:** None. **T.P. Franken:** None. **M. Sayles:** None. **B. Fontaine:** None. **P.H. Smith:** None. **P.X. Joris:** None.

Poster

226. Auditory Processing: Neural Coding, Experiment, and Theory

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 226.21/BB16

Topic: D.06. Audition

Support: Deutsche Forschungsgemeinschaft (SFB 870)

European Research Council Advanced Grant to A.K.

European Research Council Advanced Grant to I.N.

Title: 3D-landscape of single-neuron function in a cortical microcolumn

Authors: *C. H. TISCHBIREK[1], T. NODA[1], M. TOHMI[1], A. BIRKNER[1], I. NELKEN[2], A. KONNERTH[1]
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Abstract: The cortex is organized into functional regions corresponding, for example, to specific sensory modalities. The generation of functional maps of the cortex involved various electrophysiological and/or imaging approaches. A major limitation in the interpretation of such maps has especially been the lack of knowledge of cell-specific activity patterns in deep cortical layers. Here, we report the integration of several techniques allowing us to create a comprehensive 3D functional map of a microcolumn in the mouse auditory cortex. These techniques included the optimization of brain surface autofluorescence imaging, two- or multi-layer calcium-imaging with single-cell resolution of accurately aligned regions within a fine cortical column (diameter of about 100-120 um) from the pial surface down to layer 6 (about 900 um), targeted single-cell electroporation with fluorescent dyes and electrophysiology. The mouse auditory cortex is a useful model system to study the relationship between large-scale cortical

organization and its underlying neuronal landscape, because a hallmark feature of its large-scale organization, namely tonotopy, can be clearly defined and is highly preserved across species. Using flavoprotein-based brain surface autofluorescence imaging and pure tone stimulation, we first determined frequency maps of the primary auditory cortex. Next, we used the red-shifted calcium indicator Cal-590 for deep two-photon imaging of neuronal activity either in L5 or L6 in a well-defined location along the tonotopic axis. Finally, in the same experiment, we determined the corresponding activity maps in the upper cortical layer, L2/3 and/or L4, using the green calcium indicator Cal-520. Based on the response profiles of the individual neurons (> 1400), we found, within a microcolumn, a striking similarity of the median best frequencies of each cortical layer ranging from L2/3 to L6. The median best frequency corresponded remarkably well with the tonotopic location as determined at the cortical surface. In each layer, pure tone-evoked neuronal responses were similarly sparsely represented, with only few neurons responding strongly and reliably to a given frequency. Finally, in each layer, neurons had mostly similar but not identical tuning profiles, with a scatter of ~1 octave in best frequencies. Thus, the results reveal that the primary mouse auditory cortex is organized in microcolumns with an unexpectedly high degree of similarity throughout all cortical layers.

Disclosures: C.H. Tischbirek: None. **T. Noda:** None. **M. Tohmi:** None. **A. Birkner:** None. **I. Nelken:** None. **A. Konnerth:** None.

Poster

226. Auditory Processing: Neural Coding, Experiment, and Theory

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 226.22/BB17

Topic: D.06. Audition

Support: NIH R01 DC014950

DARPA D15 AP00101

Title: Integrating behavioral context into auditory encoding models

Authors: *S. V. DAVID[1], Z. P. SCHWARTZ[2], L. A. SHAHEEN[3]
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Abstract: Sensory encoding models that incorporate nonlinear adaptation and/or gain control have been shown to predict cortical responses to natural sounds better than the linear spectro-temporal receptive field (STRF). It has also been established that changing behavioral state, by engagement in auditory task or switching between tasks, can influence linear STRF fits. However, less is known about how the more comprehensive nonlinear encoding models are

influenced by changes in behavioral state. This problem is challenging because fitting nonlinear models require large quantities of neurophysiological data but data are often limited in studies of behaving animals.
To measure behavior-dependent changes in nonlinear auditory encoding, we developed a computational framework for unbiased comparison of a large number of encoding models. We identify models with minimal complexity, i.e., those which require as few free parameters as possible but are still able to optimally account for neural responses. We analyzed single-unit data collected from primary auditory cortex of awake ferrets while they switched between passive listening and a tone detection task. We identified optimal parameterizations and found that a nonlinearity modeling short-term synaptic plasticity accounted for most nonlinear response properties across the models tested. We then fit models using stepwise regression, in which individual free parameters were either fixed across behavioral states or allowed to vary between states. The majority of behavior-dependent changes in encoding occurred in the linear spectro-temporal filter. Allowing nonlinear adaptation or just the static nonlinearity to vary between behavior states did not provide additional improvement in performance. These findings suggest that behavioral context primarily impacts linear spectro-temporal filtering properties, while having relatively little impact on nonlinear adaptation properties.

Disclosures: **S.V. David:** None. **Z.P. Schwartz:** None. **L.A. Shaheen:** None.

Poster

226. Auditory Processing: Neural Coding, Experiment, and Theory

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 226.23/BB18

Topic: D.06. Audition

Support: NIH/NIDCD-R01-DC00577

NIH/NIDCD-R00-DC010439

2014BP-A00226

Title: Representation of attentional effects in neural responses in a cocktail party model in the ferret auditory cortex

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Abstract: During the cascade of neural responses triggered by sound from multiple sources hitting the tympanum, the brain needs to deconstruct the mixture by auditory scene analysis into different streams and then select the most relevant streams for further processing. Many different ideas have been proposed as to how the brain segregates sound and decodes the auditory scene,

some suggesting that scene segregation is pre-attentive, activating separate neural populations that respond to different auditory attributes, while others emphasizing the importance of attention.
Ferrets are an excellent animal model to study speech representation because the range of sounds frequencies heard by them is similar to humans, their Auditory Cortex is complex enough to encode phoneme classes (Mesgarani et al., 2008) and they can be trained to differentiate syllable sequences (Bizley et al., 2015; Duque et al., 2016). To explore the role of attention in neural mechanisms of stream segregation, we trained ferrets to discriminate tri-syllabic pseudo-words using a conditioned avoidance GO/NO-GO task. We also trained them to attend to a target word (Eg. FA-BE-KU) by a female speaker while ignoring a simultaneous male background speaker. In order to analyze neural encoding in stream segregation, we perform single unit neurophysiological recordings in primary and secondary areas of the Auditory Cortex. We explored whether responses during the tasks showed adaptively enhanced representation of the attended female speaker.
Preliminary neurophysiological data indicate that neuronal responses to words in the male distractor voice in the cocktail party scenario showed specific suppression, enhancing representation of the attended female target word. This study shows that neurons in higher order Auditory Cortex can encode pseudo-words selectively in a multi-speaker scenario. These results will help us understand the neural basis for representation of complex sound sequences and yield deeper insight into neural mechanisms underlying initial stages in human speech processing of the cocktail party problem.

Disclosures: **N.H. Joshi:** None. **D. Duque:** None. **J.B. Fritz:** None. **S.A. Shamma:** None.

Poster

226. Auditory Processing: Neural Coding, Experiment, and Theory

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 226.24/BB19

Topic: D.06. Audition

Support: R01 DC014950

F31DC014888

Title: Effects of behavioral performance on task-related gain changes in the auditory midbrain

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Abstract: The inferior colliculus (IC) is an auditory midbrain region that integrates ascending auditory information with top-down feedback from the auditory thalamus and auditory cortex

(AC). Previous work in our laboratory has found that engaging in a simple tone-detection task can modulate neural responses in the ferret IC – an effect that was previously only identified in AC. Engagement in auditory behavior involves changes in multiple internal state variables, and the current study seeks to isolate effects of one of these variables: listening effort. To explore the effects of listening effort on IC activity, we trained three ferrets on a tone-in-noise behavior. Changing the signal-to-noise ratio of the tone relative to the noise (target SNR) controlled the level of listening effort required for detection. Trial blocks alternated between difficult (low target SNR) and easy (high target SNR). The task also included occasional probe targets (fixed SNR across blocks), which could be analyzed to determine the effects of changing expected SNR (difficult or easy block) on behavioral sensitivity and criterion for target detection. Contrary to our expectations, we observed no consistent difference in sensitivity between conditions, meaning that the ferrets do not alter their ability to discriminate between the noise (distractor) and the signal (tone embedded in the noise, target). However, we did observe a decrease in criterion between difficult and easy blocks, reflecting an increased likelihood of the animals' response to any sound, either a distractor or a target, in the difficult condition. We performed single-unit tetrode recordings in the IC during passive listening, easy, and difficult behavioral conditions. Preliminary results showed that neural responses to both the non-target noise and target stimuli were generally enhanced during behavior relative to passive listening (gain increase). When we compared responses between easy and difficult conditions, we did not observe a significant difference. However, we did observe a significant correlation between gain and behavioral criterion, such that gain is higher during behavioral blocks when criterion is high. Thus, although the effects of changing task difficulty are variable, animals tend to increase their behavioral criterion in the more difficult condition. Moreover, the change in neuronal gain relative to passive listening is also correlated with criterion. Taken together these results suggest that behavioral state variables reflecting listening effort influence auditory processing as early as the auditory midbrain.

Disclosures: **D. Saderi:** None. **S.V. David:** None.

Poster

226. Auditory Processing: Neural Coding, Experiment, and Theory

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 226.25/BB20

Topic: D.06. Audition

Support: KAKENHI 16K00220

KAKENHI 17K07050

Title: A theoretical study of cortical neural dynamics for the generation of auditory continuity illusion

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Abstract: Neurons in the mammalian primary auditory cortex (AI) respond selectively to specific frequencies and intensities of acoustic stimuli. Thus far, we have reproduced receptive field profiles of AI neurons and map representations of preferred frequencies and sound intensities, performing simulations of our model for the self-organization of afferent inputs from the medial geniculate body (MGB). The auditory continuity illusion is a well-known phenomenon: When a continuous melody is partially replaced with periodic silent periods (gaps), we feel the melody to be unpleasantly fragmented. However, when the periodic gaps are replaced with noise, we hear the continuous melody as a background of the periodic noise. That is, the periodic noise recovers the sensation of continuity in the original melody although it is still fragmented. Little is known about what neural mechanisms cause the continuity illusion, however. To elucidate the neural mechanisms underlying this illusion theoretically, we examined dynamic activities of model AI spiking neurons that received the self-organized inputs from the MGB when three types of stimuli were presented: (a) continuous 800-Hz pure tone, (b) 800-Hz pure tone periodically fragmented with gaps, and (c) 800-Hz pure tone with a periodic insertion of the band-pass noise into the gaps in (b). For stimulus (b), the spike responses of 800-Hz pure tone responsive neurons were observed only during the presentation of the pure tone but not generated in the gaps. On the other hand, the same neurons elicited spikes continually in response to stimulus (c), and temporal patterns of firing were similar to those for stimulus (a). We carried out dynamic simulations with and without lateral interactions in model AI in response to the three types of stimuli. Firing rate of model cortical neurons in the noise periods were six-fold higher than that in the melody periods for stimulus (c) without lateral interactions, whereas the levels of activations were almost the same for the other two types of stimuli irrespective of the presence or absence of the lateral interactions. These results indicate that the lateral interactions are involved in the gain control of neuronal responses in AI. Next, we examined the similarity of temporal firing patterns of model neurons in response to stimulus (c) to stimulus (a), changing the noise intensity. The relation of the similarity to the noise intensity showed excellent agreement with a human psychometric function representing the relation of the sensation of continuity to the noise intensity. This suggests that the topographic map and lateral interactions in AI contribute to the generation of auditory continuity illusion.

Disclosures: M. Miyashita: None. **T. Endo:** None. **S. Tanaka:** None.

Poster

226. Auditory Processing: Neural Coding, Experiment, and Theory

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 226.26/BB21

Topic: D.06. Audition

Title: Deducing the role of nitric oxide in the american bullfrog inferior colliculus

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Abstract: Deducing the role of nitric oxide in the auditory midbrain of the American bullfrog (*Lithobates catesbeiana)*
Nitric Oxide (NO) is a gaseous molecule that functions as a retrograde messenger in several regions of the brain. Activation of glutamate N-methyl-D-aspartate (NMDA) receptors stimulates NO production via the activity of nitric oxide synthase (NOS). NO is released and subsequently enhances the presynaptic release of glutamate. Staining for β nicotinamide adenine dinucleotide phosphate diaphorase as well as immunohistochemical studies have revealed the presence of NOS-labeled neurons in a number of vertebrate brain structures including the inferior colliculus (IC), an important auditory processing center. These neurons presumably produce and release NO. **However, the function of nitric oxide in auditory processing at the level of the IC is not known**. Here we address this issue using extracellular single-unit recording combined with microiontophoresis to investigate the role of NO in the analysis of species' calls by neurons in the IC of the American bullfrog, *Lithobates catesbeiana*. Of particular interest was if/how NO modulates the responses of IC neurons to conspecific and heterospecific mating calls. *In vivo* iontophoretic application of L-NAME (a NOS inhibitor), and L-Arg (a NOS substrate), was used to evaluate the effect of NO on the sound-evoked responses of neurons (n=25) in the IC. We found that NO modulated neuronal responses in a call dependent manner. Upon application of L-NAME we've seen neuronal responses modulated via spike counts and first-spike response latencies. Recovery of original response is achieved by application of the NOS substrate, L-Arg. Our data suggest a role for NO in regulating both gain control and response selectivity in the IC and may influence the output of neural circuits engaged in the analysis of behaviorally relevant acoustic signals, such as speech.

Disclosures: A.W. Stafford: None. **J. Hall:** None.

Poster

227. Visual System: Response Modulation and Adaptation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 227.01/BB22

Topic: D.07. Vision

Support: National Natural Science Foundation of China (91432102)

National Natural Science Foundation of China (31671079)

National Key Basic Research Program of China (2014CB846101)

Title: Fear conditioning specifically alters neuronal response properties in monkey primary visual cortex

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Abstract: Previous studies have shown that response properties of neurons in the primary visual cortex (V1) can be altered by sensory experience. In real-life situations, visual stimuli are often emotionally charged due to past experience, but little is known whether the emotional valence conveyed by the stimuli can also affect V1 responses. In the current study we addressed this question in awake monkeys using a fear conditioning paradigm. Air puff delivered to the face was used as the unconditioned stimulus (US), which was paired with square-wave gratings that were tilted clockwise relative to the vertical (the conditioned stimulus, CS). Gratings tilted to the opposite direction served as the neutral stimuli (NS). The frequencies and durations of eye blinks were used as a behavioral assessment of fear responses. Neuronal activities in V1 were recorded with implanted microelectrode arrays. After the establishment of the conditioned behavioral responses, we switched the CS and NS. Neuronal and behavior responses were recorded over the course of fear conditioning and reverse conditioning. Fear conditioning markedly enhanced V1 neuronal responses at the conditioned grating orientations, whereas the response enhancement at the neutral orientations was much smaller. The learning effect was largely seen in the early component of V1 responses and was independent of neurons' orientation preferences. We also observed a general increase of neurons' spontaneously activity. When the CS and NS were switched, the learning effect in V1 reversed accordingly, showing a significant and transient enhancement at the new CS orientations. This reversal effect in V1 reached a plateau after only several hundred trials. However, the behavioral learning effect, that is, the establishment of specific blinking behavior to the newly conditioned orientations, remarkably lagged behind V1 changes, reaching a plateau after several days. Our results suggest that fear conditioning results in the formation of fear memory in the earliest stage of visual processing by altering the basic response properties of neurons. This might be a consequence of interactions between the amygdala and visual cortex over the course of conditioning.

Disclosures: L. Zhihan: None. **K. Guo:** None. **W. Li:** None.

Poster

227. Visual System: Response Modulation and Adaptation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 227.02/BB23

Topic: D.07. Vision

Support: ERC starting grant NEUROOPTOGEN

Title: Serotonin decreases the gain of the visual responses in awake macaque V1

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Abstract: Serotonin (5HT) is an important neuromodulator implicated in a variety of affective, cognitive and sensorimotor functions but its role even for basic cortical processes is controversial. Here, we examined the role of serotonin on well-defined tuning properties in the macaque primary visual cortex (V1). We combined extracellular recordings with iontophoresis in awake macaques to minimize fluctuations in brain state observed under anesthesia. Two monkeys performed a standard fixation task while we recorded 265 single units in their V1 and simultaneously applied serotonin hydrochloride (10mM; pH=3.5) or pH-matched 0.9 % saline (NaCl) as a control via iontophoresis. Stimuli presented in a neuron's receptive field were drifting gratings of varying orientation, spatial frequency, contrast or size, respectively. For all stimuli, the application of serotonin significantly decreased the mean response compared to the application of saline (orientation: $p<10^{-5}$, n=76 for 5HT, n=21 for NaCl; spatial frequency: $p<10^{3}$, n=37 for 5HT, n=10 for NaCl; contrast: $p<10^{-3}$, n=101 for 5HT, n=30 for NaCl; size: $p<0.01$, n=35 for 5HT, n=22 for NaCl). This effect was mainly explained by multiplicative changes of the tuning curves (orientation: $p<10^{-5}$; spatial frequency: $p<10^{-3}$; contrast: $p<10^{-4}$; size: $p<0.01$), and did not systematically affect neuronal selectivity. Serotonin also slightly increased the latency of the orientation selective response ($p<10^{-3}$, n=45), as quantified using orientation subspace reverse correlation. Although these changes were reminiscent of those resulting from a reduction in contrast, they differed quantitatively from changes in contrast. However the serotonin-induced modulation could be captured by a simple additive change to a threshold-linear spiking non-linearity. We also explored whether serotonin influenced the variability (Fano factor) or co-variability ("noise-correlations" between single and multi-unit activity) of the responses but observed no systematic effect ($p>0.2$ for all comparisons). Taken together, we found that serotonin mainly decreased the gain of the visual responses without affecting the selectivity, variability or co-variability of the responses. Our results indicate that serotonin is well suited to control the response gain of neurons in V1, potentially complementing other known state-dependent gain control mechanisms.

Disclosures: L. Seillier: None. **C. Lorenz:** None. **K. Kawaguchi:** None. **T. Ott:** None. **A. Nieder:** None. **P. Pourriahi:** None. **H. Nienborg:** None.

Poster

227. Visual System: Response Modulation and Adaptation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 227.03/BB24

Topic: D.07. Vision

Title: Response variability of V1 neurons in awake primate

Authors: *J. DOOSTMOHAMMADI[1,2], H. SHABANI[1], M. NEJATBAKHSHESFAHANI[1], A. YOONESSI[2], R. LASHGARI[1]
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Abstract: Sensory neurons when facing a particular stimulus show a variability in spike trains and inter-spike intervals at the replicated trials in the same time window under the same stationary conditions. However, the physiological function and behavioral pattern of neural response variability are still a matter of debate and remain remarkably an open question in neuroscience. Studies have shown a significant reduction of trial-to-trial variability during visual stimulation especially at the stimulus onset (Carandini, M 2004). It has been shown that this reduction in response variability is not limited to the optimal stimuli and can occur even for non-optimal stimuli at both the membrane potentials and spike rates (Churchland et al, 2010). It is also suggested that the reduction of variability could be a common feature of the cortical response that can be seen in different areas of brain regardless of stimulus type and behavioral state. Here, we measured the spike train irregularity of single isolated neurons in the primary visual cortex of behaving primates by using chronically-implant-ultra-thin electrode arrays (Lashgari et al, 2012). Neuronal activity was recorded before (for 500 ms; as the baseline activity) and after stimulation (for 2 sec) with a grating drifting at 2 Hz, 4 trials for each stimulus. Orientation/direction tuning was measured with 16 different directions (eight orientations) and contrast sensitivity with eight different contrasts (0-76%). We used Fano factor (FF) of the spike count (bin width 50 ms; step size 5 ms) across the repeated trials to classify neurons into two groups, quenched (Q) and not-quenched (NQ). Our results show the population of neurons associated with FF(baseline) > FF(stimulus onset) induced a significant reduction in response variability after the stimulus onset. Whereas the neurons associated with FF(baseline) < FF(stimulus onset) oppositely increased the response variability. We further demonstrated our classification of neurons is not sensitive to firing rates. Moreover, the neural response linearity (F1/F0 ratio) demonstrated the neurons showing a significant reduction or increase in response variability could be respectively classified as complex (F1/F0 ratio<1) and simple cell (F1/F0 ratio>1) neurons. The more analysis also shows that the excitatory cells more than inhibitory cells behave the quenched response activity as well.

Disclosures: **J. Doostmohammadi:** None. **H. Shabani:** None. **M. Nejatbakhshesfahani:** None. **A. Yoonessi:** None. **R. Lashgari:** None.

Poster

227. Visual System: Response Modulation and Adaptation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 227.04/BB25

Topic: D.07. Vision

Support: NIH Grant PIONEER DP1

HHMI

Title: Figure-ground signaling in the mouse visual system

Authors: ***F. LUONGO**, L. LIU, D. Y. TSAO
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Abstract: Mechanistic studies of the rodent visual system have exploded in the past few years owing to the wealth of molecular, genetic, and chemical tools available for neural circuit perturbations. Although mice have lower spatial acuity than primates, responses of neurons in mouse visual cortex show a marked resemblance to that of primates in tuning to elementary image features (e.g. spatiotemporal frequency, direction and orientation selectivity) when differences in acuity are taken into account. An outstanding question in the field concerns how these elementary visual feature representations are further transformed by the rodent visual system. For example, does the mouse visual system explicitly extract object boundaries from visual scenes to facilitate object and scene perception? In primates, one such example of a neural response strongly suggesting explicit extraction of object boundaries is figure/ground signaling, in which neurons respond differentially depending on whether a stimulus is part of the foreground or background. In this study we presented a battery of stimuli to map the figure/ground responsiveness of neurons in V1 and extra-striate visual areas using both 2-photon calcium imaging and electrophysiology in the awake mouse. We find robust figure-ground signaling in a subset of neurons in both primary and higher order visual areas. We also find that these responses often persist with naturalistic noise textures, thus ruling out center-surround luminance interactions as the mechanism. Lastly, many neurons in higher order visual areas reveal spatial tuning to the presence of figures in specific locations even when such structure is absent using reverse correlation to sparse noise stimuli, indicating a preference for second order statistics beyond luminance contrast. Taken together, these findings are suggestive of the computational capacity for neural circuits in the mouse visual system to extract increasingly object-based representations of visual features thus enabling mechanistic studies of this process while leveraging the molecular and genetic tools available in the mouse.

Disclosures: **F. Luongo:** None. **L. Liu:** None. **D.Y. Tsao:** None.

Poster

227. Visual System: Response Modulation and Adaptation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 227.05/BB26

Topic: D.07. Vision

Support: European Research Council

DFG SFB 870

Title: Dendritic spikes determine visual processing in layer 4 cortical neurons *In vivo*

Authors: *Y. CHEN, Y. ZHANG, B. SONG, A. KONNERTH
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Abstract: A well-established feature of neurons in the mammalian primary visual cortex (V1) is their pronounced tuning to preferred direction/orientation of stimuli such as drifting gratings. This property is considered to emerge from the organization of thalamic inputs originating in the lateral geniculate nucleus (LGN) and terminating in cortical layer 4 (L4). However, recent experimental evidence, including the identification of direction/orientation-tuned LGN axons in L1 and L2/3 of the mouse V1 (Kondo and Ohki 2015; Sun et al. 2015), challenged this view and suggested a higher complexity of the mechanisms underlying direction/orientation tuning in L 4 neurons. In order to obtain deeper insights into this complexity, we performed two-photon calcium imaging experiments in L4 of mouse V1 with the red-shifted calcium indicator Cal-590 AM. The results revealed a strong functional heterogeneity of direction/orientation-tuned L4 neurons, with only a small subset of neurons showing large amplitude and reliable calcium transients in response to visual stimulation. Such 'super-responsive' neurons may have a dominant contribution to the output of L4. Targeted electrophysiological recordings revealed that these neurons can produce up to 40-50 action potentials in response to their preferred stimulus direction (1 s, 0.04 cpd, 2 Hz). For the analysis of the dendritic properties of these neurons, we used a two-step experiment. First, we used Cal-590 AM population imaging to identify 'super-responders' in L4 and then injected such neurons individually with the green calcium indicator OGB-1 via the recording patch pipette. We found that, without exception, all 'super-responsive' L4 neurons had apical tuft dendrites in L1. Remarkably, these tuft dendrites reliably produced calcium transients for the preferred direction of drifting grating stimulation. Non-preferred directions/orientations of the stimuli were ineffective. Several lines of evidence indicated that the tuft calcium transients were local dendritic spikes. These include the larger amplitude of the dendritic shaft calcium transients than that of the more proximal apical dendrite, the sensitivity of the calcium transients to locally-applied antagonists of synaptic excitation (CNQX/APV), the

presence of single spine calcium signals on tuft dendrites that were tuned to the preferred direction/orientation and the sensitivity of the shaft calcium transients to agonists of GABA-B receptors (baclofen). In conclusion, we revealed in the apical tuft dendrites of a subset of L4 neurons local dendritic calcium spikes, which may decisively contribute to their 'super-responsiveness'.

Disclosures: Y. Chen: None. **Y. Zhang:** None. **B. Song:** None. **A. Konnerth:** None.

Poster

227. Visual System: Response Modulation and Adaptation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 227.06/BB27

Topic: D.07. Vision

Support: SMA 1041755

Title: Cholinergic shaping of neural correlations, and effect on neural encoding

Authors: *V. H. MINCES[1], L. PINTO[3], Y. DAN[4], A. A. CHIBA[2]
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Abstract: A primary function of the brain is to form representations of the sensory world. Its capacity to do so depends on the relationship between signal correlations, associated with neuronal receptive fields, and noise correlations, associated with neuronal response variability. It was recently shown that the behavioral relevance of sensory stimuli can modify the relationship between signal and noise correlations, presumably increasing the encoding capacity of the brain. In this work we use data from the visual cortex of the awake mouse watching naturalistic stimuli and show that a similar modification is observed under heightened cholinergic modulation. Increasing cholinergic levels in the cortex through optogenetic stimulation of basal forebrain cholinergic neurons decreases the dependency that is commonly observed between signal and noise correlations. Simulations of correlated neural networks with realistic firing statistics indicate that this change in the correlation structure increases the encoding capacity of the network.

Disclosures: V.H. minces: None. **L. Pinto:** None. **Y. Dan:** None. **A.A. Chiba:** None.

Poster

227. Visual System: Response Modulation and Adaptation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 227.07/CC1

Topic: D.07. Vision

Support: Marie Curie to HGS

ISF 51/11 (I-CORE cognitive sciences) to YN

FP7 CIG to YN

Delis Foundation to YN

Title: Noradrenergic tone modulates visual awareness and visually-evoked activity

Authors: *E. MAGIDOV[1], H. GELBARD-SAGIV[1], H. SHARON[1,3,4], T. HENDLER[1,3,2], Y. NIR[1]
[1]Sackler Sch. Of Med. and Sagol Sch. Of Neurosci., Tel Aviv Univ., Tel Aviv-Yafo, Israel; [2]Sch. of Psychological Sci., Tel Aviv Univ., Tel Aviv- Yafo, Israel; [3]Functional Brain Center, Wohl Inst. of Advanced Imaging, [4]Dept. of Anesthesiology, Critical Care and Pain Med., Tel Aviv Sourasky Med. Ctr., Tel Aviv- Yafo, Israel

Abstract: (*EM and HGS contributed equally to this work*)
How are external events incorporated into subjective experience? The locus coeruleus-noradrenaline (LC-NE) system may play a key facilitating role: its activity is low during sleep when external events typically fail to elicit conscious percepts, whereas during wakefulness strong LC-NE activity occurs when orienting towards salient stimuli. However, despite such correlations between LC-NE activity and perception, causal evidence remains absent. Here, we pharmacologically manipulated NE levels in healthy volunteers, and tested the effects on visual awareness and on visually-evoked EEG and fMRI responses. Either 0.15mg Clonidine (α2-agonist reducing NE levels), 4mg Reboxetine (NE reuptake inhibitor increasing NE levels), or placebo were delivered in three within-subject double-blind cross-over sessions. Image contrast levels associated with threshold detection and discrimination were set individually before drug administration. Two hours later, participants performed visual detection and discrimination tasks while scalp EEG (n=19) or BOLD fMRI (n=6) signals were recorded. Subjective sleepiness, blood pressure, and baseline pupil diameter confirmed effectiveness of noradrenergic drugs during experiments. Behaviourally, reduced NE levels deteriorated sensitivity (d') in visual detection without significantly affecting criterion. Likewise, reduced NE levels impaired accuracy and subjective confidence in visual discrimination. Performance on sustained-attention and suprathreshold discrimination tasks were mostly unaffected, suggesting that results go

beyond mere sedation. Increased NE levels were associated with a trend for better performance. Reducing NE levels led to degraded late visually-evoked EEG responses compared to placebo. NE effects included lower amplitude and higher latency of the ERP N1 component (170-200ms), and weaker attenuation (250-550ms) in 8-20Hz induced power, whereas early (~100ms) response signatures such as the P1 component were not affected by NE levels. Finally, we found that BOLD fMRI activations in high-order visual cortex varied in accordance with NE levels, while activity in other cortical areas was largely NE-independent. Taken together, these results suggest that NE plays an enabling causal role in visual awareness by affecting late visual processing.

Disclosures: E. Magidov: None. **H. Gelbard-Sagiv:** None. **H. Sharon:** None. **T. Hendler:** None. **Y. Nir:** None.

Poster

227. Visual System: Response Modulation and Adaptation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 227.08/CC2

Topic: D.07. Vision

Support: Funded by NERF

Title: Stimulus direction biases arousal and responses in the mouse visual system

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Abstract: Several recent studies of visual processing in rodents have linked sensory cortical responses to the animal's behavioral state. In visual cortex, arousal and movement are linked to increased sensory responses. Much less understood is how a visual stimulus can influence the animal's behavioral state. We combined genetic labelling and cellular imaging to characterize axonal projections from dorsal lateral geniculate nucleus (dLGN) to primary visual cortex (V1) in mice engaged in a head-fixed locomotion task. We measured pupil diameter and locomotion speed as proxies of the behavioral state. To probe neurons' sensory responses, we stimulated the contralateral eye with drifting grating stimuli (4 Hz, 0.08 cpd) of 12 different directions covering a 120-by-80-deg region in the visual field (centered at 45 deg azimuth). Consistent with recent studies in awake mice (Sun et al. 2016, Roth et al. 2016), dLGN neurons showed diversely tuned responses to the visual stimuli in V1. Consistent with electrical recordings in the same preparation (Aydin et al., 2017 SFN Abstract Viewer), we observed strong positive association between movement, pupil size and dLGN responses. To assess to which degree response tuning

reflects stimulus-induced changes of the behavioral state, we related pupil size to the direction of the grating stimuli. In more than half of animals, presentation of a stimulus moving in the posterior-to-anterior direction was associated with a pronounced increase in pupil size. The effect was strongest in animals moving on the treadmill less than half of the time. Due to the positive association between changes in arousal and neural activity, dLGN responses were strongly biased towards horizontal motion in the posterior-to-anterior direction. The effect had a significant impact on the inferred visual tuning preferences of the neurons. These findings demonstrate the importance of assessing the impact of sensory stimulation on the behavioural state in awake rodent neurophysiological studies. They might explain the significant differences in measurements of direction properties and preference in anesthetized and awake mice (Kondo et al. 2016, Sun et al. 2016).

Disclosures: K.Z. Socha: None. **V. Bonin:** None.

Poster

227. Visual System: Response Modulation and Adaptation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 227.09/CC3

Topic: D.07. Vision

Support: R01 EY17605

Title: Altered gain modulation in primary visual cortex in an animal model of schizophrenia

Authors: *A. SCHIELKE[1], B. KREKELBERG[2]
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Abstract: Visual perception in patients with schizophrenia is commonly neglected in clinical practice. However, patients display significant alterations in visual processing and perception. These differences are stable throughout the course of the disease, better prodromal indicators of disease progression than many traditional neuropsychological tests, and thought to be related to aberrant neural dynamics in visual cortex.
We created the hypofunction of the NMDA receptor that has been suggested as an animal model for schizophrenia by injecting a subanesthetic dose (0.3 mg/kg) of ketamine intramuscularly in two nonhuman primates (m. mulatta). To study neural dynamics in a manner akin to research with human subjects, we presented full-screen luminance flicker and measured the following response in the local field potentials (LFP) in primary visual cortex (V1) using permanently implanted multi-electrode arrays.
Compared to saline control injections, Ketamine strongly reduced the gain of the following response for approximately one hour after the injection.
These findings support the view that NMDA hypofunction could underlie visual deficits in Sz

and, more specifically, that gain control might be affected in Sz. In addition, these results show that visual processing in the macaque can be a fruitful model to investigate neural mechanisms of schizophrenia.

Disclosures: A. Schielke: None. **B. Krekelberg:** None.

Poster

227. Visual System: Response Modulation and Adaptation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 227.10/CC4

Topic: D.07. Vision

Support: NIH EY024662

Title: Correlations between perceptual and neural effects of target-background orientation similarity on target detection in primate V1

Authors: *S. C.-Y. CHEN[1], Y. Y. CHEN[2], W. S. GEISLER[3], E. SEIDEMANN[2]
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Abstract: A primary function of our visual system is to identify objects in natural environments. Object detection is strongly dependent on the properties of the background scene against which the object appears. Properties known to have major effects on detectability are background luminance, background contrast, and similarity of the background to the target. Of these, background similarity is the least understood in terms of the underlying neural mechanisms. Here, we first measured how detection of an oriented target by macaque monkeys is affected by the orientation of the background. Specifically, we trained two monkeys to detect an additive Gabor target (4 cpd, 0.84° diameter, 3° eccentricity, various contrasts) on 4-cpd backgrounds (3°, various contrasts) of various orientations. As expected from the human psychophysical literature, the monkeys' detection rate was lowest when the background grating orientation was aligned to the target ($\Delta\theta=0°$, maximal visual similarity), and increased as a function of $\Delta\theta$. We then measured how these backgrounds affected the neural responses to the target in primary visual cortex (V1). Using voltage-sensitive-dye (VSD) optical imaging, we measured V1 population activity while the monkeys performed the task. We examined two components of the VSD response (after subtracting the corresponding background-only response): i) the strength of the signal within the spatial envelope of the response to the target (the retinotopic response), and ii) the bandpass-filtered (0.8 to 3.0 cyc/mm) signal within the same spatial envelope (the columnar response). We have previously shown that the retinotopic response is a good predictor of monkeys' detection performance on uniform backgrounds (Chen 2006, Nat. Neurosci). Here, we find that the retinotopic response is a poor predictor of detection performance as a function of

background orientation; the retinotopic response is relatively flat or a *decreasing* function of Δθ. In comparison, we found that the columnar response to the target was more consistent with the monkey's behavior. The columnar response was weakest when aligned to the background (Δθ=0°), and greatest at Δθ=90°. We conclude that, like humans, monkeys' ability to detect an oriented target is reduced when background orientation is similar to that of the target. Further, this masking effect is qualitatively consistent with V1 population responses measured at the scale of orientation columns but not at the retinotopic scale.

Disclosures: S.C. Chen: None. **Y.Y. Chen:** None. **W.S. Geisler:** None. **E. Seidemann:** None.

Poster

227. Visual System: Response Modulation and Adaptation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 227.11/CC5

Topic: D.07. Vision

Support: NIH Grant 1R15EY023834

Title: Neural gain enhancement following an artificial scotoma

Authors: *M. GANNON, S. M. LONG, A. RODRIGUEZ, N. A. PARKS
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Abstract: Artificial scotoma paradigms have been used in the human and animal literature to produce effects analogous to retinal deafferentation, which can be used as a proxy for examining short-term homeostatic plasticity. In such studies, a peripherally circumscribed region of uniform luminance is placed within a background of dynamically changing white noise which, when viewed for several seconds, gradually fades from awareness. That is, the region deprived of the background stimuli becomes 'filled-in' with white noise. Such simulated deafferentation of visual cortical tissue representing the region of space occupied by the scotoma results in local disinhibition, which has been proposed to drive the filling-in phenomenon. The impact of disinhibition within the cortical scotoma projecting zone has been proposed to induce receptive field expansions and increase neural gain. Here, we sought to examine the occurrence of these two short-term visual alterations using event-related potentials (ERPs) and psychophysical measurements. Participants viewed an artificial scotoma display consisting of two gray discs superimposed on a white noise background for 6 seconds (scotoma condition) or 1 second (sham condition). The task of the participant was to indicate the tilt of a high spatial frequency (8.0 cpd) or low spatial frequency (1.0 cpd) Gabor probe which was briefly flashed within the boundaries of the artificial scotoma. Visual-evoked potentials (VEPs) were measured to the onset of the Gabor probe and orientation discrimination curves were constructed by varying the tilt of the Gabor between 0.5º and 16.0º. The P1 component of the visual-evoked potential (VEP) was used

as an index of neural gain, while changes in contrast sensitivity curves would be indicative of modulation of the tuning curve within neural populations within the scotoma zone. Preliminary analyses indicate that the scotoma conditions exhibited an enhanced P1 compared to sham conditions, consistent with increased neural gain through disinhibition. However, there was no clear signature of receptive field expansion apparent in psychophysical orientation discrimination functions for high and low spatial frequencies.

Disclosures: M. Gannon: None. **S.M. Long:** None. **A. Rodriguez:** None. **N.A. Parks:** None.

Poster

227. Visual System: Response Modulation and Adaptation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 227.12/CC6

Topic: D.07. Vision

Support: NIH Grant MH93567

Title: Most calbindin-immunoreactive neurons, but few calretinin-immunoreative neurons, express the m1 acetylcholine receptor in macaque MT

Authors: *J. J. COPPOLA, A. A. DISNEY
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Abstract: Inhibitory interneurons comprise non-homogeneous populations in cortex, with considerable structural and functional diversity. Traditionally, these populations have been classified based on their morphologies. More recently, molecular markers—such as calcium-binding proteins—have become a prevalent alternative for interneuron classification particularly in non-human primates. Parvalbumin, calbindin-D28k, and calretinin are calcium-binding proteins whose immunoreactivities are used as population markers for diverse classes of cortical interneurons. In the present study, we used dual-immunofluorescence to identify neurons expressing the m1 acetylcholine receptor with either calbindin or calretinin in macaque middle temporal area MT. We counted 2791 immunoreactive neurons in a total area of approximately 5.4mm^2 across three animals. Our results indicate that the majority of calbindin-immunoreactive neurons (56%) express the m1 receptor, while only few calretinin-immunoreactive neurons (10%) express the m1 receptor. Results from a previous study show that most parvalbumin-immunoreactive neurons (75%) in MT also express the m1 receptor. Because of the morphological and physiological variation in neurons that express calcium-binding proteins, their activation likely results in different forms of inhibitory regulation of a cortical circuit. As such, variation in the expression of cholinergic receptors by these interneuron types may result in differences in the neuromodulation of cortical areas exerted by acetylcholine. Interestingly, the m1 receptor is expressed by approximately 40% of calretinin-immunoreactive neurons in

macaque primary visual area V1. Thus, cholinergic modulation of cortical circuits through calretinin-immunoreactive neurons likely varies between MT and V1. This provides evidence for the existence of unique neuromodulatory compartments across cortex. These compartments can be defined by features of the local cortex that constrain and shape the way acetylcholine interacts with the receiving circuitry, resulting in distinct neuromodulatory regulation across cortical areas. The existence of neuromodulatory compartments calls for thinking about cholinergic modulation in terms of finer-grained control of local cortical circuits than is implied by the traditional view of this system as a diffuse and loosely topographic modulator.

Disclosures: J.J. Coppola: None. **A.A. Disney:** None.

Poster

227. Visual System: Response Modulation and Adaptation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 227.13/CC7

Topic: D.07. Vision

Support: NIH RO1 EY024912

NIH P50 MH103204

Title: Repetition suppression In macaque inferotemporal cortex is selective for feature conjunctions

Authors: *N. P. WILLIAMS, C. R. OLSON
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Abstract: Neurons of macaque inferotemporal cortex (ITC) exhibit repetition suppression. When an image is presented twice in succession, first as prime and then as probe, the probe elicits a relatively weak response. Previous studies have shown that suppression disappears when the probe is completely different from the prime. They have not, however, investigated what happens when the probe is rendered different from the prime by degrees. To cast light on this issue, we adopted an experimental design in which the prime and the probe were colored shapes. The probe could match the prime in color, in shape, in both attributes or in neither attribute. Upon recording neuronal responses to prime-probe displays, we found that suppression was strongest when the probe matched the prime in both attributes, was weaker when it matched the prime in a single attribute and was weakest when it matched the prime in neither attribute. The fall-off from perfect match to imperfect match was comparatively sharp. To explain the fall-off required a model incorporating a nonlinear term sensitive to the conjunction of shape and color. This finding is striking because ITC neurons are not themselves sensitive to color-shape conjunctions as established in a prior study (McMahon and Olson, 2009) and as confirmed by an

analysis of responses to the prime stimuli in the present experiment. This outcome is germane to the distinction between fatigue-based and correlation-based models of repetition suppression (Kohn, 2007; Barlow & Foldiak, 1989; Grill-Spector, 2006). In a fatigue-based model, selectivity of suppression should be no sharper than selectivity of the initial response. A correlation-based model easily allows for enhanced selectivity (Hosoya, Baccus & Meister, 2005). Thus the present results fit best with a correlation-based account of repetition suppression.

Disclosures: N.P. Williams: None. **C.R. Olson:** None.

Poster

227. Visual System: Response Modulation and Adaptation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 227.14/CC8

Topic: D.07. Vision

Title: Locomotion impacts early visual response amplitudes but not their tuning

Authors: *C. AYDIN[1,2,3], J. COUTO[1,3], K. FARROW[1,2,3], M. GUIGLIANO[4,5,6], V. BONIN[1,2,3]
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Abstract: Sensory responses in the cortex are strongly influenced by an animal's behavioral state. In the mouse visual cortex, neurons show a net increase in neural activity during locomotion, which has been linked to enhanced spatial acuity. However, whether this increase in neuronal activity impacts the tuning properties of individual neurons, and whether the increased neural activity is present in thalamic inputs to the cortex remains unresolved. To address these issues, we simultaneously recorded spiking activity of neurons in dorsal lateral geniculate nucleus (dLGN) and primary visual cortex (V1) of head-restrained mice that voluntarily moved on a treadmill. We presented upward-drifting sinusoidal gratings of different spatial and temporal frequencies, and compared the responses of neurons measured during periods of locomotion and rest. To quantify the tuning properties of each neuron, we measured the mean firing rate (F0) and first harmonic (F1) during the presentation of each stimulus. We found that locomotion affected the response of dLGN and V1 neurons similarly. In each area, locomotion was linked to an increase in the F1 response amplitude at each spatial and temporal frequency, while no shifts were observed in either the spatial or temporal preferences of dLGN and V1 neurons. In approximately two-thirds of the neurons, the F0 response was proportional to that of the F1 response. However, a subgroup of dLGN and V1 neurons showed a pronounced modulation that could not be explained by the neurons' F1 response. These neurons had an

elevated F0 response at high spatial frequencies. We conclude that neuronal responses in the dLGN are diversely modulated by locomotion, similar to previous observations in V1. Our study highlights the importance of considering behavioral modulations of thalamic inputs in models of cortical activity.

Disclosures: C. Aydin: None. **J. Couto:** None. **K. Farrow:** None. **M. Guigliano:** None. **V. Bonin:** None.

Poster

227. Visual System: Response Modulation and Adaptation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 227.15/CC9

Topic: D.07. Vision

Support: Swiss National Science Foundation

Title: Seeing what you think you see: The influence of auditory and retrosplenial cortex input on coding in primary visual cortex during associative learning

Authors: *A. R. GARNER, G. B. KELLER
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Abstract: The theory of predictive coding posits that the brain does not simply represent the world with feature detectors but uses internal models to predict the external environment and updates these models with new sensory experience. Synthetic activation of internal representations of an environment changes an animal's behavior depending on what the animal has previously associated with that environment (Garner et al. 2012). It has also been demonstrated that as early as primary sensory cortex, neurons respond specifically to sensory events that would not be predicted given the animal's self-generated behavior (Keller et al. 2012, Zmarz et al. 2016) and statistical regularities of the environment (Fiser et al. 2016). To address whether primary sensory cortex builds internal models using learned associations of sensory stimuli, and updates these models with continued experience, we investigated coding patterns in primary visual cortex (V1) using 2-photon calcium imaging in mice navigating a virtual environment in which paired auditory and visual stimuli were either rewarded or punished. Both auditory cortex (AuC) and a region known to be involved in associative learning, retrosplenial cortex (RsC), provide input to V1. We hypothesized that these regions could guide the formation and updating of internal models in V1, and measured functional input patterns of AuC and RsC in V1. We found that activity in axons from both regions was strongly driven by visual stimuli, and while unpaired visual stimuli elicited consistent responses across multiple conditioning days, responses to visual stimuli that were predictive of either reward or punishment changed with learning. Axons also responded to the reward and punishment, and these responses diverged in

opposing directions with learning. Our data suggests that in addition to self-generated movements and statistical regularities in the environment, primary visual cortex uses previously acquired associations with visual stimuli to represent those stimuli and predict their relevance in future encounters.

Disclosures: A.R. Garner: None. **G.B. Keller:** None.

Poster

227. Visual System: Response Modulation and Adaptation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 227.16/CC10

Topic: D.07. Vision

Support: Wellcome Trust 093104

Title: Optogenetic stimulation in V4 modulates visual responses in primate area V1

Authors: *M. A. GIESELMANN, M. BOYD, A. THIELE
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Abstract: Feedback connections from higher cortical areas alter sensory evoked activity in lower cortical areas. Experiments directly probing the specifics of these effects generally relied on methods such as electrical microstimulation. However, methods like microstimulation are unspecific regarding neuronal targets, and also potentially activate axonal fibres. Newer techniques like optogenetic stimulation provide a higher degree of target specificity by means of viral constructs that induce neurons to express light sensitive channels. Here we investigate how driving macaque extrastriate area V4 by means of Channelrhodopsin activation affects processing in area V1.
We injected AAV5-CamkII-Chr2-eYFP into area V4 of a rhesus monkey. After a 1.5 and 4 months incubation period we tested for successful transfection by recording extracellular activity from a laminar electrode (16 linear contacts, 150μm spacing) under control conditions and during optical stimulation using a LED (CoolLED pE-100, 470 nm, 90 mW) with a 2 mm diameter fibre placed extradurally inside the V4 chamber. No optically induced activity could be elicited after 1.5 months. However, after 4 months optical stimulation elicited short-latency tonic excitation (125 Hz max. rate increase, MI=0.85) of V4 neurons recorded from multiple electrode array contacts over a cortical depth of ~1.2 mm. We then conducted 16 experiments, recording neuronal V1 activity from laminar electrodes under control conditions and while optically stimulating V4 neurons. Optical stimulation and electrophysiological recordings were done in spatially separated recording chambers. The monkey performed a passive visual fixating task while square wave gratings of 5 diameters and 6 orientations centered on the receptive fields of the V1 neurons under study were presented. We extracted thresholded spiking activity of multi-

units (MUA) from each electrode contact. We analysed channels that showed robust stimulus induced transient responses (SNR>3) in non-light trials (n=148 MUAs). For these channels, we performed 3-way ANOVA with the factors size, orientation, and optogenetic stimulation (light on/off). Optogenetic stimulation significantly modulated activity in 26 units (17.6 %, significant main effects or interactions, 3 factor ANOVA). The light induced changes could be restricted to the sustained response period, reminiscent of the effects of e.g. attention or spatial working memory. Moreover, they often depended on stimulus orientation and stimulus size.
Thus, optogenetic induced activation of V4 neurons affects stimulus driven responses in macaque V1.

Disclosures: M.A. Gieselmann: None. **M. Boyd:** None. **A. Thiele:** None.

Poster

227. Visual System: Response Modulation and Adaptation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 227.17/CC11

Topic: D.07. Vision

Support: NIH Grant 1R01EY027402-01

NIH Grant 2T32EY007135-21

KTEF: Career Starter grant by the Knights Templar Eye Foundation

Title: Repetitive visual stimulation suppresses spiking responses across V1 laminae

Authors: *J. A. WESTERBERG, M. A. COX, K. DOUGHERTY, A. MAIER
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Abstract: Repetition suppression is a type of neuronal adaptation that is characterized by diminished responses following repeated presentation of the same or similar stimuli. Repetition suppression has been well characterized on the single neuron level for primate extrastriate areas, particularly the inferotemporal cortex (IT). The degree to which this phenomenon occurs at earlier stages of visual processing is less clear. Here, we report a repetition suppression-like phenomenon in striate cortex (V1) of the awake, behaving monkey. High contrast grating stimuli were shown to two fixating macaques (*Macaca radiata*) in a series of several hundred millisecond-long sequential presentations while we recorded V1 spiking activity using laminar microelectrodes that spanned the depth of cortex. Neuronal activity on each electrode channel was determined to be of either supragranular, granular, or infragranular laminar origin using neurophysiological criteria. We isolated up to 120 single units from both monkeys for each of these three laminar compartments, and studied their response to the repetitive stimulation. We found that across all layers, the initial stimulus presentation of each sequence evoked

significantly greater spiking responses than all of the subsequent presentations on both the single unit level as well as on the population spiking level. Similar to findings from IT cortex, the largest reduction in spiking responses occurred between the initial and the second presentation of the repeated stimuli. However, the magnitude of V1 spiking responses remained relatively constant from the third presentation onward, which deviates from reports of spiking suppression in IT. Characterization of the relationship between the magnitude of V1 repetition suppression and stimulus orientation as well as ocularity suggested that repetition suppression in V1 is unlikely to be entirely inherited from feedforward thalamic input. Taken together, these results suggest that repeated presentations of visual stimuli result in a systematic reduction of V1 spiking responses that resembles repetition suppression described for IT cortex in some but not all respects.

Disclosures: J.A. Westerberg: None. **M.A. Cox:** None. **K. Dougherty:** None. **A. Maier:** None.

Poster

227. Visual System: Response Modulation and Adaptation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 227.18/CC12

Topic: D.07. Vision

Support: NIH Grant EY016431

Title: Modifying the response to repetitive visual stimuli

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Abstract: Perceptual learning in response to repetitive visual stimulation has been proposed as a mechanism to improve visual performance in amblyopes. Yet, the robust response potentiation observed after repeated presentation of visual stimulus reversing at 1 Hz is specific to the attributes of the experienced stimuli (Cooke et al., 2015), similar to other types of perceptual learning. Here we manipulate the temporal frequency of the repetitive visual stimulus and the history of visual experience, to ask if these parameters impact the stimulus-selectivity of visual response potentiation. We first used the immediate early gene c-fos to assess the number of neurons activated by different frequencies of visual stimulation, finding that 10 Hz visual stimulation activates a larger number of V1 neurons in adult (>P90) C57 mice (19.2±6% of NeuN stained cells, One-way ANOVA, p=0.0045) than either 1 Hz (10.6±7%) or 20 Hz visual stimulation (7.0±9%). We next examined VEP and single unit activity response potentiation *in vivo,* 24 hours after 1-20 Hz visual stimulation, using chronically implanted linear electrode

arrays. As expected, 1 Hz stimulation induced a potentiation of VEP amplitudes that was restricted to layer IV (23.4±6%, paired t-test, p=0.003) and was not seen in response to novel stimuli (-0.3±9%, paired t-test, p=0.45). However, 10 Hz stimulation induced VEP potentiation in layers 2/3 (18.2±9%) and 5 (33.7±12%). Importantly, a similar increase in VEP amplitude was observed in response to a novel visual stimulus (Layer 3: 17.1±5%, Layer 5: 25±7%). An increase in the firing rates of regular spiking (2.2±0.3Hz before, 3.69±0.2Hz after, t-test, p= 0.0039) and fast spiking neurons (3.59±0.7Hz before, 5.49±0.7Hz after, unpaired t-test p=0.029) was also observed 24 hours after 10Hz stimulation. This increase in fast-spiking interneuron excitability is not seen with other frequencies of visual stimulation (1 Hz: 6.55±0.9Hz before, 6.69±0.9Hz after, t-test, p=0.91). In binocular adults, dark exposure followed by light reintroduction shifted the locus of 1 Hz response potentiation from layer 4 to layer 2/3 (36.6±4%, paired t-test, p=0.011), suggesting a shift in the locus of plasticity away from thalamo-cortical synapses. Interestingly, we recently reported that light reintroduction following dark exposure induced an increase in perisynaptic activity of MMP-9 at thalamic inputs to cortical neurons, which may contribute to this shift in plasticity locus (Murase et al., submitted). Thus the response to repetitive visual stimulation is modified by changing the characteristics of the visual stimulus as well as the history of visual experience.

Disclosures: **C.L. Lantz:** None. **S. Murase:** None. **E.M. Quinlan:** None.

Poster

227. Visual System: Response Modulation and Adaptation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 227.19/CC13

Topic: D.07. Vision

Support: NIH Grant EY025535

Title: Information redistribution after orientation adaptation in macaque V1

Authors: *Y.-C. LIN[1], D. J. THENGONE[2], J. D. VICTOR[2]
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Abstract: Adaptation, a process in which neuronal properties are modulated as a result of recent stimulus history, is widespread in sensory systems. It is hypothesized that a key functional role of adaptation is to adjust neural sensitivities to the changing range of inputs in a dynamic sensory environment. Here, using neural orientation tuning in macaque area V1 as a model, we studied the nature of sensory information conveyed before and after adaptation to determine whether such adaptive shifts are present.
We analyzed multi-tetrode recordings of responses of 167 V1 neurons (in 6 anesthetized and paralyzed macaques) to grating patches, before and after presentation of 400 ms and 40 sec

adapting gratings. The dataset included neurons whose preferred tuning axes were at a range of distances from the adapting orientation. Information was quantified by two measures. Shannon Information (SI), a global measure, quantified the overall reduction in uncertainty about grating orientation provided by the neural responses. Fisher information (FI), a local measure, quantified the ability to discriminate between each orientation and nearby ones. Information estimates were computed by modeling orientation tuning curves by von Mises functions, fitted to the observed responses by maximum-likelihood under the assumption of Poisson variability. To determine information carried by the population, neural responses were assumed to be conditionally independent.
Adaptation affected the two measures of information differently. On the one hand, the overall amount of information (SI) did not change between the baseline and the adapted state. This held for the population as a whole, and also for putative excitatory and inhibitory subsets as identified by analysis of extracellular waveshape. In contrast, Fisher information was redistributed: it was relatively increased for orientations near the adapting orientation and decreased at orientations that were 45 to 60 degrees away. This shift was confined to the putative excitatory cell subset; no corresponding shift was seen in narrow-spiking neurons. In summary, we find that while adaptation does not alter the overall amount of information about orientation, it redistributes this information to emphasize orientations that were recently present - and that excitatory and inhibitory neurons have different roles in this process.

Disclosures: Y. Lin: None. **D.J. Thengone:** None. **J.D. Victor:** None.

Poster

227. Visual System: Response Modulation and Adaptation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 227.20/CC14

Topic: D.07. Vision

Support: NEI Grant EY026977

Max Planck Florida Institute

Title: Temporal characteristics of contrast adaption in ferret visual cortex

Authors: S. PUSDEKAR, *J. SCHUMMERS
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Abstract: Prolonged exposure to sensory stimuli leads to a reduction in response amplitude in sensory neurons. This adaptation is a phenomenon that has been observed at multiple levels of processing across sensory modalities, and has been linked to predictable perceptual consequences. Adaptation has been proposed to function as a gain-control mechanism to ensure

adequate dynamic range of responses under different sensory conditions. Contrast adaptation, which occurs in the visual cortex, has been found to be a cortical phenomenon. However, the cellular, synaptic and circuit mechanisms for contrast adaptation remain to be fully described. Classical electrophysiological studies observe contrast adaptation over multiple timescales and suggest that they might involve different mechanisms. In this study, we characterize the temporal dynamics of contrast adaptation using in-vivo two-photon calcium imaging of virally-expressed GCaMP6s in the adult ferret visual cortex. We quantify the amount and duration of adaptation as a function of the duration of the adapting stimulus. In order to do so, we have developed a novel paradigm which allows for the measurement of responses at four second intervals for up to 56 seconds. We observe substantial attenuation of responses to the test stimulus after a 4s presentation of a high contrast grating stimulus near the preferred orientation. Our preliminary analysis of 137 neurons demonstrates that 76% of cells demonstrate a significant reduction in response immediately following the adapting stimulus, with a mean reduction of 35% (range 12% to 64%) in those cells. Importantly, responses did not recover to baseline levels until on average 28 seconds after presentation of the adapting stimulus (80% of cells), suggesting that even relatively brief stimulation can have prolonged effects. Presentation of a 1s adapting stimulus elicited substantially weaker and more variable adaptation. Ongoing studies will characterize more finely the dependence of adaptation strength and duration on the duration of the adapting stimulus.

Disclosures: S. Pusdekar: None. **J. Schummers:** None.

Poster

227. Visual System: Response Modulation and Adaptation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 227.21/CC15

Topic: D.07. Vision

Support: NSERC

Title: Co-ordinated adaptive changes of layer 2/3 and layer 5/6 multiunit activity (MUA) orientation tuning in the cat visual cortex

Authors: *N. CHANAURIA[1], V. BHARMAURIA[2], L. BACHATENE[3], F. ETINDELE SOSSO[1], J. ROUAT[4], S. MOLOTCHNIKOFF[5]
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Abstract: Multiunit activity (MUA) recorded from the cortex is inevitable for understanding the activity of a group of neurons. Single unit activity (SUA) can be sorted from MUA, and then inspected for further scrutiny. Visual cells are sectioned into orientation columns in higher vertebrates, that is, neurons exhibiting similar orientation tuning are clustered together. Indeed, at single cell level it has been shown that visual neurons typically show attractive (toward the adapter) and repulsive shift (away from the adapter) when a non-preferred (adapter) stimulus is imposed upon them for a certain duration of time. Recently, we have shown that, at single cell level, layer 2/3 and layer 5/6 neurons show comparable shifts in the primary visual cortex of cats (Chanauria et al., 2016) suggesting that columnar neurons (extending from L2/3 to L5/6) display similar shift patterns toward the adapter. We hypothesized that the population activity (multiunit) of neurons fundamentally nests behavior of individual neurons comprising it, and could be an important analytical factor in further understanding the behavior of a pool of local neurons. Building upon this, we sought to examine the shift behavior of the multiunit activity simultaneously recorded from both layers. To this goal, using tungsten multichannel depth electrode, multiunit recordings were performed in L2/3 and L5/6 of area 17 in anaesthetised cats. We computed the tuning curves of single units and the respective multiunit activity (pre- and post-adaptation) recorded at an electrode. We found that a significant proportion of sites exhibited orientation tuning changes of single and multiunit activity in a similar fashion toward the adapter. This preliminary analysis further corroborates and suggests that neurons in a single column (extending from L2/3 to L5/6) behave in a similar fashion to the adapter, thereby conserving the functional dogma of columnar processing by visual neurons after adaptation. Further analyses are targeted on computing coherence between the respective SUA and MUA of both layers at pre- and post-adaptation.

Disclosures: N. Chanauria: None. **V. Bharmauria:** None. **L. Bachatene:** None. **F. Etindele Sosso:** None. **J. Rouat:** None. **S. Molotchnikoff:** None.

Poster

227. Visual System: Response Modulation and Adaptation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 227.22/CC16

Topic: D.07. Vision

Support: NIH Grant EY 019743

NIH Grant EY026821

NINDH BRAIN Grant U01 NS099702

NSF Grant IOS 1355075

NSF Grant EAGER 1649923

University of Utah Research Foundation Seed Grant 10040877

University of Utah Neuroscience Initiative

Title: Origin of correlated variability in primate cerebral cortex

Authors: *L. NURMINEN[1], M. BIJANZADEH[2,3], A. ANGELUCCI[2]
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Abstract: Cortical neurons emit a variable number of spikes in response to repeated presentations of an identical stimulus. This spike-count variability is shared across neurons and has traditionally been interpreted as correlated Poisson-like noise. Previous experimental studies have focused on the stimulus dependence and structure of the correlated variability, but its origin has received less attention.

Here, the origin of correlated spike-count variability in the primate visual cortex was investigated by optogenetically inactivating feedback connections from the secondary (V2) to the primary (V1) visual cortex in marmoset monkeys. The optical neural silencer ArchT was expressed in V2 neurons by injecting a viral vector mixture (1:1, AAV9.CaMKII.Cre and AAV9.flex.CAG.ArchT.GFP, 480nL/injection site, 2-3 sites, 2 depths/site) into area V2 identified by optical imaging. One to two months after the injections, extra-cellular linear electrode array recordings were performed in V1 under anesthesia (sufentanil, 4-12μg/kg/h), while green light (532 nm, irradiance $\leq 43 mW/mm^2$) was targeted to the axon terminals of V2 feedback neurons within V1.

We found that inactivating feedback reduced spike-count variability (Fano factor) in supra- and infragranular layers that receive dense feedback projections from V2. Spike-count variability was unaffected by feedback inactivation in the granular layer. This finding is consistent with the idea that spike-count variability is caused by modulatory inputs such as cortico-cortical feedback. Strikingly, some of the neurons in our sample approached deterministic (noiseless) behavior when feedback from V2 was inactivated.

Hansen and Dragoi (2012) found that correlated variability is higher in the feedback recipient supra- and infragranular layers compared to the granular layer. This finding suggests that feedback plays a role in generating correlated variability. Indeed, we found that inactivating feedback from V2 reduced correlated variability in the supra and infragranular layers of V1, whereas correlated variability in the granular layer was not affected by feedback inactivation. Our results provide causal evidence that cortico-cortical feedback contributes to correlated spike-count variability in primate cerebral cortex. This suggests that neural variability is largely a by-product of on-going computations in the brain.

Disclosures: L. Nurminen: None. **M. Bijanzadeh:** None. **A. Angelucci:** None.

Poster

227. Visual System: Response Modulation and Adaptation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 227.23/CC17

Topic: D.07. Vision

Support: NIH EY026240

Title: Effects of optogenetic stimulation of feedback on the coordination of macaque V1 activity

Authors: *S. S. SOLOMON[1], A. ASCHNER[2], A. KOHN[3]
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Abstract: Feedback pathways, which project from higher to lower cortex, are thought to underlie functions such as attending, perceiving context and learning. However, the physiology of feedback circuitry is not well understood. To elucidate its properties, we recorded from neuronal populations in primary visual cortex (V1) of anesthetized macaque monkeys, while stimulating V2 optogenetically. Transfection was accomplished with AAV1 viral vectors (hSyn promoter) encoding channelrhodopsin and eYFP, injected in V2. Histology confirmed robust expression in V2, particularly in the deep layers; we also observed expression in V1, which was stronger in layers 4A, 4C and 6. We measured the effect of V2 stimulation on V1 spontaneous activity and responses evoked by drifting gratings of different orientations, sizes, and contrasts. We previously showed that V2 stimulation reduced the spiking co-variability of V1 neuronal pairs; this decrease was observed between neurons whose firing rates were modulated by V2 stimulation (‘laser cells’) as well as those that were not (‘non-laser cells’). In contrast, optogenetic stimulation of V1 had no effect on V1 co-variability. To determine further the effect of feedback on network coordination, we analyzed local field potentials (LFPs) and the structure of population spiking activity in V1. V2 stimulation enhanced V1 LFP power at high frequencies (>30 Hz), an effect that decreased in magnitude when stimulation was paired with the presentation of high contrast visual stimuli. We did not observe a preferential modulation of LFP activity in beta frequency bands. To test whether feedback alters the structure of V1 population spiking activity, we used factor analysis (FA). FA is a dimensionality reduction technique which provides an estimate of the number of factors (dimensions) needed to account for shared variability within a neuronal population. The number of factors required to explain the shared variability of V1 populations was not affected by V2 stimulation. However, more factors were required to explain the shared variability in populations of V1 ‘laser cells’ than those of ‘non-laser cells’. We conclude that feedback has robust effects on network coordination; optogenetic stimulation of this pathway modulates primarily the magnitude rather than the structure of coordination.

Disclosures: **S.S. Solomon:** None. **A. Aschner:** None. **A. Kohn:** None.

Poster

227. Visual System: Response Modulation and Adaptation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 227.24/CC18

Topic: D.07. Vision

Support: NIH Grant EY22428

HHMI

Title: Selectivity of contextual modulation in macaque V1 and V2

Authors: ***C. M. ZIEMBA**[1,2], R. K. PEREZ[1], E. P. SIMONCELLI[1,2], J. A. MOVSHON[1]
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Abstract: The activity of neurons in visual cortex is modulated by what lies beyond the classical receptive field. Surrounding contrast usually suppresses responses, and the strength of this suppression is often selective for visual features. In V1, suppression is maximal when the orientation of a drifting grating presented in the surround matches the orientation presented to the center. More broadly, V1 suppression is strongest when center and surround images match, and weaker when they differ in image statistics. Less is known about surround suppression in V2, although its influence on responses is similar to that in V1 when studied with drifting gratings. We have recently shown that V2 neurons, but not V1 neurons, respond more strongly to "naturalistic" textures containing higher-order statistical dependencies than to spectrally-matched "noise" images containing only second-order dependencies. We wondered whether these stimuli might reveal differences in contextual modulation between the areas. We measured the responses of single V1 and V2 units in both anesthetized and awake, fixating macaque monkeys to naturalistic and noise images presented within an aperture that varied in diameter. In V1, suppression was similar for both types of stimuli, with a slight tendency for naturalistic images to evoke stronger suppression. This is consistent with previous work in V1, as naturalistic images contain correlations over space that impose stronger dependencies between center and surround. In contrast, surround suppression in V2 neurons was much weaker for naturalistic textures than for spectrally-matched noise images. We wondered whether these results depended more on stimulus statistics in the center of the receptive field or in the surround. Preliminary measurements with mixture stimuli suggest that suppression is actually weakest in V2 when the center is stimulated with naturalistic texture and surrounded by spectrally-matched noise. These results suggest that the statistical structure of visual context plays a more sophisticated role in modulating the selectivity of neuronal responses in V2 than it does in V1.

Disclosures: **C.M. Ziemba:** None. **R.K. Perez:** None. **E.P. Simoncelli:** None. **J.A. Movshon:** None.

Poster

227. Visual System: Response Modulation and Adaptation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 227.25/CC19

Topic: D.07. Vision

Title: Difference of visual evoked magnetic fields with mental arithmetic tasks and verbal fluency task

Authors: *Y. GOTO
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Abstract: [Objective] The aim of this study was to investigate the detailed spatiotemporal brain processes of divided attention which related to two types of mental arithmetic tasks (simple and complex Calculation) and the verbal fluency task using visual evoked magnetic fields. **[Methods]** Fourteen healthy volunteers (8 women and 6 men, mean age 27.7±6.8 years) participated in this study. The participants performed mental arithmetic (successive subtraction and multiplication facts(ku-ku)) and verbal fluency tasks (associative recognition). The magnetoencephalography (MEG) was acquired using a whole-head 306-channel sensor array that comprises102 identical triple-sensor elements. Each sensor element consists of two orthogonal planar-type gradiometers and one magnetometer. In this study, we analyzed MEG data recorded by the 204-channel planar-type gradiometers. A hemifield black-white checkerboard pattern was phase-reversed at a rate of 1 Hz presenting or left visual hemifield with (task +) or without (task -) mental arithmetic tasks and verbal fluency task. The entire stimulating field subtended an angle of 15°; each individual square of the checkerboard subtended 50’ of arc measured at the subject’s eye. The mean luminance of stimulation was 30 cd/m^2 and the contrast was 97 %. The subjects were instructed to fixate on a red dot placed 0.2° of arc laterally from the stimulated hemifield. The VEFs were bandpass filtered between 0.1-1000 Hz. Data were digitized at a sampling rate of 1000 Hz/channel, and 100 responses of 350 ms epochs in each session were averaged. The amplitudes and latencies of VEFs components were measured. VEFs were analyzed by fast Fourier transformation (FFT), and then the distribution of each frequency band activity was made on topographic scalp. **[Results]** Lower amplitude distribution of three distinct components (N75m, P100m, N145m) were identified the contralateral to hemifield stimulation in each task to compare without task.The latencies of mental arithmetic tasks were significantly delayed in comparison with task(-) and successive subtraction in P100m. Amplitude changes in N75m on left hemifield stimulation were significantly decreased in mental arithmetic tasks. In addition, the distribution of high-gamma band activities was decreased in the right occipital area with left

hemifield stimulation by all tasks (+) condition. In contrast, those were increased in the left occipital area with right hemifield stimulation by the all mental tasks.**[Conclusion]** Our results suggest that these changes are the evidence of the inhibition of the visual information processing in the primary visual cortex by the tasks.

Disclosures: Y. Goto: None.

Poster

228. Superior Colliculus: Sensory and Motor Functions

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 228.01/CC20

Topic: D.07. Vision

Support: NIH Grant 1R01EY025627-01

Whitehall Foundation Grant 2013-08-41

Title: Disruption of visual circuit organization and function in the superior colliculus of fragile X mice

Authors: R. B. KAY, N. GABRESKI, *J. W. TRIPLETT
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Abstract: Sensory processing deficits are commonly co-morbid with neurodevelopmental disorders; however, the neural correlates underlying these deficits remain unclear. Fragile X syndrome (FXS) is a neurodevelopmental disorder caused by silencing of the *FMR1* locus and is the most common single gene cause of autism. Previous studies have demonstrated that activity-dependent synapse stabilization and plasticity are disrupted in mouse models of FXS (*fmr1*$^{-/y}$), suggesting that activity-dependent developmental processes may be disrupted as well. We and others have previously shown that the development of topography and alignment of visual inputs in the superior colliculus (SC) relies heavily upon activity-dependent processes. Based on this, we hypothesized that visual circuit formation would be disrupted in the SC of *fmr1*$^{-/y}$ mice. To test this, we determined the receptive field properties of visual neurons in the SC recorded extracellularly in response to two types of stimuli. We found a significant increase in the size of receptive fields in *fmr1*$^{-/y}$ mice compared to littermate controls. In addition, we found a significant increase in the length of the azimuth, but not elevation, axis for *fmr1*$^{-/y}$ receptive fields. Interestingly, we did not find any difference in the prevalence or tuning of direction-selective or axis-selective neurons in the SC of *fmr1*$^{-/y}$ mice, suggesting deficits may be circuit-specific. Next, we asked if there were alterations in the organization of visual inputs to the SC in *fmr1*$^{-/y}$ mice. Interestingly, we found no changes in retinocollicular topography, but a significant increase in the size of the termination zones of labeled corticocollicular projections from the

primary visual cortex (V1) in *fmr1*$^{-/y}$ mice. Importantly, we did not detect any differences in retinogeniculate or geniculocortical projection topography, suggesting the deficit may be specific to V1 corticocollicular neurons. Taken together, these data demonstrate that *fmr1* is required for proper assembly of visual circuitry in the SC and suggest that a failure of top-down cortical inputs to refine may underlie deficits in visual function.

Disclosures: R.B. Kay: None. **N. Gabreski:** None. **J.W. Triplett:** None.

Poster

228. Superior Colliculus: Sensory and Motor Functions

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 228.02/CC21

Topic: D.07. Vision

Support: NIH Grant EY024173

Title: Feedforward inhibitory circuits within the mouse superior colliculus

Authors: K. L. WHYLAND, S. P. MASTERSON, A. S. SLUSARCZYK, G. GOVINDAIAH, W. GUIDO, *M. E. BICKFORD
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Abstract: The stratum griseum superficiale (SGS) of the superior colliculus (SC) contains a dense population of GABAergic neurons that can strongly affect visual signals. To characterize GABAergic circuits in the mouse SGS, we used a combination of anatomical and optogenetic techniques. Cre-dependent virus injections in the SGS of GAD2-cre mice revealed GABAergic projections from the SC to the pretectum, ventral lateral geniculate nucleus, and parabigeminal nucleus. Injections of cholera toxin subunit B (CTB) in these SC targets in a mouse line that expresses GFP in GABAergic neurons (GAD67-GFP) indicate that projection cells labeled by retrograde transport (n = 1262) in this mouse line do not contain GFP (only 0.3% ± 0.4% of the CTB-labeled cells contained any detectable GFP). Thus, the GAD67-GFP mouse line labels SGS interneurons. Cell counts in tissue from GAD67-GFP mice stained with an antibody against NeuN (n = 2005) indicate that 31.7 ± 4.4% of SGS neurons are GABAergic interneurons. Cell counts in tissue from GAD67-GFP mice stained with an antibody against GABA (n = 616) indicate that 67.4 ± 4.7% contain GFP (intrinsic interneurons); the remaining GABAergic cells (32.6 %) do not contain GFP (potential projection neurons). In addition, 12.7 ± 6.3 % of GAD67-GFP neurons (n = 2261) could be stained with an antibody against parvalbumin, suggesting that GABAergic interneurons in the SGS can be further classified into subtypes. Ultrastructural analysis of retinotectal terminals (in tissue stained to reveal GABA), indicates that 32% of retinotectal synapses (n = 123) target dendrites that contain detectable levels of GABA, and the vast majority (98%) of these profiles contain vesicles. Ultrastructural analysis of

SGS tissue from GAD67-GFP mice confirmed the presence of GFP-labeled dendrites that contain vesicles and GABA, suggesting that intrinsic interneurons may mediate a short latency feedforward inhibition via dendritic terminals. To test this, a cre-dependent virus was intraocularly injected in calretinin-cre mice to induce the expression of channelrhodopsin in retinotectal terminals. Whole cell recordings in slices of the SC maintained in vitro revealed that photoactivation of retinotectal terminals elicited disynaptic inhibitory postsynaptic currents in neurons clamped at 0mV (n= 12). These results suggest that feedforward inhibition is common in the SGS and may be elicited primarily via dendritic terminals of intrinsic interneurons.

Disclosures: K.L. Whyland: None. **S.P. Masterson:** None. **A.S. Slusarczyk:** None. **G. Govindaiah:** None. **W. Guido:** None. **M.E. Bickford:** None.

Poster

228. Superior Colliculus: Sensory and Motor Functions

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 228.03/CC22

Topic: D.07. Vision

Support: Simons Foundation

HHWF

Title: Neural population representation of visual features in mouse superior colliculus

Authors: *Y.-T. LI, M. MEISTER
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Abstract: The mammalian retina contains ~30 distinct types of RGCs. Each type sends a specific visual feature to the brain. One principal brain center receiving direct retinal inputs is the superior colliculus (SC), which is an evolutionarily conserved structure and the most sophisticated visual center before the emergence of the neocortex. More than 90% of RGCs send their axons to SC. However, it is not clear whether the SC simply inherits retinal features or additional and potentially de novo processing occurs in the SC. To answer this question, we investigated the population coding underlying the visual features representation in the SC of awake mice. Specifically, we tested whether the threat signals and neutral features such as orientation and direction information are represented by different subpopulations of collicular neurons. We compared how neurons responded to a looming stimulus and to a bar drifting in different directions. We found that strong direction or orientation selective neurons did not respond robustly to the looming stimulus, and looming responsive neurons showed weak direction and orientation selectivity. This observation indicates that looming motion and translating motion are encoded by different neuronal populations. Furthermore, we found that

some looming responsive neurons showed strong adaptation. The neuronal response is consistent with behavioral observation that a freely moving mouse shows robust defensive reaction on its very first exposure to the stimulus. Thus our preliminary data suggests the superficial layer of SC may serve as the beginning site for isolating the threat signal. Last, we measured the receptive field of SC neurons. Surprisingly, most neurons showed only OFF dominant receptive field, which is distinct from retina and indicate substantial computation from retina to SC.

Disclosures: Y. Li: None. **M. Meister:** None.

Poster

228. Superior Colliculus: Sensory and Motor Functions

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 228.04/CC23

Topic: D.07. Vision

Support: NIH Grant NEI R01EY022117

NIH Grant NEI R21 EY026758

Title: Neurons in the mouse superior colliculus encode orientation/direction through suppression and extract selective visual features

Authors: *S. ITO[1], D. A. FELDHEIM[2], A. M. LITKE[1]
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Abstract: The superior colliculus (SC) is an integrative sensorimotor structure that contributes to multiple vision-dependent behaviors. It is a laminated structure; the superficial SC layers (sSC) contain cells that respond to visual stimuli, while the deep SC layers (dSC) contain cells that also respond to auditory and somatosensory stimuli. Although the mouse has become a popular subject for visual system study, the differences in the visual response properties between the sSC and the dSC are largely unknown. Here we used a large-scale silicon probe recording system to examine the visual response properties of neurons within the SC of head-fixed and alert mice. We find that both the sSC and dSC cells respond to visual stimuli, but the dSC cells have three key differences. (1) The majority of the dSC orientation/direction selective (OS/DS) cells have their firing rate *suppressed* by drifting sinusoidal gratings (negative OS/DS cells) rather than being stimulated like the sSC cells (positive OS/DS cells). (2) The dSC cells have large receptive fields with a weak transient response, and cortical complex-cell-like spatial summation nonlinearity. (3) The dSC cells lack Y-like spatial summation nonlinearity unlike the sSC cells. We also find that the responses of many cells in both the sSC and the dSC are modulated by locomotion of the mouse. These results provide the first description of cells that are suppressed

by a visual stimulus with a specific orientation or direction, provide a comprehensive characterization of dSC cells, and demonstrate that the behavioral state of a mouse impacts SC activity.

Disclosures: S. Ito: None. **D.A. Feldheim:** None. **A.M. Litke:** None.

Poster

228. Superior Colliculus: Sensory and Motor Functions

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 228.05/CC24

Topic: D.07. Vision

Title: An inhomogeneous direction selective map in the superior colliculus

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Abstract: Vision allows animals to extract salient features of a visual scene such as spatial orientations and motion direction. The retina is the first stage of visual processing and targets brain areas including the superior colliculus. Here the visual scene is represented by a set of overlapping, retinotopically organized feature maps. Recently it has been shown that orientation selective neurons with the same orientation selectivity cluster together, forming an inhomogeneous orientation map where, unlike in other visual areas, not all orientations are represented at each retinotopic location. However, the topographical organization of other feature maps remains unknown. Using two-photon calcium imaging, we recorded the activity of neurons spanning more than half of the superior colliculus, while simultaneously measuring their receptive field and determining their orientation and direction selectivity. We found that the preferred direction of direction selective neurons is dependent on their retinotopic position. When comparing preferred directions with orientation in the same retinotopic location, direction selective neurons showed a strong preference for directions of movement orthogonal to the preferred orientation of nearby orientation selective neurons. These findings uncover a second inhomogeneous map accounting for motion detection that can be superimposed with the spatial orientation map. Such maps appear to underlie the structure of the superior colliculus, and understanding their relationships will allow us to understand how the colliculus contributes to visually guided orientating behaviours.

Disclosures: D. De Malmazet: None. **K. Farrow:** None.

Poster

228. Superior Colliculus: Sensory and Motor Functions

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 228.06/CC25

Topic: D.07. Vision

Support: Fondecyt Grant 1151432

Fondecyt Grant 1170027

Title: Spatio-temporal characterization of the feedback signals mediating stimulus selection in the optic tectum of the pigeon

Authors: *B. REYNAERT[1], L. LOPEZ-JURY[1], J. LETELIER[1], J. MPODOZIS[1], G. MARÍN[1,2]
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Abstract: In all amniotes, a bilateral tectofugal pathway transmits visual inputs from the optic tectum (TeO), or superior colliculus, to the n. rotundus or caudal pulvinar. This pathway arises from wide-field tectal ganglion cells (TGCs), which in birds receive prominent feedback signals from axon terminals from the nuclei isthmi pars parvocellularis (Ipc). It has been shown that upon retinal stimulation, this feedback produces a gating effect on the ascending transmission of retinal inputs, while at the same time a diffuse GABAergic projection from the nucleus isthmi magnocellurais (Imc) exerts a suppressing effect over complementary locations in TeO and Ipc. Thus, under conditions of stimulus competition, this circuit implements a "winner-take-all" mechanism that promotes the selective transmission of visual activity representing the most salient stimuli. However, given the complex topology of this network it is difficult to predict the spatial-temporal configuration of the Ipc feedback that is generated in a particular visual context, and consequently the activity pattern transmitted by the TGCs. In this study, using up to 16 microelectrodes regularly disposed on the superficial tectal layers of anesthetized pigeons, we recorded the bursting feedback signals from Ipc axons in response to static and moving visual stimuli. We found that the presentation of a point visual stimulus generates a wave of feedback activity that expands centrifugally from the tectal zone receiving the retinal input, encompassing a tectal area of about 1 mm. This suggests that the Ipc feedback might generate a priming effect, ahead of the tectal zone receiving the retinal input. In addition, we observed high frequency synchrony between the simultaneously recorded feedback signals. To study the consequences of these feedback patterns upon the TGC responses, we modeled this network using leaky integrate-and-fire neurons that represent how the tectal, retinal and isthmotectal afferences interact to generate the tectofugal output. We explored the topological and physiological parameters that lead to the network's operation, as found *in vivo*. The model reproduce motion preference on the TGCs, with increasing firing rates for faster motion; and even stronger responses to looming

stimuli. These findings and the continuing analysis of the model under different stimulus conditions help to elucidate the rules by which the interaction of the isthmotectal network components modulates the visual activity patterns that are relayed by the TGCs to the thalamus.

Disclosures: B. Reynaert: None. **L. Lopez-Jury:** None. **J. Letelier:** None. **J. Mpodozis:** None. **G. Marín:** None.

Poster

228. Superior Colliculus: Sensory and Motor Functions

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 228.07/CC26

Topic: D.09. Visual Sensory-motor Processing

Support: Simons Foundation Grant 325496

Title: The collicular visual pathway is sufficient for the identification of visual threats

Authors: *Z. TURAN, D. J. ANDERSON, M. MEISTER
Caltech, Pasadena, CA

Abstract: Efficiency in avoiding predators in nature is crucial for survival. An overhead expanding disc simulating the approach of a predator has been shown to induce robust innate defensive behaviors in the wild type mouse. This *looming stimulus* can induce freezing or rapid escape. It is unclear where in the brain this visual threat is distinguished from other innocuous stimuli. The superior colliculus (SC), a midbrain structure that receives direct visual input from the retina has been shown to be involved in defensive behaviors. The superficial layer of the SC serves as the gateway for visual input from the retina but how it represents visual stimuli is poorly understood. Here we identified neurons in the superficial layers of SC that respond specifically to the looming stimulus. This sets the stage for tracing their circuitry both from the retina and towards deeper layers of the SC.
Mice that lack a cortex and hippocampus were generated to test the sufficiency of SC for this visual reflex. Here we report on the behavioral similarities and differences between the *cortexless* and wild-type animals. Similar to the wild-type mice, we observed a cluster of neurons in the superficial layers of SC that respond specifically to the looming stimulus, but not to innocuous stimuli. These results indicate that an intact superior colliculus is sufficient to induce robust defensive behaviors in response to visual threats.

Disclosures: Z. Turan: None. **D.J. Anderson:** None. **M. Meister:** None.

Poster

228. Superior Colliculus: Sensory and Motor Functions

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 228.08/CC27

Topic: D.07. Vision

Support: SNF 138719

SNF 151168

EMBO ALTF 741-2012

Title: Experience-dependent plasticity of cortico-collicular interactions in visual perception

Authors: *S. RUEDIGER[1,2], M. SCANZIANI[1,2]
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Abstract: The expansion of cortex is a major hallmark of brain evolution in mammals that is associated with increase in flexibility of perceptual and behavioral repertoires. However, cortex does not act in isolation but operates through tight interactions with subcortical structures that support elemental innate behaviors, such as reflexes. There is still a major gap in our understanding of the functional role of cortical-subcortical interactions in behavior. We investigated the role of the corticofugal projection from Visual Cortex (VC) to the Superior Colliculus (SC), a phylogenetically old midbrain structure, in the detection of changes in the visual scene in mice. We found that the mouse ability to detect and report a change in luminance contrast in the visual scene relies on the SC. In contrast, the role of VC diminishes with experience. Furthermore, by combining optogenetic methods with in vivo extracellular recordings during behavior, we established a causal relationship between the activity in VC and the activity in SC. We discovered that the impact of VC on neural activity in SC depends on both behavioral state and experience. Together these findings provide novel insight into the dynamic interactions between VC and SC in the emergence of a visually guided behavior.

Disclosures: S. Ruediger: None. **M. Scanziani:** None.

Poster

228. Superior Colliculus: Sensory and Motor Functions

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 228.09/CC28

Topic: D.07. Vision

Support: NIH Grant 1U01NS090562-01

Simons Foundation Grant 325496

Title: Distinct neural encoding in the superficial and deeper layers of mouse superior colliculus

Authors: *K. LEE, A. TRAN, M. MEISTER
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Abstract: The purpose of the visual system is to winnow the onslaught of photons that come through the retina down to the few bits of information that are useful for driving behavior. The superior colliculus (SC) is a key visual center in the vertebrate brain and is implicated in the transformation of visual input to motor output. However, little is known about the details of such computation due to the paucity of studies that densely sample neural activity in this structure. Here we report the visual response properties of the superficial and deeper layers of the SC in the awake mouse using high-density silicon probes that span its entire vertical depth. In the superficial SC, many neurons have simple center-surround receptive fields of the OFF-type response polarity and act like linear filters. These neurons encode local changes in light intensity in a way that is consistent with pooling inputs from W3-type retinal ganglion cells (Zhang et al. 2012). In contrast, neurons in the deeper SC exhibit little to no linear response. Instead, many cells there respond optimally to a black expanding disc, an ecologically relevant stimulus that elicits a robust defensive behavior (Yilmaz and Meister 2013). Furthermore, they preferentially encode the novelty of the visual stimulus by showing significant adaptation to stimuli that appear later in a sequence. Together, these results suggest that the superficial and deeper SC encode distinct features of the visual stimulus, and outline a process in which a generic visual representation is converted to a more abstract one that emphasizes novelty.

Disclosures: K. Lee: None. **A. Tran:** None. **M. Meister:** None.

Poster

228. Superior Colliculus: Sensory and Motor Functions

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 228.10/CC29

Topic: D.09. Visual Sensory-motor Processing

Support: Research Council VR-M-K2013-62X-03026 and VR-NT 621-2013-4613

European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement no 604102 (HBP)

Strategic Research Programme in Neuroscience Karolinska institute

Parkinsonfonden

Title: The SNc/VTA responds to saliency while modulating D1 and D2 expressing neurons in the lamprey tectum

Authors: *J. PÉREZ-FERNANDEZ, A. A. KARDAMAKIS, D. G. SUZUKI, B. ROBERTSON, S. GRILLNER
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Abstract: Numerous data in the lamprey suggest that the dopaminergic system was already well developed at the dawn of vertebrate evolution, including the SNc/VTA modulation of the basal ganglia through the direct and indirect pathways in the striatum. However, although the overall connectivity of the SNc/VTA is virtually identical to that of mammals, little is still known about this region from a functional point of view. Using a preparation maintaining the eyes together with the brain and rostral segments of the spinal cord, we show by applying looming stimuli that the activity in the SNc/VTA increases in parallel with their expansion rates (as a paradigm of increasing saliencies), therefore providing the evolutionary basis for salience/novelty detection. Also, as in mammals, the SNc/VTA sends direct dopaminergic projections to motor command centers, including the diencephalic and mesencephalic motor regions and the optic tectum. This last region (superior colliculus in mammals) shows well conserved features through vertebrate evolution, and controls eye and orienting/evasive trunk movements through excitatory output neurons projecting to the brainstem. By using *in situ* hybridization and patch-clamp recordings we show that D1 and D2 dopamine receptors are expressed as separate subpopulations in both output neurons and interneurons, and dopamine increases the excitability of cells expressing the D1 receptor and decreases the excitability of those expressing the D2 receptor. This modulation affects their responsiveness to sensory inputs, and is in turn reflected on the motor responses evoked by tectum. We recorded ventral roots and eye muscles activity in response to visual stimuli, and locally injected dopamine agonists in tectum, showing that dopamine performs a

complex modulation of tectal sensorimotor integration. SNc/VTA stimulation gives rise to this same effects onto tectal cells, therefore confirming the functionality of this projection. SNc dopaminergic projections to the superior colliculus have been reported also in other vertebrates, including mammals, and hence this mechanism is likely to be present also in this last group. Given the high degree of conservation of the SNc/VTA, we also explored the effects of activating/inactivating this region onto different motor aspects, and its relation with other brain areas, showing that some basic functional aspects of this key modulatory region arose very early in vertebrate evolution.

Disclosures: J. Pérez-Fernandez: None. **A.A. Kardamakis:** None. **D.G. Suzuki:** None. **B. Robertson:** None. **S. Grillner:** None.

Poster

228. Superior Colliculus: Sensory and Motor Functions

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 228.11/CC30

Topic: D.09. Visual Sensory-motor Processing

Support: R01NS079518

Title: Monosynaptic inputs into GABAergic intermediate layer superior colliculus neurons

Authors: *T. K. DOYKOS[1], A. L. PERSON[2], G. FELSEN[2]
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Abstract: The superior colliculus (SC) is a midbrain structure critical for selecting spatial targets for movement. The intermediate and deeper layers of the SC contain a topographically organized motor map, with increasingly eccentric orienting movements represented most caudally. While the SC is known to integrate input from a variety of brain regions, how these inputs modify processing in the SC circuits responsible for target selection remains poorly understood. In particular, little is known about the role of GABAergic SC neurons, which comprise nearly one-third of neurons in the intermediate and deep layers. Specifically, it is unknown whether GABAergic cells are involved in local processing or are directly innervated by inputs to the SC (or both). To address this question, we examined monosynaptic inputs to mouse GABAergic SC neurons using Cre-dependent helper viruses to restrict starter cell infection of a pseudotyped rabies virus, EnvA-SADΔGeGFP, to Gad1- and Gad2-Cre expressing SC neurons. In experiments targeting either rostral or caudal SC, we found that several regions provide input to GABAergic SC neurons. Consistent with previous work, neurons in the ipsilateral substantia nigra pars reticulata provide input to GABAergic SC neurons, with a strong bias toward the rostral SC (68 +/- 43 in rostral injections vs. 1 +/- 1.15 in caudal injections; mean +/- standard deviation; n=4 mice; comparable numbers of starter neurons were identified in rostral and caudal

injections). We also observed inputs from the contralateral cerebellar nuclei, a structure critical for making precise movements; this input also almost exclusively innervates the rostral over caudal SC (46 +/- 20 vs. 0.25 +/- 0.5; mean +/- standard deviation; n=4 mice). The bias toward rostral innervation suggests that nigral and cerebellar input may preferentially influence fixation-related behaviors. Finally, we observed reciprocal projections from rostral SC to caudal GABAergic SC neurons and from caudal SC to rostral GABAergic SC neurons. This pattern is consistent with a model whereby global interactions within the SC underlie target selection. Overall, our studies will shed light on the organization of SC inhibitory circuitry and its role in selecting targets for movement.

Disclosures: **T.K. Doykos:** None. **A.L. Person:** None. **G. Felsen:** None.

Poster

228. Superior Colliculus: Sensory and Motor Functions

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 228.12/CC31

Topic: H.01. Animal Cognition and Behavior

Support: the Ministry of Science and Technology of China grant (2015CB351701)

the National Nature Science Foundation of China grant (91132302)

the Strategic Priority Research Program (B) (XDB02010001)

Title: The impact of feeding state on receptive field in zebrafish tectum neurons

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Abstract: Functional reorganization plays an important role in compensation after neural injuries, but the mechanisms are not well known. It is recognized that the hypoglycemia and malnutrition caused by long-term hunger have damage on neural system, while the influence of hunger on responsive properties of neurons remain unclear. Recent studies indicate that feeding state changes the population preference to stimulus size in the zebrafish tectum. To investigate the neural substrate of functional reorganization, we studied the impact of feeding state on receptive field of tectum neurons in larval zebrafish.It is well documented that moving spots evoke spikes in zebrafish tectum neurons. Here we measured the receptive field of tectum neurons, using 12° moving spots sweeping across the visual space in horizontal or vertical directions. We presented the stimulus to zebrafish larvae while recording the neural activity in tectum using two-photon microscope. Calcium images of one hemisphere of the tectum were

collected every 1.1s for 572s at a resolution of 512 x 512 with a 25X lens (NA = 1.05). The spatial profile of the fluorescence responses for each neuron were calculated by multiply the responses to all the spots in all directions. The size of receptive field was estimated by fitting the spatial profile of neural response to a 2D Gaussian function. The zebrafish larvae in the experiment were divided into two groups according to different feeding states. The larvae in fed group (n = 11) were fed enough paramecium while the other group, starved group (n = 10), were not fed anything. We found that the RF size of the starved group was significantly larger than that of the fed group (p = 0.015, n = 115(fed) and 144(starved) neurons). We also computed the RF size as the area of the largest connected component above a given threshold in the response profile. By systematically varying the threshold selection, we found that the RF size of the two groups differed under a wide-range of parameters. These results suggest that feeding state not only alters the size selectivity of tectum neurons to visual objects, but also modulates their RF size. Both of these changes could make the zebrafish avoid starvation effectively.

Disclosures: **L. Xu:** None. **Z. Liu:** None.

Poster

228. Superior Colliculus: Sensory and Motor Functions

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 228.13/CC32

Topic: D.09. Visual Sensory-motor Processing

Support: ERC-StG #311159-Zebratectum

Fondation pour la Recherche Médicale Postdoctoral Fellowship

ATIP/Avenir starting grant CNRS/INSERM Starting Grant

Title: An inter-hemispheric neural circuit in the zebrafish optic tectum required for efficient prey hunting

Authors: *C. GEBHARDT[1], T. O. AUER[1], K. DUROURE[1], I. H. BIANCO[2], F. DEL BENE[1]
[1]Ctr. de Recherche, Bat. BDD, Equipe Del Bene, Inst. Curie, Paris, France; [2]Dept. Neuroscience, Physiol. & Pharmacol., UCL, London, United Kingdom

Abstract: Larval zebrafish show complex goal-directed hunting behavior that seems to be mainly guided by vision and requires sensory integration to detect the prey and a series of specific locomotor maneuvers to track it. During hunting, zebrafish larvae converge their eyes thereby considerably increasing the overlapping field of view. Furthermore, the final capture swim is being stereotypically initiated when the larva is at a distance of about 0.5mm to the prey. These evidences suggest that larva might be able to estimate object distance by using binocular visual information. However, given that the larva has entirely crossed projections from the eyes

to the visual brain, the interpretation of binocular information on this connectional level, like e.g. found in mammals, is unlikely. Thus the neural substrate for such a mechanism in zebrafish is as of yet unknown.
We recently identified a zebrafish line that expresses Gal4 in a previously undescribed commissural neuron population in the brain. We found these neurons to be bilateral-symmetrically distributed adjacent to the ventral tectum. Furthermore, they connect the tectal halves, form synapses there and were thus termed intertectal neurons (ITNs). We reasoned that ITNs might be good candidates for the potential transfer and/or the integration of binocular visual signals and that they thus might have a role during larval prey capture.
We next unilaterally ablated ITNs with 2p imaging and subsequently examined free-swimming behaviour of ablated vs. ctrl fish during an assay of prey capture. Ablated fish hunted less efficiently than wild-type but basic motor parameters were not affected. However, ablated fish showed a drastically diminished probability of initiating capture swims when close to the prey, arguing that ITNs might indeed play a role in the last step of the prey hunting sequence, the initiation of the capture swim.
Using 2p Ca imaging, we established that ITNs respond to moving bars and small dots simulating moving prey. Furthermore, after unilateral eye-ablation, we observed Ca transients in the tectal hemisphere not receiving any retinal input that were co-localized with the trajectories of the contralateral ITN arbors suggesting that ITNs might transfer prey-specific information to the ipsilateral tectum with respect to the prey.
In summary, we anatomically describe novel, previously unknown, inter-hemispheric neural connections in the zebrafish visual system, establish their role in inter-tectal visual signal transfer and show that they are important for the successful completion of the hunting behavior sequence.

Disclosures: C. Gebhardt: None. **T.O. Auer:** None. **K. Duroure:** None. **I.H. Bianco:** None. **F. Del Bene:** None.

Poster

228. Superior Colliculus: Sensory and Motor Functions

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 228.14/CC33

Topic: D.09. Visual Sensory-motor Processing

Support: EY022854

EY024831

Title: A causal study of movement generation using multi-channel recording and patterned microstimulation

Authors: *U. K. JAGADISAN, N. J. GANDHI
Dept. of Bioengineering, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Sensorimotor transformations are mediated by premotor brain networks whose evolving activities multiplex sensory, cognitive, and movement-related information. A fundamental question in neuroscience is how the brain resolves activity related to movement generation from prior activity. In the gaze control system, visuomotor neurons serve as appropriate substrates to study this question. These neurons are activated both by the onset of a visual stimulus in (visual burst) as well as a saccade to (premotor burst) their response field, and are prevalent in the superior colliculus (SC) and frontal eye fields (FEF), critical nodes in the gaze control network. Intriguingly, visuomotor neurons also have direct projections to brainstem burst generators that are involved in saccade initiation, thus raising the question - why does the high-frequency visual burst not produce a saccade? In other words, how does a decoder parse incoming sensorimotor information to guide movement generation? Extant models posit threshold-based gating or low-D population-based readouts as the solution to this demuxing problem. We recently showed, using pseudo-population analyses, that SC and FEF activity during the visual burst is temporally unstable while regaining stability during the premotor burst (bioRxiv, doi: 10.1101/132514), suggesting a combination of high firing rate and population stability as a putative mechanism for movement generation. Here, we test these alternative models in a causal framework. We first verified that the temporal stability hypothesis also holds on individual trials by using a linear microelectrode array to record SC population activity in monkeys performing the delayed saccade task. Differences observed in the temporal structure of visual and premotor bursts were similar to those mentioned above. Additionally, a linear decoder operating on reduced-D population activity was also able to discriminate between the two bursts. We then explicitly tested the alternative population-based models by applying sub-threshold patterned microstimulation simultaneously across multiple electrode sites in SC. Stimulation patterns were designed to be either stable or unstable on different trials, with matched pulse rates across the population. Stable patterns were more likely to evoke saccades, and at lower latencies, compared to rate-matched unstable patterns. Crucially, a linear decoding mechanism was insufficient to explain the differences in stimulation outcomes. This provides a causal demonstration that the temporal structure of instantaneous population activity is the key variable determining movement initiation, at least in gaze control.

Disclosures: U.K. Jagadisan: None. **N.J. Gandhi:** None.

Poster

228. Superior Colliculus: Sensory and Motor Functions

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 228.15/DD1

Topic: D.09. Visual Sensory-motor Processing

Support: NIH Grant EY022854

NIH Grant EY024831

Title: Removal of inhibition reveals latent motor potential in superior colliculus preparatory activity

Authors: *N. J. GANDHI, U. K. JAGADISAN
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Abstract: The brain plans movements well in advance of their execution. How the motor system prepares for upcoming movements before initiating them is a central question in neuroscience. In the gaze control system, premotor neurons (e.g., in the superior colliculus or SC) that produce a burst of activity for the movement are also active hundreds of milliseconds leading up to the saccade. The dynamics of such preparatory neural activity have been well described by stochastic accumulator models, and variability in the accumulation dynamics has been shown to be correlated with reaction times of the eventual saccade. However, it is unclear whether this activity is purely preparatory in nature or has features indicative of a hidden movement command. Current theories suggest that movement planning and execution occur in serial stages, separated by a decision boundary in neural activity space (e.g., "threshold"), past which, activity in premotor and motor networks represents a mature movement command. In other words, only the premotor burst itself has the "motor potential" necessary to generate a movement.
Here, we tested for motor potential in SC premotor neurons, defined as correlated variability between instantaneous neural activity and instantaneous eye kinematics across trials. We focused on the period after the GO cue in monkeys performing the delayed saccade task, when the activity is building up to a saccade-generating burst. On normal trials, the activity-velocity correlation was high only after saccade onset, indicating that the saccade-related burst is a movement command. We then explicitly tested whether preparatory neural activity in SC premotor neurons also has motor potential. We introduced an air puff to the animal's eye at different times during the preparatory period, indirectly turning off the omnipause neurons - a potent downstream source of inhibition on the saccadic system. We found that saccades can be triggered at lower-than-normal latencies, consistent with previous observations. We estimated the motor potential of accumulating low-frequency activity by computing instantaneous activity-velocity correlation as above. Preparatory activity was predictive of ocular kinematics well in advance of actual saccade onset, indicating the presence of a latent movement command. Additionally, the saccade was triggered before the activity reached levels seen under normal conditions, showing that reaching threshold is not a necessary condition for movement initiation. The results bring into question extant models of saccade generation and support the possibility of a concurrent representation for movement preparation and generation.

Disclosures: **N.J. Gandhi:** None. **U.K. Jagadisan:** None.

Poster

228. Superior Colliculus: Sensory and Motor Functions

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 228.16/DD2

Topic: D.09. Visual Sensory-motor Processing

Support: JSPS Overseas Research Fellowships

EU/FP7 no 604102 The Human Brain Project (HBP)

EU/Horizon 2020 no 720270 (HBP SGA1)

Title: Tectal microcircuits mediates the behavioral switch between orienting and avoidance movements

Authors: *D. G. SUZUKI, A. KARDAMAKIS, T. WIBBLE, J. PÉREZ-FERNANDEZ, S. GRILLNER
Karolinska Institutet, Stockholm, Sweden

Abstract: It is critical for animals to rapidly detect environmental events, integrate multisensory information and decide whether to orient themselves towards or away from the objects. The optic tectum (superior colliculus in mammals) is central for this rapid sensorimotor decision-making. We have previously shown using the lamprey that there are two types of tectal neurons, projecting ipsi- and contralaterally to the brainstem (Kardamakis et al., 2015). These two types of neurons have slightly different membrane properties, with neurons involved in orienting movements being more excitable. It could therefore be possible that a weaker stimulus preferentially elicits orienting behavior, but a stronger stimulus instead evokes avoidance, overriding the effect of the approach pathway. In addition, the GABAergic system is necessary for generating stimulus selection through local excitation and global inhibition on to brainstem projecting neurons (Kardamakis et al., 2015, 2016).
Now we developed an isolated preparation that maintains eyes, brain and spinal cord intact enabling us to simultaneously monitor neural responses from different neural regions (e.g., the optic nerve, optic tectum and ventral roots), while delivering various types of visual stimuli in a computer-controlled environment.
By monitoring bilateral neural activity in the ventral roots in the rostral spinal cord and deep layer tectal activity, we could identify two distinct motor response patterns selective to the specific type of visual stimuli applied. Fast looming (threatening) stimuli and vertical bars tend to induce a response preferentially in the ipsilateral ventral root. This would correspond to fictive evasion. On the other hand, slow looming stimuli will evoke activity in the contralateral ventral root corresponding to orienting movements.
This selectivity was abolished when we removed the action of the local inhibitory system and/or

disrupted glutamatergic synaptic transmission by local injection of gabazine or glutamate antagonists. We controlled the effect of tectal activation and inactivation by recording extracellular activity during the visual stimulus presentation as a measure to determine the causal role of tectum in visual decision-making.

Disclosures: D.G. Suzuki: None. **A. Kardamakis:** None. **T. Wibble:** None. **J. Pérez-Fernandez:** None. **S. Grillner:** None.

Poster

228. Superior Colliculus: Sensory and Motor Functions

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 228.17/DD3

Topic: E.01. Eye Movements

Support: NIH R01 EY024831

Title: A reversal pattern of the local field potential in the superior colliculus reveals a dynamic control of the ongoing saccadic activity

Authors: *C. MASSOT[1], N. J. GANDHI[2]
[1]Eye and Ear Inst., [2]Dept. of Bioengineering, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: The superior colliculus (SC) plays a major role in transforming sensory signals that register a target into motor commands that produce an eye movement to the stimulus. The sensory and movement responses are represented by two bursts of activity across the different layers of SC. The spiking activity of the movement burst is known to be correlated with saccade generation. However, the underlying network activity that produces the burst is not well understood. We address this gap in knowledge by recording spikes and local field potentials (LFPs) from a 16-channel laminar probe in the SC of two rhesus monkeys performing randomly interleaved delayed, visually-guided and memory-guided saccades. The electrode penetration was orthogonal to the surface of SC; hence the optimal target locations and/or saccade vectors were comparable across all recording contacts. The target was positioned either close to the center of the response field or at the diametrically opposite location.Here, we looked at the LFP information during the perisaccadic epoch. In particular, we focused on the location of the sources and sinks patterns of electrical currents as identified by current source density (CSD) analysis. Preliminary analyses reveal the following observations: (1) The LFP displayed a “reversal pattern”: for superficial layers, the LFP displayed a small negative deflection; for deep layers, the LFP displayed a potent positive deflection at the same time as the negative deflection of the superficial layers. This “reversal pattern” of the LFP happened *after* the peak of the movement burst (based on spikes) and before the end of the saccade. (2) At the time of the “reversal pattern” of the LFP, the CSD switched from a weak sink pattern in the superficial

layers to a strong source pattern in the deep layers. This source/sink pattern happened at the same layer location across sessions. (3) This “reversal pattern” cannot be a visual signature since it was also observed for memory-guided saccades. It is not likely due to contamination by the spiking activity because the pattern remained after application of a despiking method. Taken together, these results may reflect a local interaction between superficial and deep layers involved in the control of the ongoing saccade. Alternatively, this pattern may reflect a global input to all layers of SC by afferent signals from an external source controlling the saccadic activity.

Disclosures: C. Massot: None. **N.J. Gandhi:** None.

Poster

228. Superior Colliculus: Sensory and Motor Functions

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 228.18/DD4

Topic: D.09. Visual Sensory-motor Processing

Support: DFG

Title: Depth profile of visual and saccade-related response field characteristics in the primate superior colliculus

Authors: *X. TIAN, Z. M. HAFED
Werner Reichardt Ctr. for Integrative Neurosci., Physiol. of Active Vision, Tuebingen, Germany

Abstract: The primate superior colliculus (SC) supports visually-guided behavior by containing topographically organized retinotopic maps of visual locations and eye movement endpoints. Across SC layers, neuronal response field (RF) sizes increase with increasing depth. However, evidence for such increases was based primarily on saccade-related movement RF's, and, even then, such evidence was primarily based on single-electrode penetrations across separate sessions. This means that variations in electrode trajectory relative to the SC surface could contaminate size measurements. For example, if an electrode were to traverse SC depth with a slight lateral shift in trajectory, then bigger RF's in deeper sites could be due to sampling lower visual field representations (Hafed & Chen, Curr. Biol., 2016). Here, we used linear electrode arrays (150 micrometer electrode spacing) to simultaneously record (in 1 male, rhesus macaque) from ~7 different depths within either visual SC layers alone, visual-motor layers alone, or both visual and visual-motor layers together. The monkey performed a delayed saccade task in which an eccentric spot was presented during fixation, and after a delay, the fixation spot was removed to instruct a saccade to the eccentric spot. We isolated single units in each electrode within the SC, and we characterized visual and saccade-related activity. We carefully selected sessions in which RF's were aligned across depths, to ensure that we were not comparing units of different

preferred eccentricities and/or directions, and we also sampled either peripheral (~10 deg eccentricity) or near foveal (<3 deg eccentricity) sites. Consistent with previous results, movement RF's in visual-motor layers systematically increased in size with increasing depth, and this was accompanied by increasing amplitudes of saccade-related firing rates. However, for visual RF's, there was a reversal of RF size with increasing depth. Visual RF size first increased in the superficial layers and then started decreasing again for visual-motor layers. Such reversal was also accompanied by a reduction in visual sensitivity. In other words, as saccade-related burst amplitudes increased, visual response amplitudes decreased. In the foveal sites, the reversal in visual RF size with increasing depth was much less obvious, possibly reflecting different neural densities and/or tissue thickness in the SC's foveal representation. These results indicate that convergence patterns dictating visual or movement RF properties vary systematically across SC depths, and they also provide a foundation for better understanding of SC activity dynamics during behavior.

Disclosures: X. Tian: None. **Z.M. Hafed:** None.

Poster

229. Limb Brain-Machine Interfaces

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 229.01/DD5

Topic: E.05. Brain-Machine Interface

Support: Office of Naval Research grant number N00014-15-1-2312 to JMC

Title: Co-modulation of joint angles in control of a kinematically redundant brain-machine interface

Authors: *A. YOU[1], V. R. ATHALYE[2], S. GOWDA[2], P. KHANNA[1], H. G. MOORMAN[3], J. M. CARMENA[2,3]
[1]Bioengineering, [2]Electrical Engin. and Computer Sci., [3]Helen Wills Neurosci. Inst., Univ. of California, Berkeley, Berkeley, CA

Abstract: To learn motor skills, we must coordinate our body's numerous, redundant degrees of freedom (DOF) to achieve a common goal, such as controlling an arm's joints so the endpoint reaches a target. Previous motor control studies have shown that subjects accomplish their goals reliably while producing variability rather than stereotypy in individual DOF's, suggesting an optimal control policy in which subjects correct errors in goal-relevant dimensions while tolerating goal-irrelevant variance. How motor cortex generates and improves neural commands for redundant, DOF control is not well-understood and may be crucial for designing brain-machine interfaces (BMIs) with multiple DOF redundant actuators. To address this question, we previously tested how subjects learned to control a multi-DOF virtual actuator by controlling all

redundant DOFs through a BMI. Spiking activity was recorded from the motor cortex of 2 rhesus macaques and transformed into control of each joint for a virtual 4-link arm constrained to move within a single 2-D plane. As previously reported, subjects learned to control the arm's endpoint to hit on-screen targets, reducing the time-to-target and increasing the goal-relevance of neural commands with training. There were two key features of the subjects' late-learning control strategy during the center-out task. First, subjects relied on two primary 4-joint co-modulation patterns, as these primary co-modulations capture a large fraction of command variance and drive endpoint variance. Second, subjects also depended on high-dimensional control, as performance dropped when the BMI only decoded the two primary co-modulations for control. Here we examine how joint commands became coordinated as cursor control was improved. Using factor analysis (FA) we determined how much of 4-joint velocity command variance originated from a low-dimensional shared source which would co-modulate joints, and how much arose from a private source driving each joint independently. FA is well-suited for this question because its generative model decomposes the total joint-command covariance matrix into the sum of a low-rank shared covariance and a diagonal private covariance. Over learning, we found changes in the contributions of shared and private sources of command variance for control. Future work will need to further elucidate the control policy these neural commands execute, and how the full neural population coordinates to generate these high-dimensional commands.

Disclosures: A. You: None. **V.R. Athalye:** None. **S. Gowda:** None. **P. Khanna:** None. **H.G. Moorman:** None. **J.M. Carmena:** None.

Poster

229. Limb Brain-Machine Interfaces

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 229.02/DD6

Topic: E.05. Brain-Machine Interface

Title: Withdrawn

Authors: *D. A. ROYSTON
Bioengineering, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Withdrawn

Disclosures: D.A. Royston: None.

Poster

229. Limb Brain-Machine Interfaces

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 229.03/DD7

Topic: E.05. Brain-Machine Interface

Support: ERC Consolidator Grant Feel Your Reach (681231)

Title: Towards non-invasive decoding of cortical patterns induced by goal directed movement intentions and artificial sensory feedback in humans

Authors: *G. R. MUELLER-PUTZ[1], J. PEREIRA[2], R. KOBLER[2], C. LOPES DIAS[2], L. HEHENBERGER[2], A. SBURLEA[2]
[1]Computer Sci. and Biomed. Engin., [2]Graz Univ. of Technol., Graz, Austria

Abstract: In Europe estimated 300,000 people are suffering from a spinal cord injury (SCI). The loss of arm motor functions - 40% are tetraplegics - leads to a life-long dependency on caregivers and to a dramatic decrease in the quality of life. With the help of motor neuroprostheses, grasping and elbow function can be substantially improved. A natural solution for controlling an upper extremity neuroprosthesis would be to record motor commands from the corresponding cortical areas and convert them into control signals with the help of brain-computer interface (BCI) technology [1]. This would allow bypassing the interrupted nerve fiber tracts in the spinal cord. We showed the control of a motor neuroprosthesis in individuals with SCI using electroencephalography (EEG) [2,3]; however it is not yet intuitive and somewhat cumbersome.The objective of FeelYourReach is to develop a novel control framework that incorporates goal directed movement intention, movement decoding, error processing and sensory feedback to allow a more natural control of a neuroprosthesis. We performed studies targeting these areas and we will present current results.We show, using low-frequency time-domain EEG, that goal-directed movements have different neural correlates than movements which are not directed to a target. These differences affect movement detection accuracies [4]. Currently, we investigate externally and internally-driven target selection. The control of a robotic arm involves visual feedback, e.g. end-effector position in relation to a target. This can trigger eye saccades leading to artefacts in the EEG. We are evaluating approaches to attenuate them online, while retaining movement-related brain activity [5]. Progress was made in the decoding of 3D arm movement trajectories [6].Error decoding is used to detect eventual erroneous commands. We recorded EEG during a task with continuous control and feedback, in which errors appeared [7]. Asynchronous classification was 71% for the error trials and 83% for the correct. We hypothesize that with these approaches a user will be able to naturally control a neuroprosthesis with his/her mind only.
This work is supported by ERC-Consolidator Grant Feel Your Reach

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[2] Kobler et al. Proc. 7thGBIC 2017
[3] Ofner et al. EMBC 2012.
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Disclosures: G.R. Mueller-Putz: None. **J. Pereira:** None. **R. Kobler:** None. **C. Lopes Dias:** None. **L. Hehenberger:** None. **A. Sburlea:** None.

Poster

229. Limb Brain-Machine Interfaces

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 229.04/DD8

Topic: E.05. Brain-Machine Interface

Support: EU Project H2020-643955

Title: EEG-controlled noninvasive grasp neuroprosthesis for individuals with high spinal cord injury - decoding of multiple single limb movements and multi-pad electrodes for closed-loop grasp pattern control

Authors: *R. RUPP[1], M. SCHNEIDERS[2], B. HESSING[2,3], R. MURRAY-SMITH[3], A. RAMSAY[3,4], A. SCHWARZ[4], J. PEREIRA[4], P. OFNER[4], A. PINEGGER[4], G. MUELLER-PUTZ[4]
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Abstract: Neuroprostheses based on functional electrical stimulation (FES) can restore permanently lost functions in people with high spinal cord injury (SCI). The feasibility of EEG-based brain-computer interfaces (BCIs) [1] for grasp neuroprosthesis control by motor imagery was already shown [2]. However, intuitive BCI-control is still missing. Due to the limitations of noninvasive BCI systems for real-time control closed-loop grasp pattern control is needed. The EU-project MoreGrasp aims at the realization of both. In two high-resolution EEG studies with 15 able-bodied subjects each, the decoding classification accuracy of 6 single joint movements of the same arm and of 3 different grasp types of the same hand were investigated analyzing motor-related cortical potentials (MRCPs) in a narrow 0.3 to 3 Hz band. Following the protocol of these 2 studies, we investigated the classification of 2 subsets of movements with 5 participants with high cervical SCI. Two sets of multi-pad FES electrodes were developed: 1) a stackable

screening electrode matrix consisting of 15 (5 x 3, HxW, 6.3 x 3.8 cm) electrodes (diam. 7mm) made of conductive silicone, and 2) a personalized forearm silicone sleeve with 64 electrodes and two inertial measurement units (IMUs) for wrist rotation angle measurement. For automatic selection of the electrode pads, a depth camera recording the finger kinematics was used. The 1st study revealed a classification accuracy of 37% (chance level 16.7%), with classifier sources mainly in premotor and primary motor areas. The 2nd study showed that grasps can be decoded from MRCP features (binary classification of 74% grasp vs. grasp). Experiments with SCI showed a classification accuracy of 53 % (subset 1) and 57 % (subset 2). Multi-pad test results of 3 able-bodied subjects and 1 end user with SCI reveal that not only quantification of the degree of denervation is possible, but also robust electrode positions for palmar or lateral grasps and electrode switching strategies during wrist rotations can be defined. The studies show that it is possible to detect single movements of the same arm from EEG, either single joints or different grasps. The multi-pad concept helps to overcome major challenges of noninvasive grasp neuroprostheses for everyday use. [1] Mueller-Putz GR et al. From classic motor imagery to complex movement intention decoding: The noninvasive Graz-BCI approach. Progress in brain research. 2016; 228:39-70. [2] Rupp R et al. Functional rehabilitation of the paralyzed upper extremity after spinal cord injury by noninvasive hybrid neuroprostheses. Proceedings of the IEEE. 2015; 103(6):954-68. Supported by EU Project MoreGrasp H2020-643955.

Disclosures: The Disclosure Block has exceeded its maximum limit. Please call Tech support at (217) 398-1792 for more information.

Poster

229. Limb Brain-Machine Interfaces

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 229.05/DD9

Topic: E.05. Brain-Machine Interface

Title: Low dimensional representation of human arm movement for efficient neuroprosthetic control by individuals with tetraplegia

Authors: *I. IOSSIFIDIS[1], C. KLAES[2]
[1]Computer Sci., Ruhr West Univ. of Applied Sci., Muelheim An Der Ruhr, Germany; [2]Biol., Ruhr-University Bochum, Bochum, Germany

Abstract: Investigation in the motor, premotor, and parietal areas led to the discovery that the direction of hand's movement in space was encoded by populations of neurons in these areas together with many other movement parameters. These distributions of population activation reflect how movements are prepared ahead of movement initiation, as revealed by activity induced by cues that precede the imperative signal.
Inspired by those findings a model based on dynamical systems was proposed both, to model

goal directed trajectories in humans and to generate trajectories for redundant anthropomorphic robotic arms.
The main idea of the methodology is to choose low-dimensional, behavioral variables of the goal task can be represented as attractor states of those variables. The movement is generated through a dynamical system with attractors and repellers on the behavioral space, at the goal and constraint positions respectively.
Movement is represented by the polar coordinates φ,θ of the movement direction (heading direction) and the angular frequency ω of a hopf oscillator, generating the velocity profile of the arm movement.
Based on three parameters the presented framework is able to generate temporal stabilized (timed) discrete movements, dealing with disturbances and maintaining an approximately constant movement time. In the current study we will implant two 96-channel intracortical microelectrode arrays in the primary motor and the posterior parietal cortex (PPC) of an individual with tetraplegia. In the training phase the parameters of the dynamical systems will be tuned and optimized by machine learning algorithms. Rather controlling directly the arm movement and adjusting continuously parameters, the patient adjust by his or hers thoughts the three parameters of the dynamics, which remain almost constant during the movement. Only when the motion plan is changing the parameters have to be readjusted. The target directed trajectory evolves from the attractor solution of the dynamical systems equations, which means that the trajectory is generated while the system is in a stable stationary state, a fixed-point attractor.
The increase of the degree of assistance lowers the cognitive load of the patient and enables the acknowledgement of the desired task without frustration. In addition we aim to replace the robotic manipulator by an exoskeleton for the upper body which will enable the patients to move his or hers own limbs, which would complete the development of a real neuroprosthetic device for every day use.

Disclosures: **I. Iossifidis:** None. **C. Klaes:** None.

Poster

229. Limb Brain-Machine Interfaces

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 229.06/DP06/DD10 (Dynamic Poster)

Topic: E.05. Brain-Machine Interface

Support: H2020 Project Grant ENHANCE

Title: Gaze-based Cognition-Machine Interface for simulatenous control of exoskeleton reaching & grasping in severely paralysed

Authors: *A. A. FAISAL[1], S. DZIEMIAN[2], C. KONNARIS[3]
[1]Imperial Col. London, London, United Kingdom; [3]Brain & Behaviour Lab, Dept. of Bioengineering, [2]Imperial Col. London, London, United Kingdom

Abstract: We present a novel system, a Cognition-to-Interface that unifies head and 3D eye tracking to control a robotic exoskeleton for the and and the arm. This systems allows upper limb paralysed users to freely control the 3D end-point of their hand and trigger appropriate hand movements such as grasp. The head-worn 3D eye tracking glasses decode continuously the 3D location of the gaze target to within 3-5 cm RMSE. A fovea camera processes the information available at the location of visual attention and the signals are processed by computer vision algorithms to disambiguate the possible intended hand actions. Once a specific manipulative action is detected, an executive control system instructs the robotic arm system to first move the users arm to the location so that the hand is in the correct location and then controls the soft hand exoskeleton to e.g. grasp the object. In all the gaze-driven system allows users to continuously control a 9DOF robotic body-attached exoskeleton system for reaching and grasping. Setup and calibration time for the system (from the moment the user's wheel chair reaches the setup to putting on the eye tracking to the first controlled robot movement) is about 150 seconds for first time users and no invasive surgery or surface electrode placement are required. To achieve free high-resolution 3D end-point decoding from eye movements we developed a novel calibration routine and use computer vision to support the real-time decoding of the users action intention. We demonstrate the full system evaluated in healthy users and a severely paralysed user. Our general framework is not limited to upper-limb motion, and potentially extends to several other domains like wheelchair mobility or this reviewer believes even exoskeleton locomotion.

Disclosures: A.A. Faisal: None. **S. Dziemian:** None. **C. Konnaris:** None.

Poster

229. Limb Brain-Machine Interfaces

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 229.07/DD11

Topic: E.05. Brain-Machine Interface

Support: enHance

Title: Dimensionality Reduction techniques for different shaping of motor hand representations

Authors: *C. KONNARIS[1], A. A. FAISAL[2]
[1]Bioengineering, Imperial Col. London, London, United Kingdom; [2]Imperial Col. London, London, United Kingdom

Abstract: A central question in motor control is to understand how the brain represents movement control. Specifically in the case of the hand, it is still unclear how the CNS implements this to achieve the multitude of static and dynamic hand poses in every-day life when manipulating objects. It is commonly found that the hand is controlled on a much lower dimensional manifold than the mechanical degrees of freedom (Santello et al, 1998, Belic & Faisal, 2015). Consequently many approaches in bionic prosthetic and cortical BCI approaches make use of dimensionality reduction approaches to simplify the representation of hand movements. In contrast it is unclear if the brain's control strategy implicitly uses low dimensional control representation that are reflected in movement kinematics of low dimension. We want to probe this control representation by evaluating whether the method of dimensionality reduction (i.e. how the kinematics are correlated, constrained and what null-spaces they have) has an impact on task performance when controlling a robotic/VR hand, or whether task performances solely depends on the global reconstruction error and the degree of dimensionality reduction. Specifically, given that dimensionality reduction methods may produce very similar global reconstruction error for the same degree of dimensionality reduction, would we expect any difference in human performance? In order to test our hypothesis we developed a closed loop real time virtual reality platform using various sensor modalities in virtual environment that allows for controlled haptic sensorimotor experiments. The set-up consists of the following real-time systems: optical motion tracking for arm tracking, a CyberGlove (22 DoF 5 digit tracking), Physics simulation Engine MuJoCo which implement various dexterity tasks and a VR system (HTC Vive) that ensures we control not only motor output but also sensory input. Using this experimental platform we can directly compare the performance of the subjects under various control conditions for mapping the subjects' real hand movements to drive the artificial hand: 1) direct mapping, 2) PCA, 3) Sparse Motion Decomposition (Fenske et al 2015) , 4) Sammon Mapping, 5) Stochastic Proximity Embedding.

Disclosures: C. Konnaris: None. **A.A. Faisal:** None.

Poster

229. Limb Brain-Machine Interfaces

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 229.08/DD12

Topic: E.05. Brain-Machine Interface

Title: Brain-computer interface with transcutaneous functional electrical stimulation for upper limb fine motor control

Authors: S. COLACHIS, IV[1,4,2], *M. A. BOCKBRADER[5,2], P. B. SEDERBERG[3,2], N. ANNETTA[4], D. FRIEDENBERG[4], M. A. SCHWEMMER[4], M. ZHANG[4], G. SHARMA[4], H. BRESLER[4], W. MYSIW[5,2], A. REZAI[2]

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Abstract: Introduction: Recent advances in brain-computer interfaces (BCIs) offer a promising approach for overcoming paralysis. Our objective was to demonstrate feasibility of improving upper limb motor control for skilled precision grasps in humans with tetraplegia using a BCI.
Methods: A 22-year-old man with C5 ASIA Impairment Scale category A traumatic spinal cord injury was recruited from the Reanimation in Tetraplegia clinical trial (ClinicalTrials.gov NCT01997125), an ongoing Phase I/II study for an investigational, intracortical BCI interfaced with an 130-electrode, transcutaneous, forearm functional electrical stimulation (FES) orthotic. He underwent implantation of an FDA IDE-approved intracortical microelectrode array in his left primary motor cortex, which allowed for online recording of neural activity, decoding with machine-learning algorithms, and feedback via a physics-based virtual hand and FES-evoked movements of his own right arm. Baseline (no BCI-FES) and BCI-FES system performance were compared on standardized measures of upper limb function, including: the Graded Redefined Assessment of Strength, Sensibility and Prehension (GRASSP), Grasp and Release Test (GRT), Spinal Cord Independence Measure-Self Report (SCIM-SR), and Quadriplegic Index of Function-Short Form (QIF-SF).
Results: Total GRASSP score improved from 31 at baseline to 69/119 with the system on. Clinically important gains were observed on the strength subscale (27 points, corresponding to full wrist extension, digit III flexion and extension, thumb flexion and opposition, and partial abduction of digits V and II) and improved ability to generate cylindrical, key and tripod grips (6 points). Number of successful GRT transfers improved between baseline and stimulation conditions for: can (0 to 5), fork (0 to 5), peg (5 to 6), weight (0 to 6), and VHS (1 to 2). QIF-SF ratings improved with the BCI-FES for eating, grooming and mobility (4 to 13 out of 18 points). SCIM-SR scores improved for feeding, grooming and toileting (15 to 24 out of 74 points).
Conclusion: Our participant used the BCI-FES to evoke lateral, palmar and tip-to-tip grips, demonstrated fine motor control to manipulate objects across sizes and weights, and completed complex tasks like unscrewing lids, pouring from a bottle, and transferring pegs. His functional cervical level improved from C5/6 to C6/T1 on the GRASSP, consistent with improved functional independence when using the neuroprosthetic for self-care tasks, critical for improving quality of life.

Disclosures: **S. Colachis:** A. Employment/Salary (full or part-time):; Battelle Memorial Institute. **M.A. Bockbrader:** A. Employment/Salary (full or part-time):; The Ohio State University. **P.B. Sederberg:** None. **N. Annetta:** A. Employment/Salary (full or part-time):; Battelle. **D. Friedenberg:** A. Employment/Salary (full or part-time):; Battelle. **M.A. Schwemmer:** A. Employment/Salary (full or part-time):; Battelle. **M. Zhang:** A. Employment/Salary (full or part-time):; Battelle. **G. Sharma:** A. Employment/Salary (full or part-time):; Battelle. **H. Bresler:** A. Employment/Salary (full or part-time):; Battelle. **W. Mysiw:** A. Employment/Salary (full or part-time):; Ohio State. **A. Rezai:** A. Employment/Salary (full or part-time):; Ohio State.

Poster

229. Limb Brain-Machine Interfaces

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 229.09/DD13

Topic: E.05. Brain-Machine Interface

Support: DARPA Cooperative Agreement W911NF-14-2-0107

NIH Grant F32NS092430

Title: Peripheral optogenetic stimulation of motor function in non-human primates toward restoration of volitional motor control in a brain-machine interface

Authors: *J. J. WILLIAMS[1], A. VAZQUEZ[2], A. M. WATSON[3], A. B. SCHWARTZ[4]
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Abstract: Artificial muscle activation can be used to reanimate muscles that have been rendered inactive by disease or injury. Most approaches to muscle reanimation have used functional electrical stimulation (FES) which has several considerable drawbacks. Recently, peripheral motor nerves expressing channelrhodopsin (ChR2) have been optically stimulated to elicit functional muscle activity in transgenic mouse lines as well as through viral mediation in rodents. Functional optical stimulation (FOS) of muscle activity in this manner offers several advantages over FES in terms of its potential use in chronic BMI applications.
Prior to realizing its potential as a human gene therapy, however, viral transduction of light-sensitive opsins such as ChR2 in peripheral motor nerves must be demonstrated and optimized in non-human primates – a task which has proven difficult for viral optogenetic techniques in the brain and has yet to be demonstrated in the periphery. Here, we present successful transduction of ChR2 in peripheral motor nerves of adult macaques following injection of an AAV6 based vector into target muscles. EMG activity elicited acutely through fiber optic stimulation as well as using LED-nerve cuffs designed for chronic optical stimulation demonstrated selective recruitment of muscle fascicles within a targeted muscle. In addition, patterns of sensitivity to optical stimulation, histology, multi-photon and whole sample optical imaging techniques were used to evaluate the expression patterns of opsins in the spinal cord and periphery. These analyses showed variable opsin expression both along the length of a nerve and across axons with implications for chronic LED cuff placement. Together, these results can help direct avenues of investigation that need to be addressed before this therapy may be translated to clinical use.

Disclosures: J.J. Williams: None. **A. Vazquez:** None. **A.M. Watson:** None. **A.B. Schwartz:** None.

Poster

229. Limb Brain-Machine Interfaces

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 229.10/DD14

Topic: E.05. Brain-Machine Interface

Support: Grants-in-Aid for Young Scientists (A) (15H05357)

Title: Motion reconstruction system for trans-humeral amputees without motion tracking

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Abstract: Reconstruction of hand's position with non-invasive bio-signals such as electroencephalography (EEG) and electromyogram (EMG), is a challenging problem that has not been solved yet. The solution could be used as an intuitive and direct interface to volitionally operate prosthetic devices. To develop a predictor that maps the bio-signals to the desired position, usually supervised algorithms are used. Thus, it is necessary to obtain the position of the hand for training the predictor. Despite motion tracking is commonly used to record hand position, for amputees it is impossible to use it. In this study, we propose a hand position reconstruction method for trans-humeral amputees, without using any motion tracking systems. We used a virtual avatar's position as input for training the predictor. Twenty-four participants were asked to imitate the avatar's arm motion. During the motion, EEG and EMG signals were recorded and paired with the avatar's hand trajectory. There were two phases: training, and execution. During the training phase, the participants could watch and practice a set of avatar's motions as many times as they wanted until they were ready. Then, in the execution phase, the subject performed the same set of motions at the same time as the avatar. The data recorded during the execution were the ones used for training the predictor. We investigated which way of showing avatar motion was better to improve the accuracy of the reconstruction. There were three experimental conditions: 1) showing the avatar on a screen during the training and execution phases, 2) showing the avatar on a screen during the training but not during the execution phase, so the participants would perform the movements from memory, and 3) showing the avatar using a virtual reality headset during both phases. The mean correlation value between the avatar's hand position and the reconstructed one across three dimension for all participants was 0.851. This result is the highest in the literature. Furthermore, we did not find significant differences between the three presentation methods in terms of decoding accuracy. Also, we found that the combination of EEG and EMG is critical for reaching higher scores. We propose for the first time, a hand position reconstruction method in which the position data for training the predictor comes from a virtual avatar instead that from a motion tracking system. This approach would make the implementation of hand position reconstruction technology easier

for real world applications. In addition, the achieved accuracy is the best in the literature, showing that using EEG and EMG with the proposed predictor's architecture is a promising solution for the problem.

Disclosures: **J. Fernandez-Vargas:** None. **K. Kita:** None. **W. Yu:** None.

Poster

229. Limb Brain-Machine Interfaces

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 229.11/DD15

Topic: E.05. Brain-Machine Interface

Support: NeuroNET seed grant at UTK

Title: A brain-machine interface for a sequence movement control of a robotic arm

Authors: ***R. ABIRI**[1], J. KILMARX[1], S. BORHANI[1], X. ZHAO[1], Y. JIANG[2]
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Abstract: Brain Machine Interfaces (BMI) have become of interest during the past years. The brain activities are recorded by invasive or noninvasive approaches and translated into command signals to control external prosthetic devices such as computer cursor, wheelchair, and robotic arm. Although many studies confirmed the capability of BMI systems in controlling multi-degrees of freedom (DOF) prosthetic devices using invasive approaches, this area of research in noninvasive approaches is at the beginning stage. In this work, a new BMI robotic platform has been developed using noninvasive Electroencephalography (EEG) technology. EEG signals were acquired using 14 channels and through BCI2000 software (with high pass filter at 0.1Hz and low pass filter at 30Hz). A low-cost 6-DOF robotic arm was used for real-time object manipulation between two fixed points in the workspace. A successful manipulation task consisted of 6 sequential movements of the robotic arm to pick up an object from a point on the left side of the workspace and drop it at a fixed point on the right side of the workspace. The programmed movements were controlled by a developed 4-target cursor control task. The subject was instructed to use imagined body kinematics to control the cursor and the robotic arm movements by hitting the targets. After initial calibration and testing, the subject attempted to control the robotic arm. The most efficient target sequence consisted of hitting 6 targets in sequential order. A successful manipulation run was reported when the object was placed at the final point regardless of any mistakes. Among 10 runs of manipulation runs, a 70% success rate was reported for the overall object manipulation task (Table 1). The experiments here serve as a concept proof for the feasibility of developing a noninvasive BMI robotic platform for manipulation task with minimum training. In future work, we will test the platform on a greater

subject population with more complicated tasks such as manipulating an object between two arbitrary locations and in three dimensional space.

Trial / Run	1	2	3	4	5	6	7	8	Overall Success/Fail
1	L	B	T	R	B	T	-	-	Success No Mistakes
2	R	L	B	T	R	B	T	-	Success One Mistake T1
3	L	B	T	R	B	B	B	B	Fail
4	L	B	T	L	T	R	B	T	Success Two Mistakes T4 and T5
5	L	T	B	T	R	B	L	-	Fail
6	L	B	T	T	R	B	R	T	Success Two Mistakes T4 and T7
7	L	B	L	T	R	B	T	-	Success One Mistake T3
8	L	B	L	T	R	B	L	-	Fail
9	L	B	T	R	B	T	-	-	Success No Mistakes
10	L	B	L	T	T	R	B	T	Success Two Mistakes T3 and T5
									Average successful rate: 70%

Table 1. Success rates for 10 trials of object manipulation for one subject. The goal of the experiment was to pick up an object from the left side of the workspace, drop it on the right, and return to the initial position. The subject was instructed to follow the optimized target sequence of left (L), bottom (B), top (T), right (R), bottom, top during cursor control trials. Failure is classified as the block being dropped in an unreachable position, or the subject giving up.

Disclosures: **R. Abiri:** None. **J. Kilmarx:** None. **S. Borhani:** None. **X. Zhao:** None. **Y. Jiang:** None.

Poster

229. Limb Brain-Machine Interfaces

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 229.12/DD16

Topic: E.05. Brain-Machine Interface

Support: VA Grant I01 RX001296

NIH Grant R01 NS086100

NIH Grant R01 NS058871

VA Grant B4195

The Cleveland Clinic

Title: Extracting much more information from field potentials on the micro and macro scale

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Electrical Stimulation Ctr., Cleveland VA Med. Ctr., Cleveland, OH; [3]Biomed. Engin., Case Western Reserve Univ., Cleveland, OH

Abstract: Field potential recordings usually contain multiple sources of biological and non-biological noise regardless of whether they are recorded from the scalp surface (electroencephalograms, EEGs), the brain surface (electrocorticograms, ECoGs), via depth electrodes (stereoelectroencephalograms, sEEGs), or focally from intracortical microelectrodes (local field potentials, LFPs).
Spatial filtering is the process of creating weighted linear combinations of multichannel field potential recordings. Spatial filtering methods, such as common average referencing (CAR), can be used to remove common noise. Spatial filtering can also be used to concentrate the relevant neural information into a smaller number of more useful signals, such as with independent or principle component analysis (ICA/PCA). Previously we have shown how using 'Common Spatial Pattern' (CSP) analysis to optimize spatial filters before extracting power features can significantly improve our ability to decode arm movement information from field potentials compared to the most commonly used spatial filtering methods (e.g. CAR, PCA, ICA).
In this study, we tested if we could further improve arm movement decoding by first bandpass filtering each channel into biologically relevant frequency bands (e.g. alpha, beta, low gamma, high gamma) before applying our CSP algorithm thereby optimizing spatial filters to each unique frequency band of interest. Results showed our new method produces a very large and significant improvement in arm movement decoding accuracy (typically 50-200% improvement) across all types of field potentials from the microscale (LFPs) to the macroscale (EEGs/ECoGs). Our novel method resulted in power features that can contribute more unique non-redundant movement information compared to traditional methods. The band-specific spatial filter weights also provide useful information about the location/spread of band-specific arm movement information and the sources of different types of contaminating noise.
Such substantial improvements in the quality of information extracted from field potentials at all scales suggest field potentials may be a more useful signal for brain-machine interfacing than previously thought. These techniques may also help maintain the usefulness of intracortical microelectrodes after spiking activity has declined. Our novel spatial filter optimization process may also improve the quality of information extracted from field potentials for other clinical applications such as epilepsy detection and closed-loop control of deep brain stimulation.

Disclosures: D.M. Taylor: None. **T. Johnson:** None.

Poster

229. Limb Brain-Machine Interfaces

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 229.13/DD17

Topic: E.05. Brain-Machine Interface

Support: SPAWAR contract HR0011-15-C-0036

Title: Embedding real-time closed-loop algorithms on an ambulatory processor

Authors: E. L. BARCIKOWSKI, A. WILDER, R. ROUNDY, *D. R. MERRILL, D. MCDONNALL
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Abstract: In the development of neuroprostheses, there is a profound unmet need for the ability to run complex decodes and provide real-time, closed-loop control of stimulation systems and external peripherals. These experiments typically require rack-mounted data acquisition systems, external stimulators, and extra computers to develop and run the analyses. The need for this equipment and the difficulty of development limits these experiments to the laboratory environment where movement and behavior of the subjects are greatly constrained. As part of the DARPA HAPTIX project, Ripple has developed a system, known as Nomad, for experimenters to easily transition from a laboratory development environment to one where decode, stimulation, and control routines can be run directly on the hardware. This allows for subjects to behave in a more natural environment and for advanced clinical investigators to test their systems in an ambulatory environment. The Ripple Nomad is a portable, wireless, battery-powered data acquisition and stimulator that supports up to 512 channels plus analog and digital inputs. Additionally, the Nomad can control digital outputs and has CAN bus support, common for control of modern upper limb prosthesis. A Nomad can easily be worn by human or animal subjects. Our system only requires that investigators write MATLAB code, though C and Python are also supported, which can be compiled and run directly on the Nomad. Investigators can develop and debug experiments in their normal work environment, then move their code to the Nomad, transitioning to a freely moving or ambulatory mode when they are confident of their analysis. Algorithms running on the Nomad can be run with round trip latencies as low as 1 ms, which is well within any constraints for neuroprostheses development and additionally will facilitate advanced single unit microelectrode experiments.

Disclosures: E.L. Barcikowski: A. Employment/Salary (full or part-time):; Ripple LLC. **A. Wilder:** A. Employment/Salary (full or part-time):; Ripple LLC. **R. Roundy:** A. Employment/Salary (full or part-time):; Ripple LLC. **D.R. Merrill:** A. Employment/Salary (full or part-time):; Ripple LLC. **D. McDonnall:** A. Employment/Salary (full or part-time):; R.

Poster

229. Limb Brain-Machine Interfaces

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 229.14/DD18

Topic: E.05. Brain-Machine Interface

Support: NSF IIS-1637892

Title: A portable multichannel electrical stimulator for neuromuscular stimulation

Authors: *G. LI[1], X. HU[2]
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Abstract: Neuromuscular electrical stimulation has been widely used in research, clinical and home settings. Different stimulation systems are typically adopted based on the working environment, due to competing factors including functionality, ease-of-use, portability, and cost. In our current study, we designed and tested a portable and fully customizable multichannel electrical stimulator with user-friendly control interface. Our battery powered stimulation system can output voltage or current controlled stimulations, with a wide range of stimulation patterns, through 8 independently-controlled channels concurrently. From each channel, the device is capable of controlling the stimulation at high resolutions in amplitude, duration, and frequency, which are comparable/superior to research-grade commercial systems. Additionally, the compact size, low weight, and low cost features of the system ensure portability and accessibility in both clinical and home-use environment. The system has been tested on human subjects based on a transcutaneous nerve stimulation protocol. Our results show that our stimulator was able to evoke consistent motor and sensory responses. Overall, our stimulation system also shows great promise for applications in rehabilitation settings and for integration with neural prostheses.

Disclosures: G. Li: None. **X. Hu:** None.

Poster

229. Limb Brain-Machine Interfaces

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 229.15/DD19

Topic: E.05. Brain-Machine Interface

Support: DARPA N66001-10-C-4056

DARPA N66001-16-C-4051

Title: Grasp force encoding in human primary motor cortex during attempted isometric grasping

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Abstract: Brain-computer interfaces (BCIs) can restore limb function by controlling a prosthetic arm with signals recorded from primary motor cortex (M1) and recently have begun to incorporate sensory feedback through stimulation of somatosensory cortex (S1). With the ability to sense graded levels of tactile feedback, we aim to extend the capabilities of BCIs to control grasp force. Here we examined whether motor cortex encoded a force signal during an attempted isometric grasp in a virtual reality environment (MuJoCo). A 28-year old male with tetraplegia was implanted with two 88-channel and two 32-channel intracortical microelectrode arrays in M1 and S1, respectively. We recorded neural data while the participant used a virtual hand to grasp spherical objects at three force levels indicated by a spoken audio cue (gentle, medium, and firm ranging from 4 to 12 N). He attempted to perform the task while the computer controlled the kinematics and grasp force. Graded stimulation was provided as the object was compressed based on the measured reaction force on the index finger in MuJoCo. The participant had five seconds to close the hand around the object and was required to maintain hold of it for two seconds at the specified force level. To determine whether M1 activity encoded force-related information, we trained a Naïve Bayes classifier to obtain classification accuracy of the force levels using five sets of 27 trials collected over three test sessions. A time series of accuracies was computed by averaging each channel's firing rate over a 1 second sliding window (200 ms step) for the duration of the hold phase (2 seconds). The model was validated using leave-one-out-cross validation. Classification accuracy was high at 70 +/- 5% throughout the isometric grasp phase for all six time bins tested, with no significant differences in classification accuracy between the bins. In addition to the 70% of correctly classified force targets, 16 +/- 13% of incorrectly classified trials were to the adjacent force level when classifying data during the first second of the isometric grasp. Our results demonstrate that grasp force can be well classified from neural recordings in M1. In the future, we plan to analyze the effects of providing feedback on classification accuracy. Currently, we use a linear mapping of stimulation amplitude to force levels; however, this is not naturalistic. Future work will involve developing more effective ways of incorporating stimulation, such as using biomimetic stimulation patterns. We will also investigate the most effective ways of implementing force decoding with BCI control to provide accurate manipulation of objects of different sizes and compressibility.

Disclosures: **A.J. Herrera:** None. **J.E. Downey:** None. **J.M. Weiss:** None. **M.L. Boninger:** None. **R.A. Gaunt:** None. **J.L. Collinger:** None.

Poster

229. Limb Brain-Machine Interfaces

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 229.16/DD20

Topic: E.05. Brain-Machine Interface

Support: ImPACT Program of Council for Science, Technology and Innovation (Cabinet Office, Government of Japan)

Strategic Research Program for Brain Sciences by the Ministry of Education, Culture, Sports, Science and Technology of Japan

The Commissioned Research of the National Institute of Information and Communications Technology (NICT)

JSPS KAKENHI Grant Number 15H03049

Title: Cortical plasticity observed in an electrocorticography-based motor brain-machine interface task

Authors: *T. KAIJU[1,3], M. INOUE[3], M. YOKOTA[1,3], M. HIRATA[2], T. SUZUKI[3]
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Abstract: A brain-machine interface (BMI) is a technology that controls external devices using brain signals. One main purpose of this technology is to help patients with severe motor deficits to perform several daily activities. In addition, there is a possibility to enhance our body (e.g., simultaneous control of an extra robotic arm). To accomplish enhancement of human bodies using a BMI, it will be necessary for a new representation of the extended function to be formed on the cortex, which is already functionally differentiated. Some BMI studies, using neuronal unit activity or local field potential, reported induction of such plasticity. However, it remains unknown whether an electrocorticography (ECoG) signal, which has the advantages of low-invasiveness and high signal stability, can effectively induce plasticity. In this study, to investigate the ability of an ECoG-BMI to induce cortical plasticity, we performed a BMI task using neurofeedback. An ECoG electrode (18 channels; 3 rows × 6 columns) was placed on the motor and sensory area of one Japanese macaque (from shoulder to wrist area). A behavioral task was designed as a self-feeding trial by the manipulation of the robotic arm. Increasing similarity between a specific activation pattern defined by an experimenter (a template) and an actual activation pattern moved the robotic arm closer to a subject. First, a reaching task using the subject's own arm was performed, and a template was made based on an arm-movement-related ECoG pattern. The monkey could drive the robotic arm and feed itself using this template. However, its own arm movement did not disappear when controlling the robotic arm. We added a control rule that stops the robotic arm when the subject's arm movement was detected. In this condition, the monkey could also control the robotic arm, but performance was decreased. Next, we performed the same task with a different (movement-unrelated) template. The monkey could control the robotic arm without the movement of its own arm, but performance was decreased compared to the former template condition, without an arm penalty. Further, we confirmed that template switching induced change in the actual ECoG pattern during the task. The monkey could successfully manipulate the robotic arm with some different templates, and an ECoG-

based BMI could induce a change in the ECoG pattern. Our study provides fundamental knowledge of an ECoG-based BMI and its effect on brain plasticity.

Disclosures: T. Kaiju: None. **M. Inoue:** None. **M. Yokota:** None. **M. Hirata:** None. **T. Suzuki:** None.

Poster

230. Limb Brain-Machine Interfaces: Neurophysiology

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 230.01/DD21

Topic: E.05. Brain-Machine Interface

Support: Craig H. Neilsen Foundation

A. Alfred Taubman Medical Research Institute

NIH R01 GM111293

DARPA N66001-16-4006

NSF-GRFP

Title: Decoding of fingertip position from motor cortex in Rhesus macaque using a ReFIT Kalman Filter

Authors: *A. VASKOV[1], Z. T. IRWIN[2], C. S. NU[2], P. P. VU[2], S. R. NASON[2], A. J. BULLARD[2], P. G. PATIL[3], C. A. CHESTEK[2]
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Abstract: To date, many brain-machine interface studies have developed decoding algorithms that provide precise control of arm reaches with limited grasping (Collinger 2012, Downey 2016). However, comparatively fewer have focused on quantifying the precision of continuous finger control. The ReFIT Kalman filter (Gilja 2012) uses a two-stage training approach that improves upper limb performance by correcting online kinematics to match the user's intent during training. In reach tasks, this produces neural tuning curves with stronger modulation and less variance (Fan 2014). However, it is unclear if this method will also work for finger motion where a clear "tuning" trend has not been established. Here we apply ReFIT to decode fingertip position online in a non-human primate for the first time.
We implanted one Rhesus macaque with a 96-channel Utah microelectrode array (Blackrock Microsystems) in left primary motor cortex. Neural data was sampled at 30kHz with a spike detection threshold at -4.5 RMS. Spike counts were fed into a real-time MATLAB xPC application for decoding. The monkey performed a center-out target task in which he was given

control of finger flexion on a virtual hand along a 1D arc and required to maintain finger-on-target position for 500ms before receiving a juice reward. Targets were scaled to take up 16.1% of the arc between full flexion and extension. The initial Kalman filter was trained with normalized output from a flex sensor attached to the index finger. The ReFIT decoder was then trained by applying intention estimation to the decoded finger kinematics of the initial filter. For 1D finger control, intention estimation consisted of reversing incorrect velocities and zeroing velocities for on-target positions. Consistent with the ReFIT algorithm, position uncertainty was also removed during the Kalman gain calculation. Decoders were trained with spike counts binned in 50ms intervals, which were then fitted to both position and velocity, and used integrated velocity for the control signal.
Consistent with previous studies, the ReFIT algorithm greatly improved performance over the initial Kalman filter mainly due to a 61.6% reduction in average target orbiting time. Mean bit rate increased from 0.863bps for the initial Kalman filter to 1.139bps for the ReFIT filter, compared to 1.653bps achieved with the physical hand. Future work includes analyzing the relationships between neural activity in primary motor cortex and finger movement to better understand how these improvements arise and guide the development of continuous decoders for individual and combined finger movements.

Disclosures: **A. Vaskov:** None. **Z.T. Irwin:** None. **C.S. Nu:** None. **P.P. Vu:** None. **S.R. Nason:** None. **A.J. Bullard:** None. **P.G. Patil:** None. **C.A. Chestek:** None.

Poster

230. Limb Brain-Machine Interfaces: Neurophysiology

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 230.02/DD22

Topic: E.05. Brain-Machine Interface

Support: Office of Research and Development, Rehabilitation R&D Service, Department of Veterans Affairs (N9288C, B6453R)

Eunice Kennedy Shriver National Institute of Child Health & Human Development – NICHD-NCMRR (R01HD077220)

NIDCD (R01DC009899)

MGH-Deane Institute

The Executive Committee on Research (ECOR) of Massachusetts General Hospital

Title: System identification of the human primary motor cortex

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Abstract: Brain computer interfaces (BCIs) can be used as control sources for prostheses. However, as neuroprostheses become increasingly complex, BCIs must provide more control information to maintain current levels of performance in higher degree-of-freedom movement spaces. There are several methods to increase the information provided by BCIs without implanting more electrodes. These methods include identifying novel control signal modalities and providing more complete models of previously-described BCI control signals. Both of these methods begin by generating new hypotheses for how BCI neural signals map to motor intentions. Linear, time-invariant systems can be completely characterized by their impulse response functions or frequency response functions. For BCIs, the impulse response functions, in the time domain, and frequency response functions, in the frequency domain, describe how impulses in neural signals map to assumed motor intentions. By characterizing the impulse response functions and frequency response functions of BCIs, we can characterize the BCI systems, under the assumptions of linearity and time-invariance. A common way to derive impulse response functions and frequency response functions is to use so-called system identification.
In this work, we used linear system identification to derive the impulse response functions and frequency response functions of an intracortical BCI system recording from human motor cortex as part of the BrainGate2 pilot clinical trial. Linear system identification was performed using standard cross-correlation techniques. The study participant (with C4 ASIA A SCI) was asked to watch a virtual arm move on a computer screen. Kinematics from the virtual arm were then cross-correlated with neural spikes and high-frequency neural signals to derive the impulse response functions and the frequency response functions. A greedy search was used to select the neural features that would be subjected to system identification, and cross-validation was performed to determine the variance accounted for by our identified system. Our models accounted for at least 25% of the variance. The impulse response functions were analyzed to gain insight into the signals encoded by neurons. Future work will leverage this insight to build more complete models of the signals encoded by the human primary motor cortex.

Disclosures: D.C. Crowder: None. **W.D. Memberg:** None. **B.A. Murphy:** None. **J.A. Sweet:** None. **J. Miller:** None. **B. Walter:** None. **L.R. Hochberg:** None. **A.B. Ajiboye:** None. **R.F. Kirsch:** None.

Poster

230. Limb Brain-Machine Interfaces: Neurophysiology

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 230.03/DD23

Topic: E.05. Brain-Machine Interface

Support: Office of Research and Development, Rehabilitation R&D Service, Department of Veterans Affairs (N9288C, B6453R)

NIDCD (R01DC009899)

NINDS (UH2NS095548)

MGH-Deane Institute

The Executive Committee on Research (ECOR) of Massachusetts General Hospital

Title: Assessment of discrete state selection strategies for intracortical brain-computer interface applications

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Abstract: Background: Restoring communication to individuals with severe motor disabilities is a major application of an intracortical Brain-Computer Interface (iBCI). An iBCI system collects neural signals directly from the brain cortex and translate these signals into the user's intended command, such as the movement of a computer cursor on a screen. As a communication platform, an iBCI system has to be able to decode not only the kinematics of a computer cursor but also discrete selections or clicks. Here we focus on different classification methods to decode an intended click and the online use of these approaches. Methods: The data was collected from a research session carried out with participant T10, a 35 year old male with spinal cord injury enrolled in the BrainGate pilot clinical trial program. Neural signals were collected using two 96-channels microelectrode arrays implanted in dominant precentral and middle frontal gyri. Signals were amplified and filtered and the spike rates and signal power were used to drive the decoding algorithms. A Kalman filter was used as kinematics decoder and four different classifiers were applied as click decoders, namely: Linear Discriminant Analysis (LDA), Local Fisher Discriminant Analysis (LFDA), Support Vector Machine and a combination of principal components analysis (PCA) and Hidden Markov Model (HMM). Instead of using the LDA and

LFDA in a classical way, the probability output of these decoders were fed to a HMM which in turn, outputted a probability of a click. For the PCA HMM approach, the emission probabilities were modelled as multidimensional Gaussians of the spike rate top 4 principal components out of the 192 channels. All HMM's modelled two states: movement and click. Results: All decoders were calibrated using data from a center out task where the participant was instructed to attempt a click once the cursor reached a cued target. The performance was evaluated using 6x6 grid where one square was randomly cued per trial. Area under the ROC showed that the SVM and the PCAHMM achieved similar and superior performance than the LDA HMM and LFDA HMM. Conclusion: The addition of the HMM to the LDA based decoders showed to increase the decoders sensitivity, facilitating a click detection but also increasing the number of false positive during closed loop control. Offline analysis of these two decoders revealed that most of the false clicks happened during low speed, indicating that dividing the HHM movement state into high and low speed could improve performance. The SVM and the PCA HMM showed bit rates performances comparable to previously published in the literature which advocates for the use of these decoders in real time applications.

Disclosures: M. Vilela: None. **J.G. Ciancibello:** None. **T. Hosman:** None. **J. Saab:** None. **D.M. Brandman:** None. **B. Franco:** None. **J. Kelemen:** None. **J.D. Simeral:** None. **L.R. Hochberg:** None.

Poster

230. Limb Brain-Machine Interfaces: Neurophysiology

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 230.04/DD24

Topic: E.05. Brain-Machine Interface

Support: Office of Research and Development, Rehabilitation R&D Service, Department of Veterans Affairs (N9288C, B6453R)

NIDCD (R01DC009899)

MGH-Deane Institute

The Executive Committee on Research (ECOR) of Massachusetts General Hospital

CIHR (#336092)

Dalhousie University Killam Fellowship

NSF (DMS1309004)

Title: Noise-robust closed-loop neural decoding using an intracortical brain computer interface in a person with paralysis

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Abstract: Background: Intracortical brain computer interfaces (iBCIs) have been used to allow individuals with paralysis the ability to control objects in their environment. Effective decoding is predicated on the neural decoder, which translates high-dimensional neural signals into the low-dimensional command signal used to control an external effector (e.g. computer cursor or robotic arm). Most iBCI systems in people use linear mapping from a neural feature space to the kinematics of the effector; however, linear methods are sensitive to large outliers in neural signals. We describe a novel non-linear decoding method that combines kernel embedding and the discriminative Kalman filter (we refer to this combination as MK-DKF), and demonstrate that this neural decoding method is more robust to noise than standard linear decoders.
Methods: As part of the ongoing BrainGate2 pilot clinical trial, a research participant (T10) with a complete cervical spinal cord injury received two 96-channel multielectrode arrays, which were placed in the dominant precentral gyrus and the dominant caudal middle frontal gyrus. The participant performed BCI-enabled computer cursor tasks with the MK-DKF and Kalman filter decoders.
Results: In a double-blinded block-randomized research session, we found that neural decoding using MK-DKF was more robust to injected noise events. Importantly, the MK-DKF yielded comparable bit-rate communication performance to the standard Kalman filter.
Conclusion: The MK-DKF decoder is a novel approach that addresses unpredictable noise events in iBCI systems. Preliminary results suggest it may be a viable alternative to linear decoding methods for providing reliable control of iBCI systems with improved robustness to noise.

Disclosures: D. Brandman: None. **M.C. Burkhart:** None. **J. Saab:** None. **T. Hosman:** None. **B. Franco:** None. **J. Kelemen:** None. **M.T. Harrison:** None. **L.R. Hochberg:** None.

Poster

230. Limb Brain-Machine Interfaces: Neurophysiology

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 230.05/DD25

Topic: E.05. Brain-Machine Interface

Support: Office of Research and Development, Rehabilitation R&D Service, Department of Veterans Affairs (N9288C, B6453R, P1155R)

NINDS (1UH2NS095548)

NIDCD (R01DC009899)

NIBIB (R01EB007401)

MGH-Deane Institute

The Executive Committee on Research (ECOR) of Massachusetts General Hospital

DARPA REPAIR

Title: Wireless intracortical BCI cursor control by a person with tetraplegia

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Abstract: A high priority for BCI research is to restore communication and independence for individuals with severe motor disability. Advances in intracortical BCI (iBCI) performance (Jarosiewicz 2015, Pandarinath et al., 2017; Ajiboye et al., 2017) motivate efforts to translate the investigational BrainGate platform for independent home use. One impediment to unsupervised on-demand use of iBCIs has been the need for a recording cable that tethers the BCI user to hardware that decodes neural activity into assistive commands. Here, we demonstrate the first wireless control of a point-and-click iBCI by a person with tetraplegia.
We recorded neural activity from two microelectrode arrays implanted in the dominant precentral and middle frontal gyri of participant T10, a 35 year-old man with tetraplegia resulting from a C4 ASIA-A spinal cord injury. Each array's percutaneous pedestal was connected to a 96-channel broadband battery-powered wireless transmitter (Brown Wireless Device, BWD; Yin et

al., 2014; Blackrock Microsystems, Salt Lake City, UT) instead of the usual NeuroPort Patient Cable. Each BWD digitized neural signals at 20 kHz with 12-bit resolution before transmitting the data over its dedicated wireless band (3.3 GHz or 3.5 GHz) to antennas one meter away. Receivers up-sampled the data to 30 kHz and sent them to two Blackrock Neural Signal Processors that then delivered packets of neural data to BrainGate platform hardware regularly used to process wired data.
During research sessions in his home, T10 used the wireless system to achieve point-and-click control of a consumer tablet using intended hand and finger movements. Thresholded spikes and LFP spike power were decoded by a Kalman filter (cursor kinematics) and a discrete state algorithm (click). Starting with uncalibrated decoders, T10 used our automated closed-loop calibration process (Brandman et al., SFN 2016) to quickly achieve unassisted control of a computer cursor. He completed target acquisition assessment tasks (R8, mFitts, Grid) before using applications on the Surface Pro tablet (Windows 10 desktop, Edge browser, YouTube, Pandora, Skype). Wireless cursor control performance was comparable to his previous wired measures (e.g., 1.2 bits/s on the Grid task). This early use of the wireless system identified potential new challenges such as antenna switching noise, transmission dropout, and bit errors; nevertheless, recorded signal quality with the BWD was comparable to wired signal quality. Results demonstrate the viability of a wireless iBCI system and progress towards the clinical translation of BCIs for individuals with severe motor disability. [JS, TH joint first authors]

Disclosures: **J. Saab:** None. **T. Hosman:** None. **M. Yin:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BWD: IP rights (licensed to Blackrock Microsystems). **D.A. Borton:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BWD: IP rights (licensed to Blackrock Microsystems). **B. Franco:** None. **J. Kelemen:** None. **D.M. Brandman:** None. **M. Vilela:** None. **J.G. Ciancibello:** None. **L. Larson:** None. **D.M. Rosler:** None. **J.D. Simeral:** None. **A.V. Nurmikko:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BWD: IP rights (licensed to Blackrock Microsystems). **L.R. Hochberg:** None.

Poster

230. Limb Brain-Machine Interfaces: Neurophysiology

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 230.06/DD26

Topic: E.05. Brain-Machine Interface

Support: Office of Research and Development, Rehabilitation R&D Service, Department of Veterans Affairs (P1155R, N9288C, B6453R)

DARPA/REPAIR program (N66001-10-C-2010)

Conquer Paralysis Now (004698)

NIH BRP 5R01EB007401

The Executive Committee on Research (ECOR) of Massachusetts General Hospital

MGH-Deane Institute

Doris Duke Charitable Foundation

Title: A mobile high-performance intracortical BCI with integrated antenna-receiver

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Abstract: We present a fully mobile, wireless, high-performance intracortical brain-computer interface (iBCI) platform that provides the processing power and performance per watt necessary to implement fully-featured neural decoding algorithms across hundreds of broadband channels in real-time. A custom Xilinx Zynq-7000 embedded system (ESPA) and a novel integrated antenna-receiver device implement the iBCI in a compact package suitable for extended mobile day-to-day use.

Intracortical brain-computer interfaces that record from silicon microelectrode arrays (MEAs) provide high spatial and temporal resolution access to human cortical activity. This produces a high-bandwidth data stream (~92 Mbps given 192 channels of 30 kS/s data) that must be efficiently processed by the neural decoding system in real-time with minimal latency. To date, BrainGate BCI activities have been limited to a stationary wheelchair or bed due to the multiple personal computers and other rack-mounted signal processing/recording hardware necessary to meet these performance requirements. Alleviating these restrictions would be a critical step toward enabling participants to use BrainGate's closed-loop iBCI on demand in their day-to-day lives.

Towards this end, we have developed a mobile wireless BCI platform for broadband intracortical recording and decoding. We have previously reported our development and licensing of broadband wireless neural signal transmitters ("Brown Wireless Device", Blackrock Microsystems, Salt Lake city, UT) for use with the Blackrock percutaneous connector. Here, we present a compatible antenna-receiver device (ARD) that integrates an RF receiver circuit, antenna, and battery to facilitate mobile use for up to 11 hours of runtime per charge. Up to four ARDs each receiving 192 channels of broadband neural data from two wireless transmitters interface with our previously reported mobile neural processing system (ESPA). ESPA's Xilinx Zynq-7045 System-on-Chip (SoC) provides 450 GMACS of DSP performance while only burning an estimated 7.07W resulting in a performance per watt of ~63 GMACS per watt. This level of performance enables the use of multiple concurrent decoding algorithms running across all 192 broadband channels in real-time on a mobile platform. ESPA's medical-grade real-time

operating system (QNX) provides a robust and deterministic Unix-like environment for additional processing and system management. As the next generation of Zynq devices provide even more processing power and performance per watt, the ESPA architecture will continue to scale to meet the demands of future iBCIs with significantly increased channel counts.

Disclosures: C.D. Heelan: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ESPA (IP Rights). **J. Komar:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ESPA (IP Rights). **A.V. Nurmikko:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BWD (IP Rights. Licensed to Blackrock Microsystems). ESPA (IP Rights). **J.D. Simeral:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BWD (IP Rights. Licensed to Blackrock Microsystems). ESPA (IP Rights).

Poster

230. Limb Brain-Machine Interfaces: Neurophysiology

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 230.07/DD27

Topic: E.05. Brain-Machine Interface

Support: 5TL1TR4417

5T32EB004314-15

Office of Research and Development, Rehabilitation R&D Service, Department of Veterans Affairs (N9288C, B6453R, A6779I, B4853C)

National Institute on Deafness and Other Communication Disorders of NIH - R01DC009899

Eunice Kennedy Shriver National Institute of Child Health & Human Development – NICHD-NCMRR (R01HD077220), NICHD-NIH N01HD53403

NIDCD (R01DC009899)

MGH-Deane Institute

Title: Evaluation of neural modulation during attempted force production across multiple hand grasp configurations in intracortical BCI users with chronic tetraplegia

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Abstract: Background: Intracortical brain computer interfaces (iBCIs) have the potential to restore hand grasping in individuals with tetraplegia. While most human-operated iBCIs have utilized only kinematic information from motor cortex, natural grasping and object interaction also requires the use of force-related information. We have previously demonstrated that neural modulation to attempted hand grasping forces is preserved in one individual with tetraplegia. If these force signals happen to be task-independent, then they could be used to restore function across a wide variety of motor tasks in a straightforward way. Here, we investigate whether force signals in individuals with tetraplegia are specific to particular hand grasping configurations, or whether they are grasp-independent. **Methods**: Participants of the BrainGate2 Clinical Trial were asked to attempt to produce four discrete force levels (light, medium, hard, no force) with the dominant upper limb, using a power grasp, one of three pincer grasps, or flexion at the elbow joint. During the task, we obtained full broadband neural recordings from two, 96-channel microelectrode arrays (Blackrock Microsystems, Salt Lake City, UT) in the dominant motor cortex. From each channel, we extracted and characterized single unit activity and two time-varying neural features (spike firing rates and high frequency spike power). Features were used as inputs to a linear discriminant analysis (LDA) classifier to offline-discriminate force levels produced during each hand grasping configuration. **Results and Conclusions:** We found a population of approximately 60 neural features tuned to intended force across multiple grasp types, as well as populations of neural features that exhibit force tuning only during specific hand grasping configurations. Additionally, while classification performance exceeded chance levels for all hand grasping configurations, we found that individual force levels were best discriminated during attempted power grasping and elbow flexion. Further investigations will be necessary to determine the extent to which grasp-independent force information is present in motor cortex.

Disclosures: A. Rastogi: None. **F.R. Willett:** None. **B.A. Murphy:** None. **W.D. Memberg:** None. **B.L. Walter:** None. **J.P. Miller:** None. **J.A. Sweet:** None. **J. Saab:** None. **B. Franco:** None. **J.N. Kelemen:** None. **C.E. Vargas-Irwin:** None. **L.R. Hochberg:** None. **R.F. Kirsch:** None. **A.B. Ajiboye:** None.

Poster

230. Limb Brain-Machine Interfaces: Neurophysiology

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 230.08/DD28

Topic: E.05. Brain-Machine Interface

Support: NSF GRFP DGE0951783

NIH-NICHD R01HD077220

NIH N01HD53403

Larry and Pamela Garlick Foundation and Samuel and Betsy Reeves Foundation

NIH-NIDCD R01DC014034, NIHNIDCD R01DC009899

NIH-NINDS R01NS066311

NIH-NICHDNCMRR N01HD53403

Title: Neural population activity in the decoder's null space observed in people controlling a brain-computer interface

Authors: *F. WILLETT[1,2], D. R. YOUNG[1,2], B. MURPHY[1,2], W. D. MEMBERG[1,2], C. H. BLABE[3], J. SAAB[8,11,9], B. JAROSIEWICZ[10,11,9,12], J. KELEMEN[13], D. M. BRANDMAN[10,9], B. WALTER[14,16], J. A. SWEET[15], J. P. MILLER[15], J. M. HENDERSON[17], K. V. SHENOY[4,5,6,7,18], J. D. SIMERAL[19,8,13,9], L. R. HOCHBERG[11,8,13,20,9], R. F. KIRSCH[1,2], A. B. AJIBOYE[1,2]
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Abstract: When people control intracortical brain-computer interfaces (iBCIs) that use standard linear decoders, only a small number of neural dimensions cause movement of the controlled

device, while the other dimensions in the decoder's "null space" are free to vary without affecting task performance. Characterizing this decoder null space activity could help to inform theories of the motor cortex, which should be able to explain why this activity is produced even though it does not affect the output of the iBCI. If the decoder null space activity contains substantial task-related information, it might also be used to improve iBCI performance. Here, we investigated the decoder null space activity of four participants in the BrainGate 2 pilot clinical trial while they made 2D iBCI-controlled cursor movements. This investigation extends prior work that characterized the muscle null space activity observed while nonhuman primates made able-bodied reaching movements [1]. In all four participants, we found one "magnitude" dimension that correlated with the magnitude (but not direction) of the decoder potent space activity, and one "condition-independent" dimension that modulated sharply at the beginning of a movement but was unrelated to its kinematics (as reported in nonhuman primates [2]). To decode these dimensions, we inverted a 4D encoding model of the decoder potent space and null space dimensions, using a model of the user's feedback control policy to describe the 2D decoder potent space activity. We found that the 4D encoding model could explain the majority (>70%) of the condition-averaged neural activity aligned to target appearance, and that it explains twice as much variance as a 2D decoder-potent-space-only encoding model. To explore why these large decoder null space dimensions might exist even though they do not affect iBCI output, we show that a recurrent neural network optimized to produce the decoder potent space activity also produces both dimensions of the decoder null space activity, even though it was not trained to do so. Future non-linear decoders might be able to leverage these null space dimensions to improve iBCI performance. [1] Kaufman et al. Nat Neurosci 2014 [2] Kaufman et al. eNeuro 2016

Disclosures: **F. Willett:** None. **D.R. Young:** None. **B. Murphy:** None. **W.D. Memberg:** None. **C.H. Blabe:** None. **J. Saab:** None. **B. Jarosiewicz:** None. **J. Kelemen:** None. **D.M. Brandman:** None. **B. Walter:** None. **J.A. Sweet:** None. **J.P. Miller:** None. **J.M. Henderson:** None. **K.V. Shenoy:** None. **J.D. Simeral:** None. **L.R. Hochberg:** None. **R.F. Kirsch:** None. **A.B. Ajiboye:** None.

Poster

230. Limb Brain-Machine Interfaces: Neurophysiology

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 230.09/DD29

Topic: E.05. Brain-Machine Interface

Support: Office of Research and Development, Rehabilitation R&D Service, Department of Veterans Affairs (N9288C, B6453R)

NIDCD (R01DC009899)

NINDS (U01NS098968)

MGH-Deane Institute

The Executive Committee on Research (ECOR) of Massachusetts General Hospital

US ONR N00014-13-1-0672

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health, or the Department of Veterans Affairs or the United States Government.

Title: Replay of neural firing sequences in human motor cortex during rest following a sequenced brain-computer interface task

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Abstract: The replay of neural firing patterns during rest and sleep following learning has been proposed as a mechanism underlying memory consolidation, and has previously been observed in non-human animals. In humans, non-invasive approaches have provided indirect evidence for system-level reactivation of brain regions that were active during prior learning, but no evidence exists yet of replay of specific neural firing patterns. Here, we report the replay of firing rate patterns corresponding to a learned brain-controlled motor sequence in the motor cortex of 2 research participants (T9 and T10) implanted with two 96-channel silicon microelectrode arrays as part of the BrainGate2 pilot clinical trial. On each trial, a specific sequence of 4 radially displaced targets was presented, and the participant was asked to move a cursor under neural control from the center of the screen to the same sequence of 4 targets as quickly and accurately as possible. In a given research session, the same “repeated” sequence was presented in 66 trials, pseudorandomly interleaved with 22 “control” sequences that did not include any of the same target transitions as the repeated sequence. A 20-30 minute rest/nap period took place before (Pre-rest) and after (Post-rest) the task. For each session, the pattern of firing rates during each correct trial was used as a spatiotemporal “template” that was compared to each timestep of pre-rest and post-rest using normalized 2D cross-correlation. To identify candidate replay events, we used non-max suppression with a window size equal to the template duration and a threshold at the 95th centile of correlation coefficients (CCs) to obtain the peak CCs in each rest period. To test for replay, we compared the distribution of mean % changes in CC peak values from pre- to post-rest when using the repeated sequence trials as templates to that obtained when using the control trials as templates, which controlled for any spurious, non-learning-related changes in firing rates over time that might have affected the CCs. To check for replay at different timescales, we resampled each template to 0.08x - 2x the duration of the actual trial and repeated the above process for each timescale. We found significant replay of neuronal firing rate patterns

in 9 of the 10 sessions across the 2 participants. Across sessions, peak replay occurred near timescales of ~0.1-0.5x the actual duration of the trials (i.e. ~2-10x faster than real time), consistent with reports in non-human studies, and a smaller peak occurred near ~1.8x. These results are the first, to our knowledge, to provide direct evidence of replay of learning-related neural firing patterns during rest in human cortex.

Disclosures: **B. Jarosiewicz:** None. **J. Eichenlaub:** None. **J. Saab:** None. **B. Franco:** None. **J. Kelemen:** None. **E. Halgren:** None. **L.R. Hochberg:** None. **S.S. Cash:** None.

Poster

230. Limb Brain-Machine Interfaces: Neurophysiology

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 230.10/DD30

Topic: E.05. Brain-Machine Interface

Support: NIH NINDS BRAIN Initiative Grant 1U01NS098975-01

NSF 1533589

Tianqiao and Chrissy Chen Brain-Machine Interface Center at Caltech

Boswell Foundation

Title: Representation of motor commands, position, and angle in neural activity recorded from human posterior parietal cortex during a pole-balancing task

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Abstract: Traditional brain-machine interfaces (BMI) map arm and hand kinematics from the neural activity onto the movement of a prosthetic device. This direct association is intuitive, because it mimics the function of the healthy spinal cord. However, as BMI research expands into higher-level motor areas of cortex, such as the posterior parietal cortex (PPC), the representation of motor plans becomes more abstract. For example, previous work in human PPC has shown that this versatile brain area encodes movement goals as well as trajectories, and that these goals can be rapidly decoded. These kinds of cognitive motor signals may be useful outside the traditional position-velocity paradigm; for example, in the context of integrating BMIs with advanced machine learning algorithms such as neural networks, which can utilize high-level

inputs for training decisions. To explore representations of nontraditional motor signals in human PPC, we implemented a virtual pole-balancing task. In this task, a pole balances upright on a cart that can move laterally, and users maintain balance by pushing the cart left or right. This task was performed by one human participant in a clinical trial of a brain-machine interface. The participant is tetraplegic, and provided informed consent to have two Neuroport arrays (Blackrock Microsystems, Salt Lake City, UT) implanted in the anterior intraparietal area of PPC and Broadmann's area 5. The task proceeded as a sequence of trials in 3-minute sessions: after a brief inter-trial interval, the pole-cart appeared with a small initial velocity. Left or right input motor commands conveyed via sip-and-puff systems or brain control moved the cart. If the pole fell over, or the cart moved off the screen, the trial aborted; otherwise, the trial ended after 20 seconds of balance. Data recorded during the sip-and-puff training sessions were analyzed to evaluate how motor commands and pole/cart kinematics were represented in the neural data. We found each of these quantities represented in the activity of subpopulations of features derived from the neural signals. Furthermore, participant learned to modulate neural activity to control the movement of the cart online. These findings demonstrate the use of cognitive-level motor areas of cortex to operate a nonstandard BMI effector. Furthermore, neural representations of pole/cart kinematics and input commands could be cumulatively leveraged to provide information about the desired state of an effector to an intelligent machine. This type of interface would be a natural extension of the traditional paradigm, mimicking higher-level cognitive operations in the cortical motor planning and execution pipeline.

Disclosures: **S. Kellis:** None. **D. Handelman:** None. **K. Katyal:** None. **M. Armenta Salas:** None. **L. Bashford:** None. **M. Jafari:** None. **H. Jo:** None. **K. Shanfield:** None. **K. Pejsa:** None. **D. Kramer:** None. **B. Lee:** None. **C. Liu:** None. **R.A. Andersen:** None.

Poster

230. Limb Brain-Machine Interfaces: Neurophysiology

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 230.11/DD31

Topic: E.05. Brain-Machine Interface

Support: NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE (NINDS) Brain Initiative 1U01NS098975-01

NSF 1533589

Tianqiao and Chrissy Chen Brain-Machine Interface Center at Caltech

Boswell Foundation

USC Neurorestoration Center

Title: Mapping human primary somatosensory cortex with intracortical microsimulation for brain-machine interface applications

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Abstract: Intracortical microsimulation (ICMS) has been used in non-human primate (NHP) and human studies to artificially convey sensory information to the brain in the absence of natural cutaneous or proprioceptive signals. Feedback via stimulation could be of enormous benefit to brain-controlled prosthetics, potentially increasing performance and the embodiment experienced by the motor and sensory impaired users of the devices. However, to accurately deliver task-relevant feedback we must first characterize the responses produced during stimulation. ICMS in sensory cortex has produced discriminable percepts in NHP, but it has been impossible to explore the sensations, i.e., to ask how it 'feels'. Meanwhile, it is unlikely that the sensory descriptions reported in the human primary somatosensory cortex (S1) ICMS literature encompass the full range of inducible sensations, due to limitations and differences in stimulation technology, electrode placement, or stimulation parameters. To further characterize sensory responses to stimulation, we provide ICMS to S1 in a human clinical trial participant. The subject presents with C5-C6 level spinal cord injury resulting in quadriplegia. Implant surgery was performed approximately two years post-injury, two Blackrock stimulation microarrays were positioned in S1 and two recording microarrays in premotor and parietal areas. Recording and stimulation began in December 2016, two weeks post-surgery, and has been continuing on a regular basis. We mapped the sensory outcomes of ICMS by recording features of the percepts (i.e. the subject's verbal description of character, duration, intensity, and location) elicited by stimulation with varied parameters: amplitudes from 20-100uA and frequencies from 50-300Hz. ICMS delivered to S1 electrodes produced a range of natural cutaneous and proprioceptive sensations including but not limited to tapping, squeezing, or moving, and occurred at a repeatable range of locations on the fore- and upper arm. These sensations were different in topography and description to sensations previously reported. Furthermore, we note that the nature of the elicited sensations were modulated by changes to frequency and amplitude of the stimulation. To further the current work, we aim to reliably produce percepts that will be useful in the context of brain controlled systems with direct sensory feedback. In so doing, we hope to understand the neural mechanisms of S1 that govern the formation of sensory percepts. Being able to predict the sensory outcome of stimulations, and thus deliver relevant sensory information, will be integral to improving the quality of future brain-machine interfaces.

Disclosures: **L. Bashford:** None. **M. Armenta Salas:** None. **S. Kellis:** None. **M. Jafari:** None. **H. Jo:** None. **K. Pejsa:** None. **B. Lee:** None. **C. Liu:** None. **R.A. Andersen:** None.

Poster

230. Limb Brain-Machine Interfaces: Neurophysiology

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 230.12/DD32

Topic: E.05. Brain-Machine Interface

Support: NINDS Brain Initiative Grant 1U01NS098975-01

NSF Grant 1533589

Tianqiao and Chrissy Chen Brain-Machine Interface Center at Caltech

Boswell Foundation

USC Neurorestoration Center

Title: Discriminating and using somatosensory percepts in brain-machine tasks with a tetraplegic subject

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Abstract: Severe paralysis due to spinal cord injury affects around 200,000 people in the US alone. There is amazing research focused in restoring upper limb functionality in amputees and paralyzed patients, but most systems do not work well for the tetraplegic population. Cortical brain-machine interfaces (BMIs) offer this population the possibility to control external devices with several degrees of freedom. Recently, more research has focused on restoring sensory function along with motor cortical control. There are still many open questions about how to best encode this sensory information, the number of discernable sensations deliverable through BMIs, and how to pair them with a closed-loop BMI system. We are interested in using intracortical microstimulation (ICMS) in primary somatosensory cortex (SI) to deliver somatosensory percepts, particularly in the hand and arm, and in exploring how to use them reliably in a BMI system. We implanted a subject (32 y/o. male, C5 level injury) with a multi-port Utah array in the hand and arm regions of SI. After initial screening of array somatotopy and percepts' characterization, we began testing the use of these sensations in three discrimination tasks. For the first task, we used a 2AFC paradigm to detect the minimum current amplitude necessary to induce reproducible sensations with stimulation through a single electrode. Similarly, we used a 2AFC task to determine the minimum difference in current amplitude for the subject to

discriminate between two stimuli. For the third task, the subject matched qualitative aspects of stimuli from different electrodes (e.g. receptive field, sensation type, etc.) to different inferred arm positions or movements. To do this we use a 2AFC task where two targets are shown simultaneously and the subject has to identify which target matches the inferred arm locations. We have identified minimum thresholds to detect stimulation at 75% accuracy, and constructed psychometric curves for all the currently tested electrodes. Similarly, we have preliminary results of JNDs for stimulus amplitude current, when compared against a standard of 30 μA. Finally, we found that the subject could match somatosensory percepts to different limb positions, and had performance above chance levels. This initial survey, of reliability and discriminability of the sensations, demonstrates the potential of using ICMS to encode a wealth of sensory information through different electrodes and stimulation parameters. Moreover, the subject's ability to match sensations to different inferred arm locations could open the possibility of using similar parameters and electrodes to map a variety of movement information.

Disclosures: **M. Armenta Salas:** None. **L. Bashford:** None. **S. Kellis:** None. **M. Jafari:** None. **H. Jo:** None. **D. Kramer:** None. **B. Lee:** None. **K. Pejsa:** None. **K. Shanfield:** None. **M. Aisen:** None. **C. Liu:** None. **R.A. Andersen:** None.

Poster

230. Limb Brain-Machine Interfaces: Neurophysiology

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 230.13/DD33

Topic: E.05. Brain-Machine Interface

Support: NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE (NINDS) Brain Initiative 1U01NS098975-01

NSF 1533589

Tianqiao and Chrissy Chen Brain-Machine Interface Center at Caltech

Boswell Foundation

USC Neurorestoration Center

NSF, CSNE program at the University of Washington

Title: Volitional control of single-channel spike firing rates for bridging cortical areas with bidirectional brain-machine interfaces

Authors: ***H. JO**[1], S. KELLIS[1,2], M. ARMENTA SALAS[1], L. BASHFORD[1], M. JAFARI[1], K. PEJSA[1], D. KRAMER[2,1], B. LEE[2,1], C. LIU[2,3,1], E. E. FETZ[4], R. A. ANDERSEN[1]

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Abstract: Brain injury can produce deficits through disconnection of cortical areas. One possible treatment is to bridge damaged connections by recording from one area and delivering contingent stimulation to another with bidirectional brain-machine interfaces (BMI). Such bidirectional BMIs can not only provide a bridge between cortical areas, but also achieve a closed-loop brain stimulation system in which a subject can regulate stimulation parameters in one area by controlling neural activity in another area. This can provide an easier way to calibrate stimulation parameters in BMIs, investigate connections between stimulation patterns and evoked sensations, and explore neural plasticity induced by new connections between brain areas. For these reasons, we are interested in implementing a bidirectional BMI in human patients.

In this study, we examined anterior intraparietal (AIP) and ventral premotor area (PMv) as recording sites, and hand and arm regions of primary somatosensory cortex (S1) as stimulation sites. These regions have the advantage that the subject can evoke sensation from his hands or arms as a result of controlling neural activity in the grasp-related areas. A 33-year-old tetraplegic subject in this study, FG, was implanted with Neuroport arrays (Blackrock Microsystems) in these areas. We looked for units in AIP and PMv that were modulated during imagined tasks, like grasping, scratching, rotating the arm, and counting. We then selected a channel that was tuned to a certain imagery, and graphically showed the spike firing rates from that channel to FG. We asked FG to increase or decrease the displayed firing rate, to evaluate volitional control on the neural activity. Demonstrating such control over single-channel firing rates is an important first step toward connecting brain areas and regulating stimulation in one site based on the activity in another.

We found a significant number of units in AIP and PMv tuned to different mental tasks. Some were tuned to multiple actions, often when the actions were similar, as in scratching and grasping. FG was able to identify appropriate mental imagery to increase or decrease the firing rate measured from the selected channel, and could control such activity volitionally. In most cases, FG was able to increase or decrease the firing rate to the target level in 2 seconds. FG could also change the firing rate and hold it within a target range for a given duration. These results show that FG had reliable, volitional control over single-channel spike firing rates, and further demonstrate the potential for self-calibration and optimization of stimulation parameters and patterns in S1 to produce more intuitive sensation.

Disclosures: **H. Jo:** None. **S. Kellis:** None. **M. Armenta Salas:** None. **L. Bashford:** None. **M. Jafari:** None. **K. Pejsa:** None. **D. Kramer:** None. **B. Lee:** None. **C. Liu:** None. **E.E. Fetz:** None. **R.A. Andersen:** None.

Poster

230. Limb Brain-Machine Interfaces: Neurophysiology

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 230.14/DD34

Topic: E.05. Brain-Machine Interface

Support: NIH R01 NS053603

EU Commission FP7-PEOPLE-2013-IOF-627384

Title: Training a decoder on low-dimensional population dynamics in primary motor cortex produces stable control signals

Authors: *J. GALLEGO[1], M. G. PERICH[2], A. FARSHCHIANSADEGH[6], P. M. TOSTADO[3], K. L. BODKIN[2], S. N. NAUFEL[2], E. J. PERREAULT[2,4], S. A. SOLLA[3,5], F. A. MUSSA-IVALDI[6,3,4,2], L. E. MILLER[3,4,6,2]
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Abstract: We have developed a novel wireless Brain Computer Interface (BCI) that uses functional electrical stimulation (FES) to activate paralyzed muscles under the control of signals recorded from primary motor cortex (M1). A BCI, like any tool, should ideally “feel the same” to users from day to day. However, the neurons recorded by implanted arrays change continuously, causing undesired variations in the actions produced by the BCI. Fortunately, motor commands are represented highly redundantly across the millions of neurons in M1, allowing motor intent to be represented by a much smaller number of latent signals computed by a dimensionality reduction method such as principle component analysis (PCA). If our sample of ~100 neurons is sufficiently representative, we should be able to obtain an accurate estimate of these signals despite progressive changes in the particular recorded neurons.
The mapping to a reduced number of dimensions defines a *neural manifold*: a low dimensional surface embedded in the high dimensional space comprising the activity of each recorded neuron. Within the full space of neural recordings, the manifold can be thought of as the space spanning the subset of possible activity patterns that typically occurs. While PCA produces a set of latent signals ordered by their variance, there is no guarantee that this ordering will be equivalent from day to day, as the statistics of the neurons or the recorded neurons themselves vary. To obtain a stable BCI, we must realign the low-dimensional latent signals computed for each subsequent day to that of the first day. We are also pursuing nonlinear dimensionality reduction using autoencoding neural networks.
We collected neural data from two rhesus macaque monkeys performing a standard center-out reaching task in sessions spanning 30 days. Using canonical correlation analysis, we found that

correlations between the three leading aligned latent signals averaged 0.81±0.04 over the month of recordings. In contrast, without alignment these correlations dropped over time to 0.44±0.17. We achieved similar results in separate recordings during a two-dimensional isometric wrist task. Rather than single neurons, we have begun to use these latent signals as decoder inputs to predict EMG. For both a power grip task, and a task in which monkeys grasp and transport a ball, the accuracy of EMG predictions using ten latent signals was 88±5 % of that achieved when using all neurons. We hope to achieve stable BCI control over long spans of time despite neural turnover by computing the FES control signals from these aligned latent signals. We hypothesize that this approach will yield accurate control of our FES-BCI.

Disclosures: **J. Gallego:** None. **M.G. Perich:** None. **A. Farshchiansadegh:** None. **P.M. Tostado:** None. **K.L. Bodkin:** None. **S.N. Naufel:** None. **E.J. Perreault:** None. **S.A. Solla:** None. **F.A. Mussa-Ivaldi:** None. **L.E. Miller:** None.

Poster

230. Limb Brain-Machine Interfaces: Neurophysiology

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 230.15/DD35

Topic: E.05. Brain-Machine Interface

Support: MIUR

FIRB 2013, RBFR132BKP

H2020-MSCA-734227-PLATYPUS

Regione Emilia Romagna FSE ob.10B

Title: Decoding of real, 3D reach goals from monkey area V6A

Authors: *M. FILIPPINI[1], R. BREVEGLIERI[1], K. HADJIDIMITRAKIS[1,2], A. BOSCO[1], P. FATTORI[1]
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Abstract: Neural prostheses aim to restore motor function in patients with impaired mobility. In addition to motor cortex, recent studies reported other sites suitable to drive neural prostheses. One of these sites is the posterior parietal cortex (PPC), that is well known to mediate sensorimotor transformations required to generate plans for action. Thus, PPC represents a good source to decode movement intentions and goals in the peripersonal space. Recently, V6A, a medial PPC area has been identified as a rather unexpected source of signals to decode the grip shape during the grasping of objects (Filippini et al., 2017 J. Neurosci). Here, we aimed to

extend these results, testing whether V6A signals can reliably decode reaching goals. We recorded the activity of 107 single units from area V6A in two *Macaca fascicularis*,while monkeys performed a delayed reaching task toward 9 positions placed in the 3D space. The 9 positions were distributed over 3 different directions and 3 different depths in order to cover a large extent of the peripersonal, reachable space. Mean firing rates were calculated for different task epochs and used to train and validate a Naïve Bayes classifier. We demonstrated that goals of reaching movement can be reliably decoded from V6A neurons well in advance before the onset movement, with recognition rates close to optimal (>90%). Moreover, to ascertain whether the same neural code was used during the whole time-course of the reaching task, we applied a generalization analysis. Neural code used during early target vision was not maintained during the subsequent phases of the task. This result supports earlier findings reporting several populations of cells that process independently, or jointly, signals about eye position and arm movement planning and execution in V6A (Hadjidimitrakis et al., 2014a Cer. Cortex). Present results, together with our recent findings showing a reliable decoding of grip properties from V6A (Filippini et al., 2017 J. Neurosci), suggest that V6A is a suitable site to decode the entire prehension action . This could be exploited in the development of future generations of brain machine interfaces.

Disclosures: **M. Filippini:** None. **R. Breveglieri:** None. **K. Hadjidimitrakis:** None. **A. Bosco:** None. **P. Fattori:** None.

Poster

230. Limb Brain-Machine Interfaces: Neurophysiology

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 230.16/DD36

Topic: E.05. Brain-Machine Interface

Support: ARO MURI Contract W911NF-16-1-0368

NSF CAREER Award CCF1453868

Title: Learning the dependencies between spikes and fields in multiscale modeling

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Abstract: Multiscale modeling of spike-field activity provides the opportunity to study the encoding of behavior across spatiotemporal brain scales and to develop more accurate brain-machine interfaces (BMI) that extract information simultaneously across scales. While spiking activity provides information about the encoding of behavior in a small neural population and at fast time-scales, local field potentials (LFP) and electrocorticogram (ECoG) represent the

activity of a large neural population at slower time-scales. We have recently introduced a multiscale state-space model to characterize spike-field recordings assuming that spikes and fields are independent conditioned on the underlying brain state. However, there may be conditional dependencies between these scales of activity. Here, we develop a new multiscale model that explicitly incorporates conditional dependency across scales. We also develop an expectation-maximization learning algorithm to fit this model based on data. Since spikes and fields have fundamental statistical differences, modeling their conditional dependence is challenging. Also, to reduce computational complexity and the chance of overfitting, we need to restrict the number of parameters in the model that describe the dependence between every field and spike channel. We build a multiscale state-space model with conditional dependence. We use a Gaussian likelihood function for LFP/ECoG and model the spiking activity with a non-linear point process likelihood dependent on the underlying brain states and field signals. To reduce the number of parameters, we exploit spatial basis functions to weigh the effect of various channels. We use goodness-of-fit measures to show that the learned model can accurately describe multiscale data with conditional dependency. Additionally, using decoding analyses, we show that when the learning algorithm does not consider conditional dependence across scales for such data, decoding performance deteriorates. This multiscale model and its learning framework can help study encoding of behavior across scales and develop accurate BMIs.

Disclosures: H. Abbaspourazad: None. **M.M. Shanechi:** None.

Poster

230. Limb Brain-Machine Interfaces: Neurophysiology

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 230.17/EE1

Topic: E.05. Brain-Machine Interface

Support: ARO MURI Contract W911NF-16-1-0368

NSF CAREER Award CCF1453868

Title: Multiscale decoding of spike-field activity to improve brain-machine interface robustness and longevity

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Abstract: Invasive brain-machine interfaces (BMI) use neural activities recorded from intracortical electrode arrays to control external devices. BMIs typically employ a single scale of neural activity such as spikes from small numbers of neurons or local field potentials (LFP) from

larger populations of neurons. As the quality of control based on spikes recorded from invasive arrays degrades over time, decoding spikes simultaneously with the more robust LFP signal has the potential to improve longevity of these BMIs. Recently, we have developed a multiscale decoder that models the spikes and LFP simultaneously with different statistical models (linear Gaussian for LFP and nonlinear point process for spikes) and at multiple time scales (millisecond for spikes and tens of milliseconds for LFP). Here we apply this multiscale decoder to simultaneous spike/LFP recordings from a non-human primate (NHP) to decode upper-limb joint angles during a 3D reach-to-grasp movement offline. Recent work has demonstrated the benefit of decoding the spikes at their fast millisecond time-scale using point process modeling. Here, we demonstrate that the multiscale decoder can still run at the fast millisecond time-scale of the spikes while adding information from LFP recordings. Moreover, even using a few LFP channels, the multiscale decoder improves performance compared with a point process decoder of spikes alone. The relatively few LFP channels needed for this improvement also shows the robustness of multiscale decoding. These results suggest that multiscale decoding has the potential to improve longevity in invasive BMIs.

Disclosures: H. Hsieh: None. **Y. Wong:** None. **B. Pesaran:** None. **M.M. Shanechi:** None.

Poster

231. Posture and Gait: Afferent Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 231.01/EE2

Topic: E.06. Posture and Gait

Title: The impact that six-weeks of mindfulness-based training has on postural control in NCAA Division 1 athletes

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Abstract: Mindfulness-based training has become an increasingly useful intervention in clinical psychology and other areas of medicine to reduce stress and improve medical and attentional states. The ability to maintain attention is crucial to success in athletics and the impact on postural control may help to reduce the potential for injury (Kee et al, 2012). This study investigated the impact that 6-weeks of mindfulness training had on four different postural control conditions in NCAA Division I athletes. Thirty-seven healthy young athletes divided into control (C) (14 males, 4 females) and experimental (E) (17 males, 2 females) groups volunteered to participate in the study. Participants were baseball (BB), football (FB), women's volleyball (VB), and track (TK) athletes. Baseline testing postural control measures consisted of standing on a Bertec (BP5050) force plate covered by foam surface. Four postural conditions (quiet stance

(Eyes Open, Eyes Closed), Anterior-Posterior (AP) sway, and Medio-lateral (ML) sway) were recorded for 30s. The AP sway instructions were to rhythmically sway as far forward and backward without stepping off the foam for 30s. Similar instruction was given to sway in the ML direction as far as comfortable from side to side without stepping for 30s. The same postural control measures were conducted for post-testing on both groups after 6-weeks yet, only the E group took part in the mindfulness training. Dependent measures of the center of pressure (COP) data included path length and mean velocity. Approximate entropy (ApEn) analysis was performed to assess COP motion signal regularity. The results of this study revealed a statistically significant group by condition interaction ($P< 0.05$) in the amount and velocity of AP and ML sway. Those athletes in the E group swayed further and faster in both AP and ML directions than the C group. A significant group by condition interaction ($P < 0.05$) in ApEn values was also observed. The E group elicited lower signal regularity (higher ApEn) while standing with EO compared to those in the C group. These findings suggest that mindfulness training may positively impact postural control in healthy college-aged athletes. The ability to have greater control of posture particularly while shifting the center of mass may have positive implications when it comes to athletic performance and injury prevention during sports participation.

Disclosures: K.S. Thomas: None. **C. Freligh:** None.

Poster

231. Posture and Gait: Afferent Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 231.02/EE3

Topic: E.06. Posture and Gait

Title: Learning postural balancing in a dynamic destabilizing environment

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Abstract: This study aims to explore how motor control is achieved during postural balancing. The traditional view is that balance is governed by reflex, with no planning required from the brain. In this view, our body's sway is a continuous feedback to the motor system and results in corrections to maintain upright standing. An alternative hypothesis suggests that balance involves a planning action, based on a series of control signals that are adjusted intermittently rather than continuously, according to a higher level process. To test these hypotheses, we asked 15 subjects to perform postural balancing tasks in a dynamic environment in 4 different sessions

on separate days. All the tasks consisted in balancing a virtual inverted pendulum with parameter values consistent with physical parameters of a typical human body. Subjects had to stand upright on a stationary footplate while strapped to an actuated apparatus which haptically fed back the positional information of the pendulum. The pendulum was actuated by the participant via a pair of antagonist joint torques that were determined by activations of the corresponding antagonist muscles (Tibialis Anterior and Soleus) of both legs, recorded by surface electromyography, while additional disturbances and/or changes in control gain were applied. For this tasks which closely reproduces postural balance, the experiment results will show how humans react to sudden changes in system gain and which strategies are adopted during the learning process.

Disclosures: **A. Cherif:** None. **I. Loram:** None. **H. Gollee:** None. **J. Zenzeri:** None.

Poster

231. Posture and Gait: Afferent Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 231.03/EE4

Topic: E.06. Posture and Gait

Title: Wearable technology to enhance mobility in Parkinson's disease

Authors: *E. D. THOMPSON[1], H. REIMANN[5], T. D. FETTROW[5], P. AGADA[2], S. WEISS[3], W. WRIGHT[4], J. J. JEKA[5]
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Abstract: Motor effects of Parkinson’s disease (PD) can have a devastating impact on functional mobility, including small steps, slow velocity, and impaired arm swing. These effects are often treated using external cues for improved movement, but transferring cues to the home environment can be difficult. Additionally, many patients are unable to attend enough clinic-based therapy session to generate carryover from cued to uncued performance. Previous work has tested a portable, wireless system to measure arm swing and deliver a vibratory cue when a larger target arm swing is reached. While it was found that people with PD can increase their arm swing in response to one session of cues, and that such cues affect gait parameters such as step length and cadence, the effects of longer training with such a device are unknown. Here we present pilot results from an individual with PD before and after a 60-day training program using arm swing cues. The pilot participant was a 56-year old female who had been diagnosed with idiopathic PD for 18 months (Hoehn and Yahr stage 2). For pre-testing she walked on a self-paced treadmill and on a motion-capture walkway, with surface EMG sensors on the arms and legs and full-body kinematic information to assess baseline walking and initial response to cues. Arm swing cues were set to 120% of her baseline average arm swing amplitude, and she was

instructed to swing her arm forward with each step until she felt the vibratory cue. During the 60 days of training, she used the arm swing cuing sensors while walking for 30 minutes at a time, 3 times per week, outside near her home. Following training, she attended another lab session with uncued walking on the self-paced treadmill and walkway. When walking uncued after training, the participant demonstrated increased arm swing amplitude, step length and velocity, as well as decreased cadence, relative to her pre-test baseline. Additionally, she exhibited increased activation of her gastrocnemius and peroneus longus muscles during late stance vs baseline walking, perhaps indicating a more powerful push-off associated with the changes that occurred with larger arm swing. However, while movement amplitudes were closer to those observed in young healthy adults, arm-leg coordination was not systematic even after training. These preliminary results indicate that training with cues for increased arm swing may lead to carryover gains after the cues are removed. Further research is needed to explore optimal cuing to promote enhanced coordination as well as amplitude of movement.

Disclosures: E.D. Thompson: None. **H. Reimann:** None. **T.D. Fettrow:** None. **P. Agada:** None. **S. Weiss:** None. **W. Wright:** None. **J.J. Jeka:** None.

Poster

231. Posture and Gait: Afferent Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 231.04/EE5

Topic: E.06. Posture and Gait

Title: Interaction between visual flow and tendon vibration during postural control

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Abstract: Exposure to visual flow moving in a forward or backward direction or tendon vibration applied on the Achilles tendon (AT) or Tibialis Anterior (TA) is known to produce direction specific postural responses. The main objective of this study was to understand interaction between tendon vibration and visual flow to gain insight into sensory weighting of vision and ankle proprioception during a bipedal posture task. Center of pressure (COP) excursions were recorded in 10 healthy young adults to evaluate the magnitude and direction of sway produced by tendon vibration and/or visual flow. The subjects were tested under different conditions, which consisted of 1) Eyes open quiet stance 2) eyes open with visual flow in the forward or backward direction 3) eyes closed with TA or AT vibration 4) TA or AT vibration combined together with visual flow in the forward or backward direction. The outcome measures were final COP displacement and average COP velocity. Additionally, time to boundary (TTB), which determines the time a given COP sample will reach a theoretical stability boundary should

it continue on its current trajectory was integrated across the trials, for each condition (iTTB). The results showed that COP displacement produced by AT vibration was significantly less when paired with either forward or backward visual flow. Visual flow did not moderate COP displacement to TA vibration. Average COP velocity produced by AT or TA vibration was unaffected by either forward or backward visual flow. Average AT iTTB was significantly greater than for TA suggesting that balance was more threatened during AT vibration when compared to TA vibration. Taken together the findings indicate that the perceptual-motor system can flexibly reweight visual input depending upon the movement context such that the input can be used to moderate the effects of vibration when vibration places the individual at the risk for falling or down weighted when the potential loss of balance is minimal. This knowledge can be incorporated into therapeutic programs with patient and elderly populations who are at risk for falling.

Disclosures: R. Kabbaligere: None. **B. Lee:** None. **C.S. Layne:** None.

Poster

231. Posture and Gait: Afferent Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 231.05/EE6

Topic: E.06. Posture and Gait

Support: OCAST Grant HR-14-023

Title: Estimating the proprioceptive contribution to balance: Validation with measures of stretch reflex function

Authors: J. A. HERNANDEZ-SARABIA, A. BARRERA-CURIEL, Z. K. POPE, R. J. COLQUHOUN, M. A. MAGRINI, *J. M. DEFREITAS
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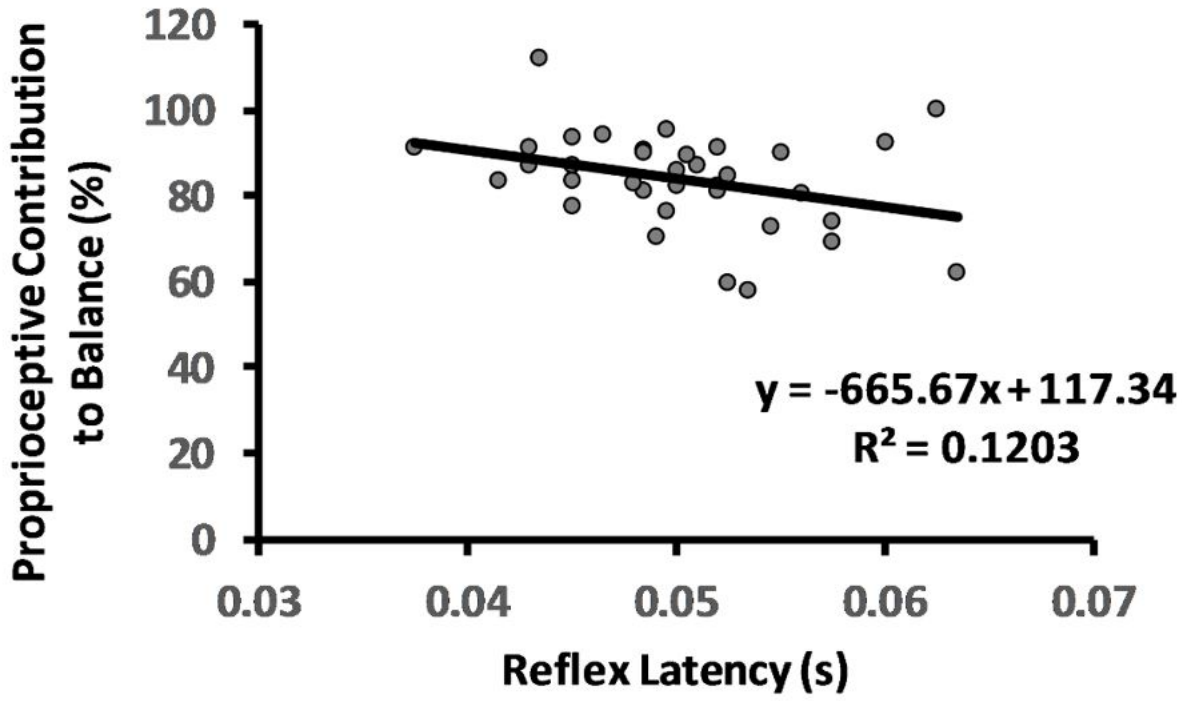
Abstract: Muscle spindles are proprioceptors that detect muscle length and velocity during a variety of postures, and may be especially important in conditions where balance is challenged or compromised. Muscle spindle function can be assessed indirectly with the patellar tendon stretch reflex. Since poor balance can lead to falls, it is important to assess individual's proprioceptive contributions to balance. **PURPOSE:** To determine the validity of a test designed to estimate an individual's proprioceptive contribution to balance (PROP) by examining its relationship with stretch reflex function. **METHODS:** 38 subjects were recruited for this study (19-83 years old). At least five patellar tendon taps were performed on each participant. A surface electromyographic signal from the rectus femoris, an accelerometer signal from the patella (for the onset of the strike), and a force signal from a load cell attached to the ankle were collected during each tap to calculate reflex latency and magnitude. Following the assessment of the

monosynaptic reflex, participants completed the Modified Clinical Test of Sensory Interaction of Balance (mCTSIB), which consists of four static conditions 1) eyes-open on a firm surface (EOFS), 2) eyes-closed on a firm surface (ECFS), 3) eyes-open on a soft surface (EOSS), and 4) eyes-closed on a soft surface (ECSS). Under the assumption that the ECFS condition relies heavily on proprioception, and the ECSS condition relies on it very little (mostly vestibular), PROP (% contribution) was calculated as (ECSS - ECFS) / (ECSS - EOFS). **RESULTS:** PROP was significantly correlated with reflex latency ($r = -.347$, $p = .041$; see figure), but was not correlated with reflex magnitude ($p = 0.697$). **CONCLUSION:** Our primary finding was that PROP was significantly related to a measure of spindle function (reflex latency from a tendon tap). This suggests that the mCTSIB may be a valid tool for estimating an individual's reliance on proprioception for balance. More importantly, it shows that individuals with a slower stretch reflex are less likely to rely on proprioception to maintain balance.



Disclosures: **J.A. Hernandez-Sarabia:** None. **A. Barrera-Curiel:** None. **Z.K. Pope:** None. **R.J. Colquhoun:** None. **M.A. Magrini:** None. **J.M. DeFreitas:** None.

Poster

231. Posture and Gait: Afferent Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 231.06/EE7

Topic: E.06. Posture and Gait

Title: Hypothyroidism and neurocardiogenic syncope: A bedside to the bench study

Authors: *K. FATIMA SHAD[1,2], S. KHAN[2]
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Abstract: Within our laboratory, it is common practice to translate results from the bench to the bedside scenario. However, recently we reversed the translation of patient profiles into bench-side science.
This study shows that thyroid hormone disturbance has a significant role in the development of cardiovascular sign and symptoms. We observed the significance of atrial fibrillation and atrioventricular block in neurocardiogenic syncope in non-epileptic patient. We report a patient with hypothyroidism diagnosed with atrioventricular block that developed neurocardiogenic syncope during sleep. A 32-year-old, right-handed woman patient was sent to the hospital for a severe headache at L occipital area, gripping in nature but did not seem to radiate anywhere else, denies photophobia, neck stiffness/fever. Systems review says no chest pain, shortness of breath, palpitation, no bowel motion changes, and no dysuria. She had no family history of hypertension, diabetes and hyperlipidemia. The patient initially admitted under the care of neuro team and subsequently transfer of care of cardiology, EEG and CT scan were normal. There was no established infarct or acute intracranial hemorrhage. She was referred to cardiology team as her ECG showed intermittent AV dissociation with left bundle branch pattern, with normal cardiac enzymes. Electrolytes, including calcium/magnesium/phosphate were normal. Her thyroid function tests shows reduced levels of circulating thyroid stimulating hormones with normal T3 and T4 (as she was on thyroxine replacement for her hypothyroidism). Her echocardiogram report shows intact interventricular and interatrial septum. The patient was put on holter which showed intermittent AV dissociation, min HR 43 Max HR 135, No sig pause (1.99sec), subsequently patient was put on continuous monitoring, Telemetry which again showed intermittent AV dissociation. Before patient was discharged Neuro-team reviewed once more as a differential to patient's presentation is an underlying epileptic disorder. Neuro-team unconvinced that it is a seizure disorder. According to her previous history, she has been on thyroxin 100µg (daily) for 8 years. From last 3 years, she was having syncope during sleep. This syncope/seizure last for 1-2 minutes occurred at a frequency of three to five in a year. We concluded that hypothyroid patients are more prone to have atrioventricular block associated with neurocardiogenic syncope in sleep due to diverge roles of Vagus nerve.

Disclosures: K. Fatima Shad: None. **S. Khan:** None.

Poster

231. Posture and Gait: Afferent Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 231.07/EE8

Topic: E.06. Posture and Gait

Support: DOD Grant MR150051

Title: Closed-loop control of a transtibial prosthesis with active ankle joint and sensory feedback

Authors: *H. PARK[1], M. S. ISLAM[2], M. A. GROVER[3], S. P. DEWEERTH[1], B. I. PRILUTSKY[4]
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Abstract: We have demonstrated previously (Park et al. 2014, 2016) that electrical stimulation of the distal tibial nerve during the stance phase of walking in the cat reverses the effects of paw pad anesthesia and improves gait symmetry. This result indicates that stimulation of the distal tibial nerve may provide artificial tactile feedback during walking with a transtibial prosthesis. Quality of prosthetic gait can be further improved by providing appropriate control signals to the prosthetic motor (Herr et al., 2012). Our long-term goal has been to develop a closed-loop adaptive control system for a transtibial prosthesis directly integrated with the residual skin and bone via a porous titanium pylon (Farrell et al. 2014) and with peripheral nerves and muscles via the same implanted pylon (Pitkin et al. 2012; Ortiz-Catalan et al. 2014). This prosthesis should provide tactile sensations and control the prosthetic ankle using recorded activity from the residual muscles and motor nerves. The specific goal of this work was to develop and test a prosthesis prototype and closed-loop control algorithms before implementing the system in an animal model. A sensing active prosthesis was fabricated using a porous titanium pylon with a passage for leads from muscle and nerve cuff electrodes (Pitkin, Raykhtsaum 2012; Pitkin et al. 2012), a J-shaped foot, and electronics, including an amplifier for muscle and nerve activity signals, a microcontroller, a linear motor, a pressure sensor, and a nerve stimulator. The linear motor provided extension and flexion of the prosthetic joint.We tested the developed prosthesis and control algorithms in a testing rig that held the prosthesis slightly above the ground. Previously recorded EMG activity of ankle extensors and flexors and experimentally obtained ankle joint moments during walking in intact cats were used to establish the EMG-joint moment regression equation that was implemented in the control of the prosthetic motor. During testing in the rig, simulated EMG patterns were used to compute the input to the motor (or the joint moment produced by the motor). In each cycle of simulated walking, the ground reaction force produced by the prosthesis and measured by the pressure sensor was compared to the desired ground reaction force profile. Based on the mean difference between the measured and desired

force profiles, the regression coefficients in the EMG-joint moment relationship were changed to decrease the mismatched in the next cycle. The developed prosthesis prototype and control algorithms allowed for accurate matching between the generated and desired ground reaction force profile.

Disclosures: H. Park: None. **M.S. Islam:** None. **M.A. Grover:** None. **S.P. DeWeerth:** None. **B.I. Prilutsky:** None.

Poster

231. Posture and Gait: Afferent Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 231.08/EE9

Topic: E.06. Posture and Gait

Support: NIH R01 HD32571

NIH R01 EB012855

DOD grant MR150051

Title: Frontal plane dynamics of quadrupedal locomotion on a split-belt treadmill

Authors: E. M. LATASH[1], H. PARK[2], W. H. BARNETT[1], A. N. KLISHKO[3], B. I. PRILUTSKY[4], *Y. I. MOLKOV[1]
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Abstract: In the past, dynamic stability of human locomotion in the frontal plane has been investigated using an inverted pendulum model and notion of the extrapolated center of mass. It is not known whether a similar approach could be applied to a quadrupedal locomotion. The goal of this study was two-fold: (1) determine if the frontal plane dynamics of the cat center of mass (COM) during split-belt locomotion could be accurately described by an inverted pendulum model and (2) examine if the model can explain previously obtained experimental results. We developed a mathematical model of the balance control system based on an inverted pendulum model whose dynamics was controlled by shifting the pendulum pivot point at the time instances when the COM approached the limits of dynamic stability, i.e. stability thresholds. These thresholds were computed using Bayesian inference based on experimental data obtained in different experimental conditions. The data included 3D full body cat kinematics and ground reaction forces recorded during split-belt locomotion with different speeds in control conditions and with the fore- and hind paws on the same side of the body anesthetized. The inverted pendulum model described the experimental dynamics of the cat COM in the frontal plane with

high accuracy. The model revealed a mechanism of controlling dynamic stability in the frontal plane. According to this mechanism, when the COM is approaching the threshold of dynamic stability on one side of the body, the animal lifts the contralateral limbs, and the gravitational force reverses the direction of COM movement so that the margin of dynamic stability increases. This mechanism produces frontal plane oscillations of the COM during locomotion that are synchronized with transitions between specific locomotor phases. The developed model helped explain why the COM shifts towards the slower belt during split-belt walking. This happens primarily due to the medial shift of the stability threshold on the fast side of the area of support. This results in a reduction of the amplitude and the period of the COM oscillations in the frontal lane. Furthermore, anesthesia of ipsilateral paws leads to a shift of the COM towards the anesthetized paws caused by symmetric shift of both thresholds in the direction of the anesthetized side. This result is interpreted as an illusion of an increased stability on that side due to reduced tactile perception of the anesthetized paws.

Disclosures: E.M. Latash: None. **H. Park:** None. **W.H. Barnett:** None. **A.N. Klishko:** None. **B.I. Prilutsky:** None. **Y.I. Molkov:** None.

Poster

231. Posture and Gait: Afferent Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 231.09/EE10

Topic: E.06. Posture and Gait

Support: NIH Grant HD032571

Title: Effects of stretch-reflex removal from ankle and knee extensors on mechanics and EMG activity during locomotion in the cat

Authors: A. N. KLISHKO, K. OH, T. R. NICHOLS, R. J. GREGOR, *B. I. PRILUTSKY
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Abstract: In previous studies (Cope et al. 1994; Lyle et al. 2016), self-reinnervation of cat triceps surae or quadriceps resulted in loss of autogenic excitatory length feedback (stretch reflex) from the corresponding muscles. Mechanics of level and upslope walking, but not downslope walking, and patterns of EMG activity generally recovered after self-reinnervation of either ankle extensors (Maas et al., 2007; Pantall et al., 2016) or knee extensors (Mehta et al. 2014). Here, we tested the hypothesis that removal of autogenic excitatory length feedback from major ankle and knee extensors at the same time would lead to much greater deficits in walking mechanics and EMG activity. Major hindlimb muscles were implanted with EMG electrodes in 4 adult cats and baseline locomotor mechanics and EMG activity were recorded during level, downslope (-50%) and upslope (+50%) walking. After baseline data collection, branches of the

tibial and femoral nerves innervating triceps surae, quadriceps and sartorius muscles were surgically transected and repaired using fibrin glue. The animals recovered for 9 months before the final measurements of locomotor mechanics and muscle activity were made. The most pronounced effect of self-reinnervation of ankle and knee extensors was an exaggerated ankle yield in the stance phase of level, upslope and downslope walking ranging between 4.7 and 8.5 deg. The knee yield in stance significantly decreased by 2.7 deg during downslope walking only. The patterns and peak values of extension moments at the ankle, knee and hip joints did not change after self-reinnervation of ankle and knee extensors. EMG patterns of self-reinnervated ankle extensors and vasti did not change, however the EMG pattern of self-reinnervated rectus femoris became more similar to that of vasti. The mean EMG magnitude of all self-reinnervated muscles substantially increased compared to the baseline values. Some intact hindlimb muscles (e.g., biceps femoris posterior and anterior, iliopsoas) also changed their EMG patterns and/or magnitude. We concluded that despite removal of autogenic excitatory length-dependent feedback from major hindlimb extensors, cats generally recovered mechanics of walking and EMG activity possibly due to recovered force-feedback in self-reinnervated muscles (Lyle et al. 2016). The increased ankle yield in stance of level, upslope and downslope walking after self-reinnervation of ankle and knee extensors demonstrated a greater locomotor deficit compared to that seen after self-reinnervation of triceps surae alone. Removal of monosynaptic excitatory length feedback from vasti to soleus (Wilmink, Nichols, 2003) could contribute to this result.

Disclosures: **A.N. Klishko:** None. **K. Oh:** None. **T.R. Nichols:** None. **R.J. Gregor:** None. **B.I. Prilutsky:** None.

Poster

231. Posture and Gait: Afferent Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 231.10/EE11

Topic: E.06. Posture and Gait

Title: Bipedal robot locomotion with feedback compensation of foot contact by a cerebellar model

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Abstract: Rehabilitation is repetition of trial and error. For each patient, therapists test different rehabilitation methods until they find an effective one for the specific patient. This process could take very long time and be painful. If we can eliminate the trial-and-error process, this will be beneficial for the patients. A potential way to do this is to use computer simulation. It is possible to build a brain-body model that takes conditions of a specific patient into account, and test

various rehabilitation using the model. Thus, a personalized brain-body model will provide a means to reduce the cost and pain in rehabilitation, which would realize taylor-made rehabilitation for individual patients.In this study, we built a brain-body model that combined a bipedal robot with a cerebellar model. We used central pattern generators(CPGs) to generate locomotion of the robot. However, there are 14 parameters to be tuned for bipedal walking in this model. It is difficult to tune the parameters by hand. Therefore, we employed genetic algorithms (GAs) for the parameter tuning. At the beginning of the iteration, the robot fell down immediately. During the iteration, the robot gradually increased the duration of the walk and the walking distance. After 1500 generations, the robot acquired stable bipedal walking. Next We introduced a certain delay in proprioceptive feedback signals, especially from the foot to detect the ground contact. During the initial phase of walking, the cerebellum learned the timing of foot contact on the ground, and after that stable bipedal walking was realized.These results suggest that the cerebellum plays an essential role in smooth gait control.

Disclosures: D. Ichimura: None. **T. Yamazaki:** None.

Poster

231. Posture and Gait: Afferent Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 231.11/EE12

Topic: E.06. Posture and Gait

Support: Dalhousie Medical Research Foundation

Natural Sciences and Engineering Research Council of Canada

Title: Swing movement during walking is an aimed movement controlled by proprioceptive feedback from the muscle spindles

Authors: W. P. MAYER[1], A. J. MURRAY[2], W. G. TOURTELLOTTE[3], *T. AKAY[1]
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Abstract: During walking, a step cycle consists of a swing and a stance phase. During stance, the foot is on the ground and the leg provides body support and propulsion, and moves backward relative to the body. During swing, the foot lifts off the ground at the posterior extreme position (PEP), and moves forward to be placed on the ground at the anterior extreme position (AEP) to start the next stance phase. Contrary to the stance to swing transition, proprioceptive control of AEP at the swing to stance transition is not well understood. We investigated how AEP of hind leg (AEP_{HL}) is determined during walking by using *in vivo* physiological recordings and motion

analysis during walking in wild type mice (WT) and mutant mice in which proprioceptive feedback from muscle spindles (PFMS) was selectively removed (*Egr3-KO*). We found that in WT mice the AEP_{HL} is on average 7.5mm (SD: 5mm) posterior to the PEP of the forelimb (PEP_{FL}) during normal walking. A similar distance of 7.0mm (SD: 5mm) was observed when the progression of the swing phase is perturbed by a stumbling corrective reaction (SCR) ($P=0.46$ after t-test). Furthermore, we show that the AEP_{HL} is significantly correlated to the PEP_{FL} during normal swing and SCR, suggesting that the AEP_{HL} is determined by the PEP_{FL} (walking: $R=0.5$, $P<0.001$; SCR: $R=0.46$, $P<0.001$). In *Egr3-KO* mice, the AEP_{HL} to PEP_{FL} distance was 9mm (SD: 6.4mm) and significantly greater ($P<0.05$) and more variable ($P<0.01$ after f-test) than in WT mice during normal steps. By contrast, the AEP_{HL} to PEP_{FL} distance in Egr3-KO SCRs were 5.9mm (SD: 7.9) and not significantly different from WT mice ($P=0.43$), but with a significant increase in variation ($P<0.001$), suggesting that MS feedback is important for AEP_{HL}. The AEP_{HL} and the PEP_{FL} were, although weakly, still correlated during walking ($R=0.28$, $P<0.05$). We considered the possibility that this weak correlation might be the result of the central interaction of the premotor network controlling the hind- and fore limbs. Therefore, we have investigated the AEP_{HL} to PEP_{FL} correlation in SCR when the swing movement was perturbed. The AEP_{HL} and the PEP_{FL} were not significantly correlated in *Egr3-KO* SCR ($R=0.34$, $P=0.13$), suggesting that PFMS is important for the AEP_{HL} determination. These data suggest that the swing movement during walking is an aimed leg movement that requires proprioceptive sensory feedback and that the target is determined by the foreleg position. A possible mechanism of how this coordination might work will be discussed.

Disclosures: **W.P. Mayer:** None. **A.J. Murray:** None. **W.G. Tourtellotte:** None. **T. Akay:** None.

Poster

231. Posture and Gait: Afferent Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 231.12/EE13

Topic: E.06. Posture and Gait

Support: JSPS KAKENHI Grant-in-Aid for Exploratory Research JP26560324

Title: Postural responses to skin stretch stimuli around the leg joints during quiet standing

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Abstract: The purpose of this study was to determine the role of skin stretch information around leg joints during quiet standing. This study consisted of two experiments: 1) skin stretch stimulation at the front of knee; and 2) skin stretch stimulation around 3 joints of the leg. In Experiment 1, 31 healthy young subjects participated. In Experiment 2, randomly-selected twelve of subjects who showed clear postural response in Experiment 1 participated. The subjects maintained their quiet standing with eyes closed, and then their skin of both legs, on which two pairs of separated small chipboards (distance: 10 mm, size: 10 × 10 mm^2) with electric motors were attached, was simultaneously stretched (amplitude: 3 mm, duration: 200 ms) in the long axis direction. In Experiment 2, stimulation parts were the front and back of hip, knee, and ankle, and 6 conditions of single stimulation to each parts (SS) and 15 conditions of double stimulation to 2 parts (DS) were conducted. In each experiment, a maximum of 5 trials per a condition were repeated until same postural response was observed 3 times. Center of pressure in the anteroposterior direction was measured for the evaluation of postural response. In Experiment 1, postural response was observed in more than 70% of trials and subjects, and the number of forward leaning (FL) response was significantly larger than that of backward leaning (BL) response. In all conditions of Experiment 2, postural response was observed in most trials and subjects. For the SS to the front, the number of FL response was significantly larger than that of BL response at the knee and ankle. For the DS to the front and back of each joint, postural response direction in many trials consisted with that for the SS to the front. For the DS to the front of two joints, the number of FL response was significantly larger than that of BL response in all pair of joints. The subjects with FL response in the SS to the front of the knee or ankle also tended to lean forward in the DS to the front of Hip-Knee and Hip-Ankle. For the DS to the back of two joints, there was no significant direction of postural response in all pair of joints. For the DS to the front and back of two joints, the number of FL response was significantly larger than that of BL response in the combinations of Knee front-Hip back, Knee front-Ankle back, and Ankle front-Hip back. These results suggest that 1) skin stretch stimulation around leg joints would be important sensory information for the maintenance of standing posture; and 2) skin stretch stimulation to the front of each joint, especially the knee and ankle, would be more important information, and they would be perceived as the information of backward leaning of the body.

Disclosures: **K. Fujiwara:** None. **N. Kiyota:** None. **F. Sato:** None. **H. Toyama:** None. **T. Nakamura:** None. **A. Hyodo:** None.

Poster

231. Posture and Gait: Afferent Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 231.13/EE14

Topic: E.06. Posture and Gait

Support: SNSF

Title: Genetic and functional characterization of rubral pathways

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Abstract: The cortico-rubral and rubro-cerebellar pathways sustain the integration and correct modulation of somatosensory feedback and fine motor coordination. At the level of the red nucleus two anatomical sub-divisions have been identified (magnocellular and parvocellular segments) that participate in segregated afferent and efferent circuits. A characterization of these and other neuronal classes within the red nucleus at a genetic and functional level is lacking. Using single molecule mRNA in situ fluorescent hybridization (smFISH) we have identified a rubral cell population that while expressing the calcium binding protein parvalbumin (PV) it largely co-expresses the excitatory Vesicular glutamate transporter (Vglut2). At the anatomical level the boundaries of this cell cluster are markedly delineated by the encircling expression of the inhibitory Vesicular GABA transporter (Vgat). Activation of PV rubral neurons induces robust postural deficits and heavily impairs fine motor coordination. Ongoing experiments aim to evaluate the participation of these neurons in the cortico-rubral and rubro-cerebellar pathways. Pathway specific modulation of parvalbumin containing rubral neurons could prove instrumental in ameliorating motor deficits characterized by abnormal muscle tone and slowness of movement initiation in pathological conditions resistant to classical Parkinsonian syndrome treatments.

Disclosures: G. Rizzi: None. **A. Merli:** None. **K. Tan:** None.

Poster

231. Posture and Gait: Afferent Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 231.14/EE15

Topic: E.06. Posture and Gait

Support: NINDS P01NS057228

Title: Voltage-gated sodium channel expression by muscle-spindle receptors in a rat model of chemotherapy induced peripheral neuropathy (CIPN)

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Abstract: Damage to peripheral sensory nerve endings is commonly held responsible for CIPN. While damage might manifest as dying-back degeneration of sensory endings, we hypothesized

that it might also be restricted to specific ion channels. Our hypothesis was based on studies of muscle spindle receptors in rats several weeks following chronic treatment with the anticancer agent Oxaliplatin (OX). Ia afferents failed to sustain firing as they do normally when muscles were stretched to fixed muscle length, but they exhibited normal firing in response to dynamic muscle length changes (1-3). We traced this selective functional deficit to the muscle spindle's primary-sensory ending, and pharmacological studies (3) suggested impairment of persistent inward currents (PIC) associated with voltage-gated sodium (NaV) channels that we verify present in muscle spindles (4). Here we test our hypothesis that impaired firing by muscle spindle afferents results from downregulation of NaV 1.1 and 1.6. Preliminary findings were obtained for 5 female Wistar rats studied 5 weeks following 8 weeks of OX injections. Immunoreactivity (IR) for neurofilament, heavy chain, (NF-H) and NaV 1.1 and 1.6 revealed normal structure of primary sensory endings and NaV channels in the majority of muscle spindles sampled. However, substantial loss of NF-H IR evinced structural degeneration of distal nerve endings in about 20% of spindles. Degeneration was not observed in our earlier studies - possibly because OX doses were lower, but its occurrence reproduces the dying back neuropathy observed in human OX patients. In addition, these early results lead to provisional rejection of our hypothesis that chronic OX simply downregulates PIC channel expression in primary endings of muscle spindles. We cannot rule out the possibility that OX modifies NaV channel biophysics - while the antibodies used here demonstrate channel presence, they do not test the status of subunits, which if modified, for example in NaV1.6, might reduce PIC capacity.
1. Bullinger et al., *J Neurophysiol* 106: 704-709, 2011.
2. Vincent et al., *J Anat* 227: 221-230, 2015.
3. Vincent et al., *Neurobiol Dis* 95: 54-65, 2016.
4. Carrasco et al., *J Neurophysiol* 1117: 1690-1701, 2017.

Disclosures: D.I. Carrasco: None. **P. Nardelli:** None. **T.C. Cope:** None.

Poster

231. Posture and Gait: Afferent Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 231.15/EE16

Topic: E.06. Posture and Gait

Title: The effect of painful peripheral neuropathy on gait for adults with Type 2 diabetes

Authors: *E. JENKINS, S. MORRISON
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Abstract: For older adults with Type 2 diabetes (T2DM), the emergence of peripheral neuropathy is a burdening condition that affects their quality of life in a number of ways. The impact of the condition goes beyond symptomatic pain and altered sensations, having a negative

effect on general motor function as well. For example, diminished balance control, increased falls risk and/or changes in walking ability have all been reported for T2DM persons with neuropathy. The aim of this study was to assess the impact of painful neuropathy on falls risk and gait dynamics for older T2DM individuals. Twenty-seven T2DM subjects with PN participated in this study. Falls risk was measured using the Physiological Profile Assessment (PPA). The PPA is a validated tool which includes tests of vision, sensation, posture, and leg strength. Values from each test are combined to provide an overall risk score with higher scores denoting greater risk. Self-reports of pain and fear of falling were also administered. Gait data were collected while subjects walked at their preferred pace over a 25 ft marked distance. Kinematic and kinetic data relating to each person walking patterns were collected using a 10 camera VICON motion capture system with two AMTI force plates. For the kinematic data, lower limb joint angles were calculated throughout all steps, while inverse dynamics were calculated to determine joint moments while in contact with the force plate. The results revealed that all T2DM persons had a heightened falls risk coupled with pronounced pain related to walking and general daily activities. Assessment of the kinetic data revealed increased variability of the ground reaction forces. In particular, many of the subjects exhibited pronounced braking forces during walking. Alteration and variability of the gait kinetics were also reflected by differences in lower limb joint kinematics and joint moments during walking. Overall, it would appear the development of painful neuropathy associated with diabetes resulted in greater variability across both force and kinematic metrics during gait. One suggestion is that the alteration or loss of sensation in the distal nerves of the lower leg and foot will cause sensory feedback issues while walking, resulting in a large variability of force applied during each foot-strike. This strategy may emerge due to the need for a certain expected threshold of feedback from the ground reaction force to ensure that the foot is in a proper position to transfer weight and continue the gait cycle.

Disclosures: E. Jenkins: None. **S. Morrison:** None.

Poster

231. Posture and Gait: Afferent Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 231.16/EE17

Topic: E.06. Posture and Gait

Title: Altered muscle spindle function in murine models of muscular dystrophy

Authors: *L. GERWIN[1,2], S. ROSSMANITH[1], C. HAUPT[1], H. BRINKMEIER[3], R. BITTNER[4], S. KRÖGER[1]
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Moritz-Arndt-Universität Greifswald, Greifswald, Germany; [4]Ctr. for Anat. and Cell Biol., Med. Univ. of Vienna, Vienna, Austria

Abstract: Muscular dystrophies comprise a heterogeneous group of hereditary diseases which is characterized by progressive degeneration and weakness of skeletal muscles, leading – among others – to a poor balance and a progressive inability to maintain posture. We investigated the hypothesis that an altered proprioceptive feedback contributes to the instable gait and frequent falls in patients with muscular dystrophy. Proprioceptive feedback is generated by muscle spindles, complex sensory organs that are sensitive to changes in muscle length and the speed of stretching.

We analyzed muscle spindle function and morphology from wildtype-, as well as from dystrophin-, utrophin- and dysferlin-deficient mice. Immunofluorescence staining demonstrated the presence of these three proteins in the central region of muscle spindles from wildtype mice and their absence in spindles from the respective mutants. Dystrophin was concentrated in intrafusal fibers in the area between the sensory nerve terminals. The total number of muscle spindles found in soleus muscles of dystrophin- and utrophin-deficient mice appeared unchanged, demonstrating that intrafusal muscle fibers are less sensitive to degeneration due to mechanical stress compared to extrafusal muscle fibres. Moreover, extracellular recordings from single units of Ia sensory afferents from muscle spindles of the extensor digitorum longus muscle were performed during ramp-and-hold stretches, as well as during sinusoidal vibrations. We show that dystrophin-deficient mice have an increased resting discharge. Additionally, dystrophin- and dysferlin-deficient mouse strains showed a reduced proprioceptive sensitivity during the dynamic phase of ramp-and-hold stretches and less entrainment during sinusoidal vibrations. No difference could be observed during the static phase of a muscle stretch. Utrophin-deficient mice reacted to ramp-and-hold stretches and sinusoidal vibrations similar to wildtype mice.

These results demonstrate that dystrophin and dysferlin are required for normal muscle spindle function and suggest that an impaired proprioceptive feedback might contribute to the instable gait and the frequent falls in patients with muscular dystrophy.

Disclosures: L. Gerwin: None. **S. Rossmanith:** None. **C. Haupt:** None. **H. Brinkmeier:** None. **R. Bittner:** None. **S. Kröger:** None.

Poster

231. Posture and Gait: Afferent Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 231.17/EE18

Topic: E.06. Posture and Gait

Support: NIH Grant HD32571

Title: Positive force feedback may ameliorate muscle weakness

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Abstract: Functional electrical stimulation has been used to activate weakened or paralyzed muscles during locomotion using kinematic signals to control the stimulator. Evidence for the effectiveness of positive force feedback from Golgi tendon organs in load-bearing tasks such as locomotion (Prochazka et al, 1997, J. Neurophysiol 77: 3226) suggested to us that an engineered feedback controlled stimulation system could be used to increase muscle force in patients with muscle weakness. By amplifying the weak signals recorded by the muscle, the time course of muscle activation could be determined voluntarily. We tested this approach using the unanesthetized decerebrate cat preparation by recording muscular force during muscle stretch. The force signal was then fed back to electrically stimulate the muscle through intramuscular electrodes and increase force output over that due to the stretch reflex. Stretches and releases of the medial gastrocnemius muscle were imposed by a linear motor and used to initiate and terminate the electrical stimulation of the muscle, respectively. Thresholds and gains of the feedback could be selected in the computer interface and were varied to determine the limits of the system's stability in order to controllably activate the muscle. It was found that intramuscular stimulation remained stable through a wide range of these parameters. During stable behavior, the stimulation terminated when the muscle was returned to its original length. At higher gains and lower thresholds than within the stable range, stimulation outlasted the return to the starting length, causing an undesirably prolonged muscle contraction. In a clinical setting, the feedback signal could be obtained from electromyographic recordings, and stimulation could be delivered by intramuscular or surface electrodes.

Disclosures: H. Shi: None. **M.A. Lyle:** None. **C. Tuthill:** None. **T. Nichols:** None.

Poster

231. Posture and Gait: Afferent Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 231.18/EE19

Topic: E.06. Posture and Gait

Support: NSERC

Title: The effect of pairing startling acoustic stimuli with displacements of a light touch reference on balance corrective responses

Authors: S. D. C. CHODAN[1], K. K. FENRICH[1], *J. E. MISIASZEK[2,1]
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Abstract: Lightly touching (<1 N vertical force) a stable reference is well documented to provide sensory feedback that is incorporated into balance control. Recently, we demonstrated that unexpected displacement of a touch reference triggers a balance reaction in tibialis anterior (TA). However, these reactions to the touch displacement are not consistently expressed across subjects, are only observed on the first displacement trial, and are replaced by an arm-tracking behavior with subsequent exposures. It is argued that the initial response to an unexpected balance disturbance is due, in part, to a startle response. Unexpected tactile stimuli can also trigger startle reactions. Therefore, the inconsistent first-trial responses evoked by touch displacement could be startle-related responses to peri-threshold tactile stimuli. If so, combining touch displacement with a startling acoustic cue should summate and generate more consistent expression of the balance corrective response. To test this, naïve healthy young adults stood on foam atop a force plate to record the center of pressure. EMG from leg, arm, neck and face muscles recorded neuromuscular reactions to touch disturbances or acoustic startles. Elbow and ankle joint angles were recorded. Responses to touch displacement (T), acoustic startle (S), and combined stimuli (C) were tested. T consisted of unexpected rapid forward movement (12.5 mm, 127 mm/s peak velocity) of a touch plate. S consisted of a brief (100 ms) calibrated tone (103 dB, 450 Hz) delivered via indwelling earphones. Combined stimuli were delivered simultaneously. Responses in TA were observed in 33% of T, 40% of S, and 50% of C trials. Responses in sternocleidomastoid (SCM) were observed in 11% of T, 40% of S, and 65% of C trials. The increased response frequency in SCM with C suggests that T is a startling stimulus that is subthreshold most of the time, until combined with S. Response frequency in TA did not exhibit the same degree of increase with the combined stimuli, suggesting that startle contributes to the responses in TA, but is less pronounced than for the responses in SCM. Anterior deltoid (AD) exhibited responses in 50% of T trials, and was consistent with the emergence of an arm-tracking response with repeated exposures. AD responded in only 30% of S, but 80% of C trials, suggesting facilitation of the arm-tracking behavior with startle. These results support the argument that repeated exposure to a touch displacement results in a change in behavior, from a balance corrective response initially to an arm-tracking response, mediated by distinct neural processes that are differentially influenced by the co-presentation of a startling cue.

Disclosures: S.D.C. Chodan: None. **K.K. Fenrich:** None. **J.E. Misiaszek:** None.

Poster

231. Posture and Gait: Afferent Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 231.19/EE20

Topic: E.06. Posture and Gait

Support: DARPA Young Faculty Award, D15AP00112

Brown Presidential Fellowship

Title: A neuromusculoskeletal model of rhesus macaque muscle spindle activity during locomotion

Authors: *R. DARIE[1], D. A. BORTON[1,2,3]
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Abstract: In an intact organism, locomotion and posture are effortlessly controlled, even in the absence of vision, due to feedback from a group of mutually complementary somatosensory pathways: touch and proprioception. As motor prostheses become more complex, it is becoming increasingly important to restore that rich sensory feedback to the user, but it is not clear which features of the sensory experience are most important for motor performance, nor is it known how to effectively convey them to an damaged or diseased nervous system. Proprioception, for instance, is a sense crucial to balance and kinesthesia underlain by the activity of muscle spindles, specialized sensory organs that encode the length and velocity of muscles. This information is relayed to the CNS through the firing rates of afferent sensory fibers. The firing responses of single spindles to simple manipulations is well understood based on acute experiments and has been described using computational models. However, the profiles of these responses during complex naturalistic behaviors in large animals has not been characterized to date. Physically recording such signals from freely behaving animals remains elusive due to technological limitations. Here, we have constructed an accurate neuromusculoskeletal model of the hindlimb of a rhesus macaque that translates animal movements identified from a video recording to a collection of simulated afferent firing patterns. The model is based on a CT reconstruction of the animal skeleton and is formulated in the MuJoCo physics engine. The damped least squares method is used to pose the model into the positions identified from the video, and the kinematic trajectory of 8 simulated muscles is used to derive firing events from NEURON models of the group Ia and II fibers that originate from those muscles. We have validated the model based on anesthetized electrophysiological recordings. Thus, we can approximate spindle activity from a non-invasive recording method and, in the future, we expect that this can be used to better understand the contribution of proprioceptive signals to locomotor performance and how these signals can be manipulated or emulated via electrical stimulation for the production of artificial proprioception.

Disclosures: R. Darie: None. **D.A. Borton:** None.

Poster

231. Posture and Gait: Afferent Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 231.20/EE21

Topic: E.06. Posture and Gait

Title: Transient responses in muscle activations during perturbed treadmill walking

Authors: *F. EHTEMAM[1], H. WANG[2], A. J. VAN DEN BOGERT[2], T. KIEMEL[1]
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Abstract: The nervous system in humans ensures stability of walking under perturbations through modulation of muscle activations. The underlying mechanisms of this modulation process are not well understood. Perturbations of the treadmill belt have been used in the past to elicit responses in muscle activations. However, discrete perturbations used have only provided information on responses during parts of the gait cycle. To understand how the neural controller modulates muscle activity, it is essential to characterize responses during the entire cycle. Discrete perturbations also tend to be large which may disrupt normal walking behavior as a local limit cycle. The purpose of this study was to investigate transient changes in muscle activations in response to small continuous perturbations of the treadmill to better understand how the nervous system corrects the small kinematic deviations through the gait cycle. Five subjects walked on an instrumented treadmill under mechanical perturbations. The mean treadmill speed was 1.3 ms^{-1} with continuous random deviations with power between 0 and 5 Hz. Transient responses in muscle activations were captured by electromyography (EMG). Harmonic transfer functions were calculated to characterize kinematic and EMG responses in the frequency domain. Results were then converted to phase-dependent impulse response functions (φIRFs) in the time domain. A φIRF describes the response to a small brief perturbation (an impulse) applied at any phase of the gait cycle. φIRFs showed transient decreases in tibialis anterior (TA) activity at heel-strike in response to forward movement of the tread during the swing. When the belt accelerated forward during stance, there was a short-latency decrease in the activity of plantarflexors. These responses were observed consistently in all subjects across all perturbations applied. These results show the viability of the experimental and computational approaches used in this study in probing neural control of gait under mechanical perturbations. The observed responses provide information on modulation of muscle activations as control signals and can advance future research on design of neural controllers for smart prosthetics.

Disclosures: F. Ehtemam: None. **H. Wang:** None. **A.J. van den Bogert:** None. **T. Kiemel:** None.

Poster

231. Posture and Gait: Afferent Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 231.21/EE22

Topic: E.06. Posture and Gait

Support: DFG Grant RE 3780/1-1

Title: Balance respones to visual perturbations during walking

Authors: *H. REIMANN[1], T. D. FETTROW[2], E. D. THOMPSON[3], J. J. JEKA[2]
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Abstract: The human body during bipedal locomotion is mechanically highly unstable and maintaining upright balance requires continuous control. Using sensory information about the state of the body from different sensory systems to detect the onset of a fall, the central nervous system (CNS) modulates muscle activity to stabilize the walking body. Previous studies have identified two main mechanisms used by the CNS to regulate lateral balance. The foot placement strategy shifts the location of the next footstep in the direction of a sensed fall, leading to gravitational acceleration of the body center of mass (CoM) that counters the fall. The lateral ankle strategy modulates activity of the stance leg ankle muscles during single stance, pulling against the sensed fall. These balance mechanisms have been observed in steady state locomotion, after mechanical perturbations and in response to Galvanic vestibular stimulation. We designed an experiment to study the role of the visual system for the control of balance during locomotion. Subjects walked on a self-paced treadmill, immersed in a virtual reality environment projected onto a curved dome that covered most of the visual field. A virtual fall stimulus was delivered by rotating the virtual scene laterally around the central axis of the pathway. Rotation accelerated at 60deg/s^2 for 600ms, then remained at the resulting orientation of 10.8deg for 2s, before resetting with uniform velocity over 1s. Stimuli were triggered on heelstrike. We collected whole-body kinematic data, EMG and ground reaction forces from nine healthy young adults. We observed a shift of the first foot placement after stimulus onset in the direction of the fall stimulus, in accordance with the foot placement strategy. Before this step response, during the first single stance phase after stimulus onset, the center of pressure relative to the body CoM shifted in the direction of the fall stimulus. This shift was accompanied by changes in the ankle inversion angle and peroneus longus muscle activity of the stance leg, all in accordance with the lateral ankle strategy. In addition to these two expected balance responses, we observed a systematic response in the ankle plantarflexion angle during the first push-off after stimulus onset. The push-off tended to be stronger if the fall stimulus is towards the previous stance leg, and weaker if away from the previous stance leg. This modulation of the

push-off force of the trailing leg in response to a visual perturbation is an additional mechanism for balance control during locomotion. The unfolding view is that the nervous system employs the temporal coordination of multiple mechanisms to maintain upright during walking.

Disclosures: H. Reimann: None. **T.D. Fettrow:** None. **E.D. Thompson:** None. **J.J. Jeka:** None.

Poster

231. Posture and Gait: Afferent Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 231.22/EE23

Topic: E.06. Posture and Gait

Support: Shriners Hospitals for Children Research Fellowship #84295

Title: Balance control strategies due to sensory perturbation during walking in children with cerebral palsy: preliminary results

Authors: *S. HWANG[1], C. FRANKLIN[2], B. LIPA[2], C. TUCKER[3], J. J. JEKA[4]
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Abstract: Decreased dynamic postural control diminishes functional mobility in individuals with Cerebral Palsy (CP), but the neural control strategies underlying their walking patterns have not been addressed. Currently, rehabilitation interventions in children with CP focus on improving functional performance and decreasing motor deficits associated with muscle spasticity and weakness, but with limited consideration of sensory impairments whose deficits affect flexible motor control. In this study, we investigate balance control strategies due to sensory perturbations during walking in a child with spastic diplegic CP who is able to walk without assistance (Gross Motor Function Classification System level 1). The subject walked on a self-paced, instrumented treadmill surrounded by a virtual environment matched to the speed of the treadmill and the position of the subject. The visual perturbation consisted of a visual scene rotation every 10-13 steps around the sagittal axis to the right or left at a constant acceleration of 60°/sec². The vestibular perturbation consisted of a 0.5 mA current Galvanic Vestibular Stimulus (GVS) with the same visual scene setup but without a visual perturbation. Each perturbation was initiated on heel strike. The results showed that two mechanisms play a role in the control of balance during walking: a shift in the center of pressure (CoP) under the stance foot and a shift in step width. We found that the step response was relatively larger and earlier with a vestibular perturbation compared to the visual perturbation. A shift in the CoP was also larger with a vestibular perturbation. However, these differences were only observed with the right limb.

Sensory stimuli elicit balance responses during walking through the coordinated response of both the foot placement mechanism and the lateral ankle strategy (shift in CoP). Asymmetric responses reflect that balance is achieved unilaterally and may contribute to the well-known instability during walking in children with CP. These findings support a multi-dimensional clinical approach to potentiate typically motor-centric strategies for improving mobility in children with CP.

Disclosures: S. Hwang: None. **C. Franklin:** None. **B. Lipa:** None. **C. Tucker:** None. **J.J. Jeka:** None.

Poster

231. Posture and Gait: Afferent Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 231.23/EE24

Topic: E.06. Posture and Gait

Title: Adapting to perturbations during rhythmic arm and leg movements

Authors: *H. J. HUANG, S.-Y. SHIRAZI
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Abstract: Recent studies have suggested that rhythmic arm and leg movements such as cycling or recumbent stepping may help improve walking ability and balance. Studies have also shown that people adapt movement patterns in response to errors. These findings suggest that humans would likely adapt arm-leg movements to minimize stepping errors during recumbent stepping. The purpose of this study was to determine how arm-leg movements adapt in response to stepping errors during recumbent stepping. We hypothesized that subjects will alter their hand and feet forces to minimize stepping errors created by perturbations. We predicted that subjects would step more slowly upon first experiencing the perturbations but would adapt to return to a normal stepping pattern, despite the perturbations. We also predicted that subjects would use their legs more than their arms to respond to the perturbations and that feet forces would increase with adaptation. Subjects (healthy, n = 3) performed rhythmic arm-leg movements using a customized recumbent stepper that could create perturbations. During the middle of right (or left) leg extension, the stepper applied a perturbing resistive force for 0.2 seconds. For each perturbation trial, there were 2 minutes of unperturbed (normal) stepping, then 6 minutes of perturbed stepping, and another 2 minutes of unperturbed stepping. We analyzed the stepper velocity and the forces exerted by the left hand, right hand, left foot, and right foot during each limb extension (or a step). Our results indicated that subjects stepped more slowly when they first experienced the perturbation but stepped normally after adapting to the perturbation. Subjects also relied more on their legs than their arms to respond to the perturbations. During the

right leg perturbation, the right foot force increased immediately in response to the perturbation and continued to increase with adaptation, while the left foot force decreased immediately but then also increased slowly with adaptation. A similar pattern was observed during the left leg perturbation, where the left foot force increased throughout adaptation while the right foot force decreased initially before increasing with adaptation. These preliminary results suggest that humans adapt hand and feet forces to reduce stepping errors to step normally during recumbent stepping. This suggests that adding perturbations during rhythmic arm and leg movements may improve arm-leg coordination, which may be beneficial for gait rehabilitation.

Disclosures: H.J. Huang: None. **S. Shirazi:** None.

Poster

231. Posture and Gait: Afferent Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 231.24/EE25

Topic: E.06. Posture and Gait

Support: NSERC DG250348

Title: The effects of orthotics and increased plantar sole mechanoreceptor activation on turning performance in individual's with parkinson's disease

Authors: *K. A. ROBB, S. D. PERRY
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Abstract: Locomotion and turning are complex movement patterns essential to ADLs. Individuals with Parkinson’s disease (PD) report difficulties turning, often coupled with impaired balance and increased fear of falling. Previous turning research has demonstrated a slower turning speed and an altered intersegmental movement coordination in PD individuals. The purpose of this study was to determine if orthotics, with and without a textured top cover, can improve gait stability and turning performance within Parkinson’s participants. Eight participants with a diagnosis of idiopathic Parkinson’s disease, aged 55-80 years old, participated in the study. Participants completed three testing sessions; baseline, 4 weeks post-baseline, and 5 weeks post-baseline. The ‘footwear only’ and ‘footwear + non-textured orthotic’ conditions were tested at baseline, ‘footwear + non-textured orthotic’ and ‘footwear + textured orthotic’ conditions were testing at 4-weeks, and the ‘footwear + textured orthotic’ condition was repeated at 5 weeks. Kinematic, kinetic, electromyographical and video data were collected during the turning task. Participants were instructed to either turn towards their dominant direction or towards their non-dominant turn direction. The turn had to be made within a pre-determined area. Turning performance (strategy) was categorized during the turning trials with both the turn direction (dominant vs. non-dominant) and the braking foot (same side vs. opposite side to the

turn). The evaluation of the potential stability of the turn was based upon the participant's use of stable or unstable combinations of turn direction and braking foot. Using the same side foot as the turn direction was considered most stable. The results (see figure 1) demonstrated an increase in the frequency of this strategy during week 5 of the textured orthotic condition compared to the initial week 1 footwear only condition (x^2=4.89, df=1, $p<0.05$). The one week exposure to the textured top cover may indicate an increase balance confidence that resulted in the adoption of a more stable stepping strategy.

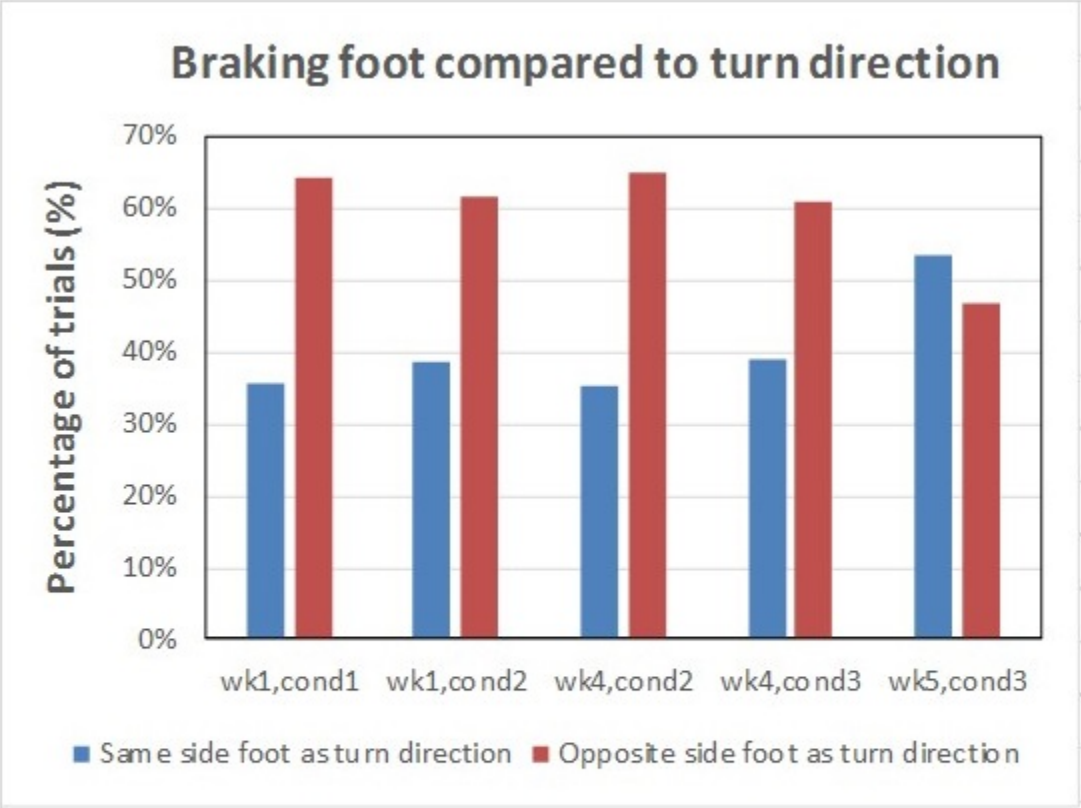

Figure 1: Comparison of braking association with turn direction. (wk - week, cond1 - baseline, cond2 - footwear+non-textured orthotic, cond3 - footwear+textured orthotic).

Disclosures: K.A. Robb: None. **S.D. Perry:** None.

Poster

231. Posture and Gait: Afferent Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 231.25/EE26

Topic: E.06. Posture and Gait

Support: CDMRP RIF127D23(W81XWH-13-C-0189)

Title: Vestibular habituation and balance training protocol for sensory reweighting

Authors: *W. WRIGHT, K. O. APPIAH-KUBI
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Abstract: Postural stability depends on the integration of the multisensory system to produce motor outputs. When visual and somatosensory input is reliable, this reduces reliance on the vestibular system. Despite this, vestibular loss can still cause severe postural dysfunction. Training one or more of the three sensory systems through vestibular habituation can alter sensory weighting and change postural behavior. The purpose of this study was to assess sensory reweighting of postural control processing after combined vestibular habituation with voluntary weight-shift training in healthy adults performed on NeuroCom SMART Balance Master. We hypothesized that even in a relatively short, high dosage training regimen, it effects would significantly alter the pattern of sensory weighting by changing the ratio of visual, somatosensory, and vestibular dependence needed to maintain postural stability. Thirty-three healthy individuals (18-35 y.o.) were randomly assigned to one of three groups: No training (CTL), visual feedback weight shift training (WST) coupled with an active horizontal head-shake (HS) activity to elicit a vestibular perturbation, or the same WST without HS (No-HS). Training was performed 2x/day, every other day, 3x/week. Pre- and post- assessments on the Sensory Organization Test (SOT) were performed. Separate between- and within- repeated measures ANOVAs were used to analyze the six SOT equilibrium scores, composite scores, sensory ratios and center of pressure (COP) variables by comparing baseline to post-training. Alpha level was set at $p<.05$. The results show there was a significant change ($p=0.03$) in the COP mediolateral standard deviation (Std ML) in the HS group during SOT condition 6, while a decrease stability was found in the CTL group post-training. The No-HS group showed no significant difference. COP multiscale entropy (MSE) velocity yielded a significant change ($p=0.01$) in the HS group during conditions 5 and 6. SOT equilibrium and composite scores were not significant, although mean differences may depict slight improvement in HS group and no change in No HS and CTL groups. The training effect was related to the visual condition as it relates to vestibular weighting. In conclusion, postural training can alter sensory organization after a relatively short training protocol. The benefits cannot be explained by a practice effect since similar changes were not seen in the CTL group or No-HS group. The study suggests a

possible sensory reweighting induced by the provocative vestibular training. These study results may help shape the design of therapeutic interventions in individuals with vestibular-related balance impairments.

Disclosures: W. Wright: None. **K.O. Appiah-Kubi:** None.

Poster

231. Posture and Gait: Afferent Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 231.26/EE27

Topic: E.06. Posture and Gait

Support: NIH Grant R00 HD073240

Title: Does startle impair or support balance during postural disturbances?

Authors: *X. ZONG, C. F. HONEYCUTT
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Abstract: The fact that balance disturbances trigger a startle response has been accepted for a long time (Yeomans et al., 2002); however, it is unclear if this is advantageous. In seated upper extremity studies evaluating reaching and grasping, the presence of a startle reflex allows for faster release of a planned movement (Valls-Sole, 1999). Startle has shown to enhance upper extremity movement in stroke survivors (Honeycutt et al., 2012, 2014). Still, balance and upper extremity movement are very distinct. Most other studies evaluating the role of the startle reflex on balance have used a loud acoustic stimulus in addition to a balance perturbation to generate a startle. These papers show that startle accelerates the onset of the corrective postural muscle response and increases their amplitude (Nonnekes et al., 2013, 2015). Still, this report used an external stimulus to evoke a startle - as opposed to the perturbation itself. The objective of this study was to evaluate how the presence of startle affects the compensatory balance response when startle is evoked by the perturbation. While startle enhances the response in the upper extremity, we hypothesized that the presence of startle would disrupt the balance response (e.g. decreasing trunk stability).
Seven subjects (age 24 ± 5) randomly received 6 different perturbations (3 forward, 3 backward) of 3 different intensities (total = 96 perturbations). Each trial was inspected for the presence of startle using the SCM muscle (Carlsen et. al. 2011). Stepping leg muscle activity and kinematics were compared between trials where startle was present/absent (SCM+/-).
Similar to previous work, we found that SCM+ trials had faster muscle onset latencies but this early activity diminished trunk stability. Muscle onset latency was faster during SCM+ trials in forward stepping (GA: Δ =24 ± 0.7ms; $P < 0.001$, TA: Δ =21 ± 0.5ms; $P<0.001$, RF: Δ =46 ± 1.1ms; $P < 0.001$); however, trunk flexion angle and angle velocity at toe off were larger in

SCM+ trials(Angle: $\Delta = 2.5 \pm 0.40°$; $P < 0.001$, Angle Velocity: $\Delta = 12.4 \pm 5.83°/s$; $P < 0.05$). Further, trunk flexion remained larger during the first 700ms of the trial. No differences were found in step length and step time.
Despite earlier muscle onsets in SCM+ trials, diminished trunk stability was present. Stroke survivors (Honeycutt et al., 2016), older adults (Grabiner, 2008) and amputees (Rosenblatt et al,. 2014) all have diminished capacity to control their trunk. Therefore, even small changes that disturb trunk stability could contribute to these population's increased fall risk. In conclusion, startle impairs the overall ability of subjects to respond to postural disturbances.

Disclosures: X. Zong: None. **C.F. Honeycutt:** None.

Poster

232. Motor Systems: Sensory Input and Descending Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 232.01/EE28

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

Title: action potentials are present in dorsal roots containing spinal cord interneuron axons in the neonatal mouse

Authors: *L. P. OSUNA CARRASCO[1], J. R. LOPEZ RUIZ[2], B. DE LA TORRE[3], J. M. DUENAS JIMENEZ[4], S. H. DUENAS JIMENEZ[5]
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Abstract: Primary afferent depolarization (PAD) might produce antidromic action potentials (dorsal root reflex; DRR) mediated by activation of synaptic $GABA_A$ receptors located at the afferent terminals. Interestingly, antidromic action potentials can also be originated from some interneurons that send its axons along the dorsal roots. In this study we assessed whether dorsal interneurons produce DRR in the neonate mouse. Experiments were performed in 10 Swiss-Webster mice, of 2 to 13 postnatal days. We used .isolated spinal cords *in vitro* Dorsal and ventral roots of the L4 and L5 segments were placed for stimulation and recordings. We found that in presence of bicuculline DRR recorded in L4 dorsal root evoked by L5 dorsal root stimulation was reduced. Simultaneously, the monosynaptic reflex recorded in L5 ventral root was not affected; nevertheless, a long lasting after discharge was induced. Addition of AP5 an antagonist of NMDA receptors abolished the monosynaptic reflex without affecting the after discharge. Action potentials persisted in ventral and dorsal roots even in low Ca^{2+} concentration and some of them seem to occur simultaneously. Spinal cord interneurons send axons by dorsal roots. These findings could be a particular characteristic of the neonatal mouse probably disappearing in adulthood.

Disclosures: **L.P. Osuna Carrasco:** None. **J.R. Lopez Ruiz:** None. **B. De la torre:** None. **J.M. Duenas Jimenez:** None. **S.H. Duenas Jimenez:** None.

Poster

232. Motor Systems: Sensory Input and Descending Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 232.02/EE29

Topic: E.07. Rhythmic Motor Pattern Generation

Support: CONACYT Grant 59873

CONACYT Grant 219707

NIH Grant NS45248

Title: Pharmacological analysis of the modulating inhibitory effects produced by activation of D_2-like receptors on pathways mediating PAD in the mouse spinal cord

Authors: *J. J. MILLA CRUZ[1], D. L. GARCÍA-RAMÍREZ[1], J. R. CALVO[1], C. M. VILLALON[2], S. HOCHMAN[3], J. N. QUEVEDO[1]
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Abstract: It has previously been shown that dopamine (DA) and the dopamine D_2-*like* receptor agonist, *quinpirole,* markedly depressed low-threshold afferent stimulation-evoked primary afferent depolarization (PAD) in the *in vitro* mouse spinal cord, with no effect on afferent synaptic transmission (SFN Abstract 422.04/Q5, 2015). The present work has examined the D_2-*like* receptor subtypes (i.e. D_2, D_3 and D_4) involved in the modulatory depressant actions of DA on PAD evoked by stimulation of myelinated afferents. Experiments were carried out on P6 sagittally-hemisected mouse spinal cord with peripheral nerves attached for selective afferent stimulation. Stimulus strength was based on multiples of threshold (xT) of the most excitable fibers recorded from the incoming afferent volley, with strengths $\leq$ 2 xT recruiting only myelinated afferents. PAD was inferred from dorsal root potentials (DRPs) recorded at L_3-L_4 dorsal roots, while monosynaptic responses were recorded in the deep dorsal horn as intraspinal extracellular field potentials (EFPs) at the same spinal segments. All drugs were applied at 1 μM. The D_2-*like* receptor agonist, *quinpirole*, depressed DRPs to 67±2% (n=4) of control, with no effect on EFPs (99±3%, n=4). In separate experiments we tested the effects of "subtype-selective" D_2-*like* receptor antagonists. Hence, *quinpirole*-induced inhibition on DRPs was: (i) partially, but significantly, blocked in the presence of *L-741,626* (D_2) and *SB277011-A* (D_3) [83±1% (n=4) and 81±5% (n=5), respectively]; and (ii) resistant to blockade in the presence of

L-745,870 (D_4) (60±8% of control, n=5). Since *quinpirole* had no effect on EFPs, co-application with these D_2, D_3 and D_4 receptor antagonists was similarly without effect (104±5%, 104±3% and 99±5% of control, respectively). Although, admittedly, there are no selective agonists for the D_2-*like* receptor subtypes, we found that the D_4-preferring agonist, *PD168077*, depressed DRPs and EFPs to 44±3% and 82±7% of control (n=3), respectively. Unexpectedly, the D_2 receptor agonist, *sumanirole*, depressed both DRPs and EFPs to 19±1% and 42±1% (n=3) of control, respectively. We conclude that the modulating inhibitory effects of DA on pathways mediating PAD are produced by co-activation of D_2 and D_3 receptor subtypes, and possibly by the activation of D_4 receptors. It remains to be determined whether the effects of *sumanirole* and *PD168077* are mediated by other receptors/mechanisms.

Disclosures: J.J. Milla Cruz: None. **D.L. García-Ramírez:** None. **J.R. Calvo:** None. **C.M. Villalon:** None. **S. Hochman:** None. **J.N. Quevedo:** None.

Poster

232. Motor Systems: Sensory Input and Descending Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 232.03/FF1

Topic: E.07. Rhythmic Motor Pattern Generation

Support: CONACYT Grant 59873 (JQ)

CONACYT Grant 219707 (CMV)

NIH Grant NS45248 (SH)

Title: The role of α_1-, α_2- and β-adrenoceptors in the modulatory depressant actions of noradrenaline on synaptic transmission of myelinated afferents and pathways mediating PAD in the *In vitro* mouse spinal cord

Authors: E. MENA-AVILA[1], J. J. MILLA-CRUZ[1], J. R. CALVO[1], C. M. VILLALON[2], S. HOCHMAN[3], J. A. ARIAS-MONTANO[1], *J. N. QUEVEDO[4]
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Abstract: Noradrenaline (NA) decreases primary afferent depolarization (PAD) evoked by stimulation of myelinated cutaneous and muscle afferents in the *in vitro* mouse spinal cord, with no apparent effect on afferent synaptic transmission (García-Ramírez et al., PLoS One, 2014). This study investigated the possible role of
α_1-, α_2- and β-adrenoceptors in the modulatory depressant actions of NA on synaptic transmission of myelinated afferents and on pathways mediating PAD evoked by stimulation of

the same type of afferents. Experiments were performed on P6-7 sagittally-hemisected mouse spinal cord with intact peripheral nerves for selective afferent stimulation. Stimulus strength was based on multiples of threshold (xT) of the most excitable fibers recorded from the incoming afferent volley, with strengths ≤ 2 xT recruiting only myelinated afferents. PAD was inferred from dorsal root potentials (DRPs) recorded at L_3-L_4 dorsal roots, while monosynaptic responses were recorded as intraspinal extracellular field potentials (EFPs) in the deep dorsal horn. Excitability of afferent fibers was tested by means of the Wall's technique. NA (1 nM-100 μM) depressed both DRPs and EFPs with maximal inhibition values (I_{MAX}) of 70±8% and 26±10% (n=4) of control, and IC_{50} values of 188 and 191 nM, respectively. This effect was mimicked by the α_1-adrenoceptor agonist, phenylephrine (1 nM-100 μM), with I_{MAX} values of 68±7% and 25±6% (n=4) of controls, and IC_{50} values of 188 and 776 nM for DRPs and EFPs, respectively. Moreover, the α_2-adrenoceptor agonist clonidine (1 nM-100 μM) depressed DRPs with I_{MAX} values of 38±5% and IC_{50} values of 2.6 μM (n=4), but produced no significant effects on EFPs (11±8% at 100 μM; n=4). In contrast, the general β-adrenoceptor agonist, isoproterenol (1 nM-100 μM), produced no significant effects on EFPs (15±3% at 100 μM; n=4), with inconsistent effects on DRPs (n=4). NA produced no change in the excitability of fast conducting afferent fibers (1±2%; n=6), but it depressed the DRP evoked by intraspinal microstimulation (68±4%; n=6). We conclude that NA depresses monosynaptic transmission of myelinated afferents by activating α_1-adrenoceptors and reduces the excitability of interneurons mediating PAD through activation of α_1 and α_2-adrenoceptors. NA depressant actions on myelinated afferent transmission may not be causally linked to observed depressant actions on PAD, and further that observed actions are predominantly due to actions at α_1-adrenoceptors.

Disclosures: E. Mena-Avila: None. **J.J. Milla-Cruz:** None. **J.R. Calvo:** None. **C.M. Villalon:** None. **S. Hochman:** None. **J.A. Arias-Montano:** None. **J.N. Quevedo:** None.

Poster

232. Motor Systems: Sensory Input and Descending Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 232.04/FF2

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NYSCF

ENP

Title: Mapping connectivity of sensory neurons linking cerebrospinal fluid to motor circuits in vertebrates

Authors: M.-Y. WU[1], K. FIDELIN[2], A. PRENDERGAST[3], P.-E. TSENG[2], P. GARNERET[4], *C. WYART[1]

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Abstract: The cerebrospinal fluid (CSF) is a complex solution circulating around the brain and spinal cord. Behavior has long been known to be influenced by the content and flow of the CSF, but the underlying mechanisms are elusive. CSF-contacting neurons by their location at the interface between the CSF and the nervous system are in ideal position to sense CSF cues and to relay information to local networks. We previously demonstrated that neurons contacting the CSF detect local bending of the spinal cord and in turn feedback GABAergic inhibition to interneurons driving slow locomotion and motor neurons controlling posture in the ventral spinal cord. Here we performed quantitative behavior analysis on a large scale to show that CSF-contacting neurons perform a state-dependent modulation. These neurons decrease locomotor frequency in the slow locomotor regime while they increase locomotor frequency in the fast locomotor regime. The neuronal targets previously identified cannot explain these effects on locomotor speed. Anatomical evidence suggest that CSF-contacting neurons project onto axons of V2a interneurons as well as onto the soma of V3 interneurons, both of these glutamatergic interneurons being involved in locomotor speed. We are now combining electrophysiology, optogenetics and imaging of specific transgenic lines *in vivo* in zebrafish larvae to investigate the physiology of these putative connections. Altogether, this body of work sheds light on the cellular and network mechanisms enabling sensorimotor integration of mechanical and chemical cues from the CSF onto motor circuits controlling locomotion and posture in the spinal cord.

Disclosures: M. Wu: None. **K. Fidelin:** None. **A. Prendergast:** None. **P. Tseng:** None. **P. Garneret:** None. **C. Wyart:** None.

Poster

232. Motor Systems: Sensory Input and Descending Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 232.05/FF3

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH Grant DE021849

Title: Incising CPG modulates load duration and peak force inversely with incising frequency in non-pain and pain states

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Abstract: In our previous study, the amplitude and load duration of masticatory muscle force during incising was shown to be negatively correlated to incising frequency. However, it is unclear if the slope of force development varies across incising frequencies. The slope of force development is an indirect measure of excitatory drive in the masticatory system. It was hypothesized that the slope would be similar across different incising frequencies but would be lower in a muscle pain condition compared to a non-pain condition at similar incising frequencies. The purpose of this study was to evaluate the slope of force development at different incising frequencies in the absence and presence of persistent masseter (jaw closing) muscle pain.
Methods: We have developed a technique to record incising forces in three dimensions in the home cage environment. Ten female and male CD-1 mice were injected with acidic saline (pH = 4.0) into the left masseter muscle. This injection was repeated in the same location after five days to create a persistent jaw closing muscle pain condition. Over a period of 24 hours, incising forces were recorded in the home cage environment using a multi-axis force transducer (ATI Industrial Automation) that was attached to mouse chow. Incising force recordings during a baseline and a pain condition (day 7 after the second injection) for each mouse were evaluated. Pairs of incising force peaks were assessed (peak 2 amplitude, peak 2 load time, inter-peak interval between peak 1 and 2) in incising epochs that had a minimum of 20 incisions per epoch. Peak 2 amplitude, peak 2 load duration and the slope of force generation of peak 2 were calculated for each peak at each frequency. Medians were calculated for each of these parameters and differences among incising frequency and between no pain and pain conditions were evaluated using a Friedman's analysis of variance for repeated measures and Wilcoxin Matched-Paired Signed-Rank tests and a probability level of less than 0.05.
Results: Peak amplitude and load time were found to decrease with increasing incising frequencies of 4.6, 5.3, 6.2 and 7.6 Hz ($p < 0.05$). During the pain condition, peak 2 amplitude and load time were significantly smaller compared to the non-pain condition ($p<0.05$). However, the slope of force development increased with higher incising frequencies and was significantly smaller for the pain condition vs non-pain condition ($p<0.05$).
Conclusions: Incising force at progressively higher incising frequencies requires an increased excitatory drive to jaw closing motoneurons in both non-pain and pain muscle conditions with a smaller excitatory drive during the pain condition.

Disclosures: C.G. Widmer: None. **J. Morris-Wiman:** None.

Poster

232. Motor Systems: Sensory Input and Descending Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 232.06/FF4

Topic: E.07. Rhythmic Motor Pattern Generation

Support: local

Title: Amino acids act on dorsal roots to trigger limb central pattern generators

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Abstract: The vertebrate spinal cord contains the neuronal circuit for locomotion (Brown, 1911). Poon (1980) applied amino acids to the lamprey spinal cord that triggered the circuit for locomotion. Also, in response to amino acids, four types of interneurons have been discovered in salamanders that are correlated with walking (Wheatley, et al. 1992). Further study is needed to establish (1) the causal relationships underlying neuronal control of vertebrate locomotion and (2) the sites of action of amino acids. In a search for those sites, we discovered that low concentrations of amino acids act quickly if application is restricted to the dorsal roots. Our hypothesis is that coordinated limb movement involves a cascade of neurons with specific neurotransmitter receptors, afferent activation of which by the dorsal root can trigger locomotion. Our goal is three-fold: (1) Identify neuronal networks that cause locomotion; (2) Extend previous work using a preparation that has the principle components for vertebrate walking; (3) Use pharmacological agents that pinpoint mechanisms of neuronal organization. Adult axolotls were anesthetized with benzocaine, and then covered in ice for 20 minutes. After the preparation was dissected to isolate the thoracic spinal cord and its spinal nerves along with flexor and extensor muscles, it was superfused with oxygenated Ringer's solution at room temperature. A nozzle restricted application to individual dorsal roots (2, 3, 4, or 5) of kainate, homocysteate, or N-methyl-D-aspartate (NMDA) in concentrations of 1 to 50 µM. Extracellular muscle recordings of action potentials were performed with bipolar electrodes on the biceps and triceps. The brief application to a dorsal root of amino acid produced rhythmic bursts of muscle action potentials with a latency as short as one second. Kainate was the most potent followed by homocysteate and then NMDA. Frequency of bursts was concentration dependent. Long duration application demonstrated little desensitization. The muscle response terminated on return to normal solution. The bursting activity was characteristically coordinated rhythmic alternation between antagonistic muscle within each limb and between the opposite limbs as in intact locomotion. In conclusion: Applied to the dorsal root, NMDA and kainate receptors act to trigger the limb central pattern generator. The result may provide a therapeutic approach without having to penetrate the CNS. Examining the rhythmic activity can lead to neuron identification, circuit analysis, and simulations. The search is underway to identify the relevant sensory pathways that may be integral to locomotion.

Disclosures: J.T. Hackett: None.

Poster

232. Motor Systems: Sensory Input and Descending Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 232.07/FF5

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH R01 NS095366

Wings for Life

Title: Spinal Shox2 interneurons preferentially receive proprioceptive input from flexor afferents

Authors: *E. Z. LI, D. L. GARCIA-RAMIREZ, L. YAO, K. J. DOUGHERTY
Neurobio. and Anat., Drexel Univ. Col. of Med., Philadelphia, PA

Abstract: Spinal neural networks known as central pattern generators (CPGs) coordinate and control rhythmic motor outputs such as locomotion. Development of appropriately patterned motor output from these networks is dependent on sensory input, as is the restoration of coordinated locomotor activity following spinal cord injury. Despite this, the organization and interaction of afferent input within these spinal circuits is poorly understood. Studies of spontaneous and evoked perturbations of locomotor rhythm and pattern have suggested a two-level CPG organization in which a rhythm-generating layer directs a pattern-generating layer which ultimately controls motor output. During locomotion, sensory input can modify ongoing activity at either level and may therefore reset the rhythm or affect the pattern of the motor output. Afferent input onto rhythm-generating neurons is expected to have the most profound consequences on locomotor activity. Recently, a putative subset of the rhythm-generating kernel was found to be labeled by the transcription factor Shox2. The goal of the present study was to determine the types of afferent input Shox2 neurons receive. We characterized the connectivity of dorsal root and peripheral nerve input into lumbar-level Shox2 interneurons using whole cell patch clamp in reduced isolated spinal cord preparations from neonatal Shox2::Cre ; Ai9 mice. Excitatory and inhibitory postsynaptic potentials (EPSPs and IPSPs) evoked by dorsal root or peripheral nerve stimulation were recorded from visually identified Shox2 interneurons. Most Shox2 neurons were found to receive monosynaptic and polysynaptic EPSPs and/or IPSPs in response to stimulation of the lumbar (L) 5 root. Additionally, many responded to L2 stimulation, with some receiving input from both dorsal roots. No relationship between spinal level and presence of L2 or L5 input was noted. Stimulation of sciatic nerve branches revealed evoked EPSPs or IPSPs in many Shox2 neurons with preferential response to common peroneal nerve stimulation. Asymmetry between flexor-related and extensor-related afferent inputs suggests that Shox2 neurons predominantly modulate CPG activity in response to flexor inputs. In summary, Shox2 neurons at all lumbar levels receive sensory input and may play a role in integrating afferent signaling within the locomotor CPG.

Disclosures: **E.Z. Li:** None. **D.L. Garcia-Ramirez:** None. **L. Yao:** None. **K.J. Dougherty:** None.

Poster

232. Motor Systems: Sensory Input and Descending Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 232.08/FF6

Topic: E.07. Rhythmic Motor Pattern Generation

Support: ERC Grant to OK

Swedish Research Council

Title: An excitatory midbrain motor circuit for evoking freezing behavior

Authors: ***R. LEIRAS**, H. GOÑI-ERRO, D. MASINI, V. CAGGIANO, G. FISONE, O. KIEHN
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Abstract: In a threatening situation, mice commonly run away looking for a place to hide if the danger is imminent –corresponding to a flight response– or they freeze to avoid being detected by a predator passing far away. In both cases, locomotion and precise motor control are essential to perform these opposing defensive responses. Innate naturalistic freezing can be evoked by the presentation of a passing visual stimulus, or by optogenetic activation of glutamatergic neurons in the ventrolateral periaqueductal grey (vlPAG), a midbrain nucleus related since long ago with the performance of fear induced defensive behaviors. However, in this work we show for the first time, using viral approaches in a cell-specific manner, that episodes of defensive freezing can also be specifically evoked in the pedunculopontine nucleus (PPN) by optogenetic activation of Chx10 neurons. This subpopulation of glutamatergic PPN neurons, more abundant in the rostral part of the nucleus, is segregated from the other glutamatergic and cholinergic cells present in the PPN. The evoked freezing events terminate after the offset of the stimulation train. Moreover, we found that Chx10 neurons are also present in the vlPAG, and their optogenetic stimulation is as well sufficient to evoke periods of freezing. We study the inputs to Chx10 neurons in the PPN and vlPAG by trans-synaptic tracing with rabies virus, and we define the target areas of their outputs by the analysis of projections from Chx10-ChR2 transfected neurons, using transmitter specific anterograde tracing. Our results show that Chx10 glutamatergic neurons present at the midbrain PPN and vlPAG are specifically involved in the generation of the motor commands that trigger defensive freezing behavior.

Disclosures: **R. Leiras:** None. **H. Goñi-Erro:** None. **D. Masini:** None. **V. Caggiano:** None. **G. Fisone:** None. **O. Kiehn:** None.

Poster

232. Motor Systems: Sensory Input and Descending Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 232.09/FF7

Topic: E.07. Rhythmic Motor Pattern Generation

Support: KAKENHI 15H04266

Title: The role of the superior colliculus in vibrissa movement

Authors: *M. KANESHIGE[1], K.-I. SHIBATA[2], J. MATSUBAYASHI[1], A. MITANI[1], T. FURUTA[2]
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Abstract: Rhythmic movements, such as breathing, chewing, and walking, are essential behaviors in our life. These rhythmic movements are generated by networks referred to as the central pattern generators (CPGs) in the brain stem and the spinal cord. The CPGs are then modulated by higher-order brain regions such as motor cortices hierarchically. In rodents, their vibrissae are rhythmically moved backward and forward in order to sense the environments. Vibrissa movement is generated by the CPGs located in the intermediate reticular formation (IRt) of the medulla and the pre-Bötzinger complex (PreBötC). In addition, some studies suggest that the superior colliculus (SC) modulates rhythmic whisking as one of the higher-order brain regions. However, how the SC controls vibrissa movement and whether SC neurons project to the CPGs are unknown. In order to understand the role of the SC in vibrissa movement, we performed the following experiments. First, SC-lesioned rats were prepared by passing direct electrical current into the unilateral SC. We recorded vibrissa movement of head-fixed normal rats (control) and SC-lesioned rats in awake by using high-speed video cameras. Repeated forward and backward movements of a vibrissa was represented as a wave. We evaluated the vibrissa position, amplitude, duration (the time when protraction began and retraction ended in one whisk) and the coherence of right and left vibrissa movements. Lesion of the unilateral SC led to the hold contralateral vibrissa at retracted position when rats do not their vibrissae. Also, contralateral vibrissa movements showed different amplitude distributions from control and ipsilateral side. In addition, the durations in bilateral vibrissa movements were longer. In summary, unilateral SC lesion gave the different effects on unilateral (contralateral) and bilateral vibrissa movement at once. In order to identify the neural structures that may generate these effects, we next visualized the projections from the SC to the CPGs. Recombinant virus expressing pal GFP was injected into the unilateral SC and axons of SC neurons were labeled anterogradely. The axons of the SC projected mainly to the contralateral IRt, PreBötC, and facial nucleus. Especially, neurons which reside in lateral region of the SC had marked projections to

the CPGs and facial nucleus. In conclusion, the SC is likely to modulate the position and amplitude of contralateral vibrissa movement by sending the inputs to contralateral CPGs and facial nucleus. Our results suggest the SC involves the execution of precise movement through the control of muscle activity.

Disclosures: **M. Kaneshige:** None. **K. Shibata:** None. **J. Matsubayashi:** None. **A. Mitani:** None. **T. Furuta:** None.

Poster

232. Motor Systems: Sensory Input and Descending Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 232.10/FF8

Topic: E.07. Rhythmic Motor Pattern Generation

Support: HHMI

Title: Birthtime-related hierarchical organization among descending neurons in larval zebrafish

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Abstract: Nervous systems grow substantially after birth in many animals, presumably forming new circuits that implement increasingly complex behaviors animals acquire after birth. Molecular and genetic mechanisms underlying integration of new neurons have been studied extensively. However, relatively little is understood how new neurons are integrated functionally at circuit level. One way to integrate new neurons is to place them in “serial” to existing circuits. This allows the system to directly control the coordination between new neurons and existing circuits but can reduce redundancy of the system. Alternatively, new neurons can be placed in “parallel” to existing circuits. This provides robustness to the system by setting up an alternative pathway to existing circuits however potentially introduces interference to the system because of the lack of explicit coordination. To examine how these arrangements are used to integrate neurons born later, we focus on identifiable descending neurons in larval zebrafish in the context of escape, a behavior that begins with fast body bends but then transitions to slow swim. The oldest neurons of the group, Mauthner cell (M-cell), plays a critical role for the initial powerful body bend during the escape. On the other hand, some of the neurons born later were shown to be active during the slow swim. Thus, we have an opportunity to examine how the nervous systems use “parallel” and “serial” arrangements to integrate neurons born at different time points and produce one cohesive sequence of movements during the escape. Here we examined the response of descending neurons during the sensory-driven escape and the response triggered by single-cell M-cell stimulation with two-photon Ca2+ imaging and whole-cell recording. This allowed us to dissociate neurons under “serial” arrangement that can be driven by M-cell, from

neurons under “parallel” arrangement that require sensory inputs for recruitment. Results so far indicate that descending neurons are hierarchically organized using both “parallel” and “serial” organizations but to different extents depending on the age: the older group is largely “parallel” to M-cell thus require sensory inputs for recruitment and contribute to the initial phase of escape. In contrast, the younger group is in “serial” arrangement thus can be driven by M-cell alone and contribute to the late phase of escape. Femtosecond laser ablation of each group exhibited deviations from typical escape behavior that appear to be consistent with this hierarchical organization. Regional cell-type specific manipulations will reveal the implementation of this organization at the level of defined cell-type.

Disclosures: **M. Tanimoto:** None. **A. Pujala:** None. **M. Koyama:** None.

Poster

232. Motor Systems: Sensory Input and Descending Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 232.11/FF9

Topic: E.07. Rhythmic Motor Pattern Generation

Support: Ministère de l'enseignement superieur et de la recherche

Title: Serotonergic modulation of locomotor outputs induced by sacral dorsal root stimulation in the isolated neonatal rat spinal cord preparation

Authors: *Z. OUEGHLANI, F. M. LAMBERT, G. COURTAND, L. CARDOIT, F. MASMEJEAN, J.-R. CAZALETS, G. BARRIÈRE
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Abstract: Serotonergic projections from the brainstem’s raphe nuclei to the spinal cord play a major neuromodulatory role in the integration of segmental sensory afferent information and the control of motor activities. For instance it is well established that serotonin is involved in the control of the spinal motoneuron and interneuron excitability and also sensory afferent transmission (reflex pathways). Thanks to electrophysiological and pharmacological approaches, we show in our study that electrical stimulation of sacral dorsal root induces locomotor-like activity in lumbar segments. But, even though left-right alternation at L2 level was observed in every preparation, flexor-extensor (L2/L5) alternation seems to occur in an age-dependent manner. Indeed L2/L5 activity was mainly alternate in P0/P1 preparations whereas it was mainly synchronous in P4/P5 preparations. However, in presence of serotonin at subthreshold concentrations (10µM), all the preparations of all ages presented both left-right and flexor-extensor alternation. This study brings additional data to the importance of both descending serotonergic pathways and sensory afferents in shaping locomotor activity.

Disclosures: **Z. Oueghlani:** None. **F.M. Lambert:** None. **G. Courtand:** None. **L. Cardoit:** None. **F. Masmejean:** None. **J. Cazalets:** None. **G. Barrière:** None.

Poster

232. Motor Systems: Sensory Input and Descending Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 232.12/FF10

Topic: E.07. Rhythmic Motor Pattern Generation

Support: Grant-in-Aid for Scientific Research KAKENHI 15H01587

RIKEN Medical Sciences Innovation Hub Program

Title: Sensory-motor interaction in the Parabrachial nucleus for relationship between body movement and respiration

Authors: ***A. ARATA**[1], S. IWANO[2], T. NOMA[2], S. TONOMURA[3], A. TAMAKI[2]
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Abstract: Parabrachial nucleus (PB) located in the dorsal part in the pons. It is thought to be correlated with the autonomic function and the relationship of sensory-motor procedure. The PB is also known as a respiratory modulating center and the PB plays a crucial role in the inspiratory-expiratory phase switching. In this study, we focused to examine how the PB participates in the relationship between respiration and body movement using pons-medulla-spinal cord preparations obtained from 0 to 4 days old rats. First, the effects of C8 dorsal root/L4 dorsal root electrical stimulation on C4 ventral root inspiratory activity were examined. The electrical stimulation of dorsal root in C8 (brachial input) level or L4 (pedal input) level induced respiratory rhythm resetting. Here we describe the respiratory neurons in the dorsal pons and their interacting the respiration and body movement (fetal movement). We found several types of respiratory neurons; inspiratory, tonic inspiratory, expiratory and inspiratory-expiratory (I-E) neurons in the PB using whole cell patch clamp method. The population of I-E neuron was major of the recorded neuron. When PB was stimulated electrically, respiratory rate was increased. I-E neurons might determine respiratory cycle using inspiratory-expiratory phase switching. On the other hand, the body movement remained activity even if medulla was removed, but the frequency of body movement significantly decreased. It was suggested that the body movement generated in spinal cord might receive some excitatory input from the medulla. When the neuron in the spinal cord was recorded, the neurons receiving both respiratory and body movement inputs; the neurons receiving respiratory only; and the neurons receiving only body movement input were existed in C4 area. Moreover, the dorsal root stimulus of C8 was projected to PB was

confirmed using optical imaging. It was considered that these C8 (or L4) dorsal root stimulation, pretended hand (or foot) sense stimulation, were induced respiratory facilitation via PB; because it could not occur without pons. These results suggested that sense of hand and foot is projected on PB, then I-E neuron in the PB activated respiratory rhythm. In the relationship between respiration and body movement, the respiratory rhythm excitation might activate the body movement that circuit possibly exists in the spinal cord.

Disclosures: A. Arata: None. **S. Iwano:** None. **T. Noma:** None. **S. Tonomura:** None. **A. Tamaki:** None.

Poster

232. Motor Systems: Sensory Input and Descending Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 232.13/FF11

Topic: B.09. Physiological Properties of Neurons

Support: DFG CRC 1080

Title: Differences in phasic burst activity *In vivo* revealed by axonal projection-specific characterization of DA neurons within the medial substantia nigra

Authors: *N. FARASSAT[1], K. M. COSTA[1], M. SOMAYAJI[3,1], G. SCHNEIDER[2], J. ROEPER[1]
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Abstract: Based on their axonal targets, midbrain dopamine (DA) neurons might be segregated into at least three major populations - nigrostriatal, mesolimbic and mesocortical DA neurons. These distinct DA neurons are distributed across the substantia nigra (SN) and ventral tegmental area (VTA) in a loose and partially overlapping topographical order (Lammel et al. 2008). This is particularly relevant in the medial SN(m-SN), where nigrostriatal and mesolimbic DA neurons intermingle and can therefore not be distinguished solely by *in vivo* juxtacellular labeling to define their respective positions (Subramaniam et al. 2014). Therefore, we combined in vivo projection-specific retrograde labeling with Fluorogold (FG) with single-unit in vivo extracellular recording and juxtacellular labeling of DA SN neurons in anaesthetized adult 3 month-old C57Bl6N mice. In comparison to anatomical retrograde labeling studies of the DA system in mice (Liu et al. 2003; FG 4%, 0.5 µl), an about 2000-fold reduction of the FG concentration (0.002% FG, 0.5µl) was necessary to prevent not only intrastriatal lesions but also disturbed *in vivo* activity of FG-overloaded DA midbrain neurons.
We then applied our validated method to record from DA neurons in the m-SN that either projected to the dorsal striatum or the lateral shell of the nucleus accumbens.

We found that while the tonic background activities of identified mesolimbic and nigrostriatal DA m-SN neurons were similar, mesolimbic DA m-SN neurons displayed a significantly higher burstiness with increased maximal frequencies as well as a higher number of pauses (nigrostriatal (n=18): firing frequency 3.4 ± 0.3 Hz, CV 43.8 ± 4.1 %, AP duration: 2.2 ± 0.1ms, SFB 1.9 ± 1.1 %, bursts per minute 2.4 ± 1.8, max. firing frequency 16.6 ± 1.5 Hz, pauses per minute 1.1 ± 0.1; mesolimbic (n=14): firing frequency 3.4 ± 0.3 Hz, CV 53.8 ± 8.0%, AP duration: 2.1 ± 0.1 ms, SFB 8.0 ± 4.1%, bursts per minute 5.4 ± 1.8, max. firing frequency 26.6 ± 3.9 Hz, pauses per minute 1.5 ± 0.1). These distinct features might help to differentiate mesolimbic and nigrostriatal DA m-SN neurons under recording conditions where juxtacellular labelling and retrograde tracing methods are not easily applicable, e.g. in awake freely moving animals.

Disclosures: **N. Farassat:** A. Employment/Salary (full or part-time):; Goethe Universität Frankfurt. **K.M. Costa:** None. **M. Somayaji:** None. **G. Schneider:** None. **J. Roeper:** None.

Poster

232. Motor Systems: Sensory Input and Descending Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 232.14/FF12

Topic: E.07. Rhythmic Motor Pattern Generation

Title: Molecular characterization of a spinal sacral interneuron population with long ascending propriospinal projections to high lumbar locomotor regions

Authors: *D. A. DESKA-GAUTHIER, Y. ZHANG
Med. Neurosci., Dalhousie Univ., Halifax, NS, Canada

Abstract: The spinal cord has the innate ability to generate locomotion in response to sensory stimuli, independent of input from the brain. In particular, propriospinal neurons within the intermediate region of the lumbosacral spinal cord can mediate sensory induced locomotion in rodents. However, the genetic identity and precise connectivities of these locomotor initiating interneurons (INs) are unknown and therefore cannot be directly targeted, *in vivo*. Our current work has begun to characterize molecularly and anatomically distinct populations of excitatory lumbosacral INs that are anatomically reminiscent of sacral INs previously described as locomotor inducing sacral INs. We have identified a lumbosacral excitatory IN population marked by the unique expression profile of transcription factors, Sim1 and Nr3B3, and the calcium binding protein, calretinin (CR). Sim1/Nr3B3/CR-expressing (SNC+) INs form a distinct intermediate column throughout the lumbosacral spinal cord. SNC+ INs possess large dendritic branches and receive dense local excitatory and sensory inputs. Additionally, SNC+ INs project long propriospinal commissural axons that heavily innervate laminae VII and VIII of the lower thoracic and higher lumbar spinal cord segments. Taken together, our preliminary

results indicate SNC+ INs as potential sacral relay INs that have previously been linked to mediating sacral induced locomotion.

Disclosures: D.A. Deska-Gauthier: None. **Y. Zhang:** None.

Poster

233. Respiratory Rhythm and Pattern Generation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 233.01/FF13

Topic: E.08. Respiratory Regulation

Support: Intramural Research Program of NIH/NINDS

NIH Grant NS069220

NIH Grant AT008632

Title: Inhibitory interactions in the brainstem respiratory circuits: Insights from optogenetic studies and computational modeling

Authors: *J. AUSBORN[1], H. KOIZUMI[2], W. H. BARNETT[3], T. JOHN[2], R. ZHANG[2], Y. I. MOLKOV[3], J. C. SMITH[2], I. A. RYBAK[1]
[1]Neurobio. & Anat., Drexel Univ. Col. of Med., Philadelphia, PA; [2]Cell. & Systems Neurobio. Sec., NINDS, NIH, Bethesda, MD; [3]Dept. of Mathematics and Statistics, Georgia State Univ., Atlanta, GA

Abstract: The circuit organization within the mammalian ventral respiratory column, specifically within and between the pre-Bötzinger (pre-BötC) and Bötzinger (BötC) complexes and their involvement in respiratory pattern generation are under continuous debate. To shed light on this organization, we used *in situ* perfused brainstem-spinal cord preparations of transgenic mice expressing ChR2 in both GABAergic and glycinergic inhibitory neurons. Site-specific laser stimulations were used to selectively activate inhibitory neurons in the pre-BötC or BötC regions. We used single light pulses (0.1 - 3 s) delivered at different phases of the respiratory cycle, series of pulses, and sustained light stimulations (20 Hz, 20 ms pulse trains). The effects of these stimulations were dependent on stimulation intensity and phase of application. Specifically: (1) Low intensity (< 2 mW) pulses delivered to the pre-BötC during inspiration did not terminate activity, whereas stronger stimulations (≥ 2 mW) reliably terminated inspiration. When the pre-BötC stimulation ended in or was applied during expiration, a rebound activation of inspiration occurred after a fixed latency. (2) Relatively weak sustained stimulation (20 Hz, 0.5 - 2 mW) of the pre-BötC increased respiratory frequency, while a further increase of stimulus intensity (≥ 2mW) reduced frequency and finally (≥ 4mW) terminated respiratory oscillations. (3) Single pulses (0.1 - 3 s) of low or high intensity applied to

the BötC inhibited rhythmic activity for the duration of the stimulation. (4) Sustained stimulation (20 Hz, 0.5-3 mW) of the BötC reduced respiratory frequency and produced apnea when stimulation intensities where increased further (≥ 3 mW). (5) Series of pulses applied to the pre-BötC or BötC were able to entrain the respiratory rhythm.
We have revised our computational model of the pre-BötC and BötC microcircuits by incorporating an additional population of post-inspiratory inhibitory neurons in the pre-BötC that is involved in inhibitory interaction with other neurons in the network. The model assumes that the early-inspiratory neurons in the pre-BötC are less sensitive to light stimulations than the other inhibitory neurons. The model was able to reproduce the above experimental findings as well as previously published results of optogenetic activation of pre-BötC and BötC neurons (Asahafi et al., 2015; Sherman et al., 2015). The proposed organization of interactions between and within the pre-BötC and BötC leads to a number of testable predictions about their specific role in respiratory pattern generation and provides important insights into circuit organization in the respiratory brainstem.

Disclosures: **J. Ausborn:** None. **H. Koizumi:** None. **W.H. Barnett:** None. **T. John:** None. **R. Zhang:** None. **Y.I. Molkov:** None. **J.C. Smith:** None. **I.A. Rybak:** None.

Poster

233. Respiratory Rhythm and Pattern Generation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 233.02/FF14

Topic: E.08. Respiratory Regulation

Support: NIH Grant R01 HL104127 (PI: Del Negro)

Title: Optogenetic inhibition of Dbx1 preBötzinger complex neurons perturbs breathing in vagus-intact adult mice

Authors: N. C. VANN, F. D. PHAM, K. DORST, *C. A. DEL NEGRO
Dept. of Applied Sci., Col. of William and Mary Dept. of Applied Sci., Williamsburg, VA

Abstract: Breathing is essential behavior for humans and all terrestrial mammals. The rhythmic oscillations for inspiratory breathing movements originate from a heterogenous region in the ventral medulla called the preBötzinger complex (preBötC). Within the preBötC interneurons derived from Dbx1-expressing precursors (i.e., Dbx1 neurons) putatively comprise the core oscillator circuit. Data supporting the Dbx1 core hypothesis have been obtained from embryonic and neonatal rodents, but are sparse for mature adults. Here we test the Dbx1 core hypothesis in adult mice using intersectional mouse genetics. Using the Ai40D reporter mouse (lsl-ArchT-EGFP) crossed with a Dbx1-Cre^{ERT2} driver, we expressed the proton pump Archaerhodopsin-3 (ArchT) in Dbx1 neurons. In a slice model of breathing, ArchT activation resulted in a ~12 mV

hyperpolarization in ArchT-expressing Dbx1 neurons in patch-clamp recordings as well as ~30s cessations of rhythm and motor output. In vagus-intact adult mice, Graded optogenetic inhibition of Dbx1 preBötC neurons with 5-s light pulses caused graded reductions in respiratory frequency up to and including apnea. Shorter duration (100 ms) light pulses caused phase dependent shifts in respiratory rhythm. By inhibiting Dbx1 neurons in an attempt to reset the core oscillator during post-inspiration we induced a phase advance and conversely during the preinspiratory or early inspiratory phases a phase delay was induced. During the peak of the inspiratory phase ArchT resets resulted in either no phase shift or a phase delay. These data suggest that Dbx1 preBötC neurons generate respiratory rhythm in adult mice, as already shown for embryonic and neonatal mice, i.e., the Dbx1 core hypothesis. These data do not rule that Dbx1 preBötC neurons play other roles (respiratory and non-respiratory) too. Dbx1 preBötC provide a well-defined target for investigations that elucidate the cellular, synaptic, and molecular-level neural mechanisms of breathing in mammals.

Disclosures: **N.C. Vann:** None. **F.D. Pham:** None. **K. Dorst:** None. **C.A. Del Negro:** None.

Poster

233. Respiratory Rhythm and Pattern Generation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 233.03/FF15

Topic: E.08. Respiratory Regulation

Support: NIH - NIHDS / DIR

Title: Imaging and spatial mapping of the rhythmic glutamatergic neuron population by genetically-encoded calcium sensor within the pre-Botzinger complex of neonatal transgenic mouse

Authors: *N. KOSHIYA, H. KOIZUMI, T. JOHN, Y. CHEN, R. ZHANG, J. C. SMITH
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Abstract: Inspiratory rhythmic activity is generated in mammals within the pre-Bötzinger complex (pre-BötC) region located in the ventrolateral medulla. Calcium-sensitive dye imaging and electrophysiological studies have indicated that the excitatory neuron population crucial for rhythm generation is distributed within the reticular formation ventral to the nucleus ambiguus semicompacta (NAsc). We do not know, however, the 3D spatial layout of these rhythmic excitatory neurons and how this spatial organization may reflect their rhythmogenic function. We are imaging the activity and mapping locations of these neurons in rhythmically active neonatal medullary *in vitro* slices from a transgenic mouse line expressing the fluorescent genetically-encoded calcium sensor GCaMP6f in glutamatergic (VgluT2-expressing) neurons. The rhythmically active medullary slice (~400 µm thick) was cut so that rhythmic neurons were

exposed on the caudal surface, and we systematically imaged the pre-BötC region and surrounding reticular formation through this surface with two-photon laser scanning microscopy employing high-speed image acquisition (512 x 512 pixels, 438 µm square at ~28 fps). XYZ image stacks were acquired while oscillating the focal plane through the depth of the slice (~300 µm from the caudal surface) for T cycles (typically T=200) to obtain an XYZT volume. This volume was acquired along with the hypoglossal nerve activity, which reflects pre-BötC activity as a monitor of inspiratory circuit activity in the slice, and XY frames during inspiratory phases were extracted and compared to baseline (expiratory) frames at each Z-level to compute dynamic fluorescence ratios to identify the rhythmically active inspiratory neurons. Active cells were computationally segmented and located in the XYZ coordinate by cluster computer-based semi-automated imaging analyses. The set of inspiratory cells located in 3D ventral to NAsc comprised a subpopulation of the glutamatergic neurons expressing GCaMP6f distributed though the depth of the slice. The present results indicate that our transgenic mouse line and dynamic imaging approach should allow a volumetric reconstruction of the active population of inspiratory pre-BötC excitatory neurons.

Disclosures: **N. Koshiya:** None. **H. Koizumi:** None. **T. John:** None. **Y. Chen:** None. **R. Zhang:** None. **J.C. Smith:** None.

Poster

233. Respiratory Rhythm and Pattern Generation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 233.04/FF16

Topic: E.08. Respiratory Regulation

Support: NIH Grant R01-HL104127

NIH Grant R21-NS087257

NIH Grant R15-HD077624

NSF Grant 1257895

Title: Transcriptome of neonatal preBötzinger complex neurons in Dbx1 reporter mice

Authors: *J. A. HAYES[1], A. KOTTICK[4], M. D. PICARDO[5], A. D. HALLERAN[2], R. D. SMITH[3], G. D. SMITH[7], M. S. SAHA[6], C. A. DEL NEGRO[8]
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Abstract: We sequenced the transcriptome of brainstem interneurons in the specialized respiratory rhythmogenic site dubbed preBötzinger Complex (preBötC) from newborn mice. To distinguish genetic features of the core oscillator we compared preBötC neurons derived from Dbx1-expressing progenitors that are respiratory rhythmogenic to neighboring non-Dbx1-derived neurons, which support other respiratory and non-respiratory functions. Here, we first find that Dbx1 preBötC neurons express κ-opioid receptors four-fold in excess of μ-opioid receptors that heretofore have been associated with opiate respiratory depression, which may have clinical applications. Second, we detected a suite of transcription factors including *Hoxa4* that may define the rostral preBötC border, *Pbx3* that may influence ipsilateral connectivity, and *Pax8* that may differentiate a ventrally-derived subset of Dbx1 preBötC neurons. Third, Dbx1 preBötC neurons express the hypoxia-inducible transcription factor *Hif1a* at three-fold higher levels than non-Dbx1 neurons, which links core rhythmogenic microcircuits to O_2-related chemosensation for the first time. These data can be exploited both to manipulate the development and physiology of Dbx1 and non-Dbx1 preBötC neurons and thus further test their roles in respiratory neurobiology.

Disclosures: J.A. Hayes: None. **A. Kottick:** None. **M.D. Picardo:** None. **A.D. Halleran:** None. **R.D. Smith:** None. **G.D. Smith:** None. **M.S. Saha:** None. **C.A. Del Negro:** None.

Poster

233. Respiratory Rhythm and Pattern Generation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 233.05/FF17

Topic: E.08. Respiratory Regulation

Support: JSPS KAKENHI Grant

Title: Identification of respiratory modulated astrocytes in the ventrolateral medulla of the isolated brainstem-spinal cord by confocal calcium imaging

Authors: *Y. OKADA[1], I. YAZAWA[2], S. OKAZAKI[3,1], S. YOKOTA[4], K. TAKEDA[5,1], H. SOMEYA[6], Y. TAMURA[7], H. ONIMARU[8]
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Abstract: It has been clarified that astrocytes are involved in nearly all aspects of the brain function by actively communicating with neurons. Indeed, we discovered respiratory modulated

astrocytes in rhythmically active medullary slices, suggesting the participation of astrocytes in respiratory rhythm generation (Okada et al., 2012). In the present study, we aimed to reveal the involvement of astrocytes in respiratory rhythm generation in the isolated brainstem-spinal cord preparation of the neonatal rat, which has a more integrated network structure than slices. The preparation was bent at the medullo-spinal cord junction so that the rostral cut surface, which was at the level rostral to the preBotzinger complex, was horizontal. A calcium indicator Oregon Green was pressure-injected into the ventrolateral medulla. Cellular activities in the ventrolateral medulla together with inspiratory C4 output were firstly recorded in the normal condition, and secondly in the presence of TTX with a confocal calcium imaging system (Yokogawa Electric, Tokyo). Then, recorded cells were classified into neurons and astrocytes by lowering the superfusate potassium concentration to 0.2 mM with TTX. Lowered potassium induced vigorous intracellular calcium rises in astrocytes but not in neurons (Dallwig and Deitmer, 2002). Cross correlation with inspiratory C4 output revealed that activities of a number of astrocytes were respiratory modulated. We found astrocytes with various patterns of respiratory modulation, including inspiratory, pre-inspiratory and expiratory patterns. These astrocytes had intrinsic oscillatory properties, because they were spontaneously active in the presence of TTX. Further studies are needed to clarify the precise role of astrocytes in respiratory rhythm generation.

Disclosures: **Y. Okada:** None. **I. Yazawa:** None. **S. Okazaki:** None. **S. Yokota:** None. **K. Takeda:** None. **H. Someya:** None. **Y. Tamura:** None. **H. Onimaru:** None.

Poster

233. Respiratory Rhythm and Pattern Generation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 233.06/FF18

Topic: E.08. Respiratory Regulation

Support: Grant-in-Aid for Scientific Research B (26280109)

Grant-in-Aid for Scientific Research C (15K08196)

Grants from the Deutsche Forschungsgemeinschaft (DFG) (HI1414/2-1)

Grants from the Deutsche Forschungsgemeinschaft (DFG) (HU797/7-1)

Title: Neuronal type-dependent stochastic activation sequence among inspiratory neurons during rhythmic burst in the pre-Bötzinger complex of the mice medulla slice

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Abstract: The pre-Bötzinger complex (preBötC) is one of the important medullary regions, which are required for generation of spontaneous respiratory rhythm, especially inspiratory rhythm. In the medullary transverse slice, inspiratory neurons can be detected as cells activated synchronously with inspiratory rhythmic bursts at the preBötC. We had already shown that activation sequences among inspiratory neurons change stochastically at every rhythmic burst while under loose regularities. In this study, assuming that neuronal types might be involved in establishment of the loose regularities, we investigated the activation sequences with classification according to neuronal types. Ca^{2+} imaging was conducted to observe neuronal activities using slice prepared from TG mice expressing EGFP in GlyT2+ neurons and tdTomato in GAD65+ neurons, which enabled inspiratory neurons to be identified as glycinergic, GABAergic or putative excitatory neurons. Inspiratory neurons could be further classified into regular or irregular types with reference to correlation between Ca^{2+} fluctuation and bursting pattern in a local field potential. We classified five types of inspiratory neurons, which were regular and irregular types of putative excitatory and GlyT2+/GAD65- neurons, and irregular types of GlyT2+/GAD65+ neurons. Peak timing of Ca^{2+} fluctuation during a rhythmic burst was compared among inspiratory neurons for evaluation of the activation sequence. Then, the ratio of activation occurrence at each activation order was calculated in each type of neuron. In the activation sequences, irregular types of putative excitatory and GlyT2+/GAD65- neurons were mainly activated at the initial phase, next both regular types of neurons, and then regular type of putative excitatory neurons sequentially. At the last phase, irregular type of GlyT2+/GAD65+ neurons were mostly activated. Moreover, there was no obvious relationship between spatial distribution of inspiratory neurons and the trends of activation occurrence on the activation sequence in individual inspiratory neurons. Therefore, we suppose that neuronal types rather than spatial location of inspiratory neurons might contribute to establish the loose regularities for the activation sequences during the rhythmic bursts.

Disclosures: Y. Oke: None. **F. Miwakeichi:** None. **Y. Oku:** None. **S. Besser:** None. **J. Hirrlinger:** None. **S. Hülsmann:** None.

Poster

233. Respiratory Rhythm and Pattern Generation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 233.07/FF19

Topic: B.05. Transporters

Support: 5SC1MH086070

CORE:NIH-NIMHD-RCMIGrant No. 5G12MD007592

RISE R25GM069621-11

Title: Diversity of glycinergic neurons in the PreBotzinger complex of mice

Authors: *S. L. RODRIGUEZ, V. GARCIA, R. A. PEREZ, M. MIRANDA
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Abstract: The PreBotzinger Complex, located in the hindbrain, is the primary breathing rhythm generator in the autonomic system. Previous studies have shown that the PreBotzinger Complex contains a large portion of glycinergic interneurons, labeled by the presence of the glycine transporter 2 (GlyT2). Although the glycine transporter 1 (GlyT1) has been reported to be found in glial cells, our results demonstrate that GlyT1 is located mainly in neurons from several areas of the medulla, including the PreBotzinger nuclei. We used brain sections from a transgenic line expressing GFP under control of GlyT2 promoter combined with immunostaining to show the presence of GlyT1 in GFP-positive neurons and others devoid of GFP. These two types of neurons were found within the PreBotzinger and surrounding areas. Staining with several neuronal markers such as MAP2 and NeuN, as well as GlyT1 displayed compelling evidence of co-localization of GlyT1 in neurons. Altogether, this data strongly support the presence of GlyT1 in neurons in the PreBotzinger Complex. We speculate that these new GlyT1-containing neurons represent an additional neuronal population that participates in the hindbrain respiratory functions.

Disclosures: S.L. Rodriguez: None. **V. Garcia:** None. **R.A. Perez:** None. **M. Miranda:** None.

Poster

233. Respiratory Rhythm and Pattern Generation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 233.08/FF20

Topic: E.08. Respiratory Regulation

Support: F32HL13407

NIH HL 126523

Title: Inhibition is critical for permitting rapid dynamic respiratory rhythms

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Abstract: The preBötzinger Complex (preBötC), located in the medulla, generates the inspiratory phase of breathing. Glutamatergic neurons derived from precursors that express the transcription factor Dbx1 during development ("Dbx1 neurons") are necessary for breathing and form the rhythmogenic "core" of the preBötC. However, the preBötC is a heterogeneous network that contains multiple subpopulations of molecularly defined neurons and receives a rich array of neuromodulatory and sensory feedback inputs. Only ~50% of preBötC glutamatergic neurons are derived from Dbx1 expressing precursors, and an additional ~50% of preBötC neurons are inhibitory. In rhythmically active brainstem slices containing the preBötC, optogenetic stimulation of Dbx1 neurons closely following a population burst cannot evoke a subsequent burst. This "refractory period" persists for ~2 seconds suggesting excitatory Dbx1 neurons have a limited ability to drive high respiratory frequencies (rf). How excitatory preBötC mechanisms overcome this refractory period to accommodate the rapid and dynamic breathing typical in behaving animals is unknown. In this study, we combined targeted optogenetic manipulations with electrophysiology in rhythmically active brainstem slices and anesthetized adult mice to explore how subpopulations of excitatory and inhibitory preBötC neurons interact to control breathing frequency. We hypothesized that hyperactivity of excitatory neurons results in a refractory period for preBötC bursting, while the phasic activity of inhibitory neurons limits the refractory period. We demonstrate that 1) preBötC neurons have an intrinsic refractory period that is proportional the amount of depolarization during simulated network activity, 2) inhibitory neurons limit depolarization of excitatory neurons during preBötC bursting, 3) blockade of inhibition lengthens the refractory period and slows, but does not stop, the preBötC rhythm, 4) inhibitory sensory feedback plays a critical role within the preBötC to limit the refractory period, 5) the refractory periods of Dbx1 and excitatory non-Dbx1 neurons are differentially modulated by inhibitory sensory feedback, 6) stimulation of inhibitory neurons during inspiration paradoxically increases breathing frequency far beyond frequencies achieved by excitation. Thus, we propose a preBötC architecture in which inhibitory neurons integrated within the active network are critical to limit hyperactivity of excitatory neurons and permit the rapid and flexible breathing frequencies that are essential for life.

Disclosures: **N.A. Baertsch:** None. **J.M. Ramirez:** None.

Poster

233. Respiratory Rhythm and Pattern Generation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 233.09/FF21

Topic: E.08. Respiratory Regulation

Support: NIH HL074011

NIH HL028785

NIH HL108609

Title: Characterization of the retrotrapezoid nucleus by mRNA expression

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Abstract: The retrotrapezoid nucleus (RTN) comprises the glutamatergic, non-catecholaminergic, Phox2b-expressing neurons and resides below and around the facial motor nucleus. A large but undefined fraction of RTN neurons are activated by hypercapnia and drive breathing. Their intrinsic CO_2 sensitivity is primarily mediated by two proton detectors, TASK-2 and GPR4. Here, we used single-cell (sc) RNA-Seq (61 GFP-labeled RTN neurons isolated from P5-P118 Phox2b-GFP BAC (JX99) transgenic mice; N=7) and *in situ* hybridization (ISH, from adult JX99 and C57B6 mice) to identify neuropeptides expressed by mouse RTN neurons and to determine whether these neurons contain TASK-2 and GPR4 mRNA. We also identified RTN neurons that express c-Fos after exposure to room air (21% O_2, balance N_2 ; N=11), hypercapnia (15% CO_2, 21% O_2, balance N_2; N=7) or hypoxia (8% O_2, balance N_2; N= 5) for 35 min, and determined whether the c-Fos-expressing RTN neurons contain GPR4 mRNA. By *in situ* hybridization, Neuromedin B (Nmb) mRNA was expressed by ~700 neurons in the mouse RTN (with Abercrombie correction). All Nmb^+ RTN neurons expressed Phox2b and VGlut2, but contained neither GAD1 nor tyrosine-hydroxylase transcripts. The Nmb^+ neurons contained transcripts for prepro(pp)-PACAP (90%, by ISH), pp-galanin (70%, by ISH), and pp-enkephalin (67%, by ISH). In parallel, these same transcripts were detected by scRNA-Seq in a large majority of RTN neurons (Nmb and PACAP transcripts in 100% of RTN neurons; Gal in 88.5% and Penk in 98.4%), albeit at highly variable levels in individual cells. By ISH and scRNA-Seq, most Nmb^+ neurons contained TASK-2 (>90% and 88.5%) and GPR4 mRNA (~80% and 93.4%, respectively), with GPR4 the most highly expressed G protein-coupled receptor in RTN neurons. In CO_2-exposed mice, >90% of Nmb^+ /$GPR4^+$ neurons contained c-Fos-mRNA; the proportion was ~2% and 5% in the control and hypoxia cohorts, respectively. Nmb^+ neurons without GPR4 (~18% by ISH) did not express c-Fos in mice exposed to either hypercapnia or hypoxia (<1%); these neurons were larger than average and often resided more laterally and further from the ventral medullary surface. Quantitative analysis by sc-RNA-Seq revealed an inverse relationship between the level of NMB transcripts and those of GPR4 and TASK-2. In conclusion, in the perifacial region of the mouse, Nmb identifies a large subset of RTN neurons. Most perifacial Nmb+ neurons express GPR4 (>80%) and TASK-2 (~90%) and are likely RTN respiratory chemoreceptors in mice. A small subset of Nmb^+ neurons, particularly those with high levels of Nmb, express GPR4 and TASK-2 at low or undetectable levels and appear to respond neither to hypercapnia nor to hypoxia.

Disclosures: R.L. Stornetta: None. **Y. Shi:** None. **D.S. Stornetta:** None. **S. Onengut-Gumuscu:** None. **E. Farber:** None. **S.D. Turner:** None. **D.A. Bayliss:** None. **P.G. Guyenet:** None.

Poster

233. Respiratory Rhythm and Pattern Generation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 233.10/FF22

Topic: E.08. Respiratory Regulation

Support: NIH/NCCAM R01 AT008632

FAPESP 2013/17251-6

Title: Local glutamatergic transmission in the RTN/pFRG is critical for active expiration and sympathetic overactivity during hypercapnia

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Abstract: The retrotrapezoid nucleus (RTN) contains chemosensitive cells that distribute CO_2-dependent excitatory drive to the brainstem respiratory network. This drive facilitates the function of the respiratory central pattern generator (CPG), modulates sympathetic activity and determines the emergence of active expiration during hypercapnia via activation of the late expiratory (late-E) oscillator in the parafacial respiratory group (pFRG). However, the microcircuitry responsible for distribution of the chemoreflex signal to the pFRG and the respiratory CPG is not well understood. Previously, we developed a computational model of the brainstem respiratory network, which was subsequently extended to include the central and peripheral chemoreflexes as well as pre-sympathetic circuits. We present here experiments performed on the decerebrated, arterially-perfused *in situ* rat, aimed to test a key assumption of this model that chemosensitive and late-E neurons in the RTN/pFRG are two distinct populations, and the latter receives local glutamatergic input from the former. The model predicts: (1) suppression of RTN chemosensitive neurons will diminish the changes to the respiratory pattern and the emergence of active expiration associated with hypercapnia; (2) the disruption of local glutamatergic neurotransmission in the RTN will specifically suppress active expiration and the appearance of late-E discharges in the sympathetic motor output. To test prediction (1) we lesioned $NK1_R$-positive chemosensitive neurons of the RTN with microinjections of substance P-saporin (SSP-SAP) conjugate. This suppressed the emergence of late-E activity in abdominal (AbN) and sympathetic nerves, and attenuated the increase in phrenic burst amplitude during hypercapnia. However, SSP-SAP and control animals exhibited late-E AbN activity in response to peripheral chemoreflex activation. Prediction (2) was tested

with bilateral microinjections of kynurenic acid (Kyn, 100 mM) in the RTN/pFRG, which suppressed the emergence of late-E AbN activity but not the change in phrenic nerve amplitude during hypercapnia. Our results support the notion that RTN chemosensitive neurons are critical for inspiratory and expiratory reflex responses to hypercapnia. Our findings indicate that activation of late-E neurons in the pFRG during hypercapnia requires glutamatergic inputs from a separate neuronal population in the RTN that intrinsically detects changes in CO_2. During peripheral chemoreflex stimulation, pFRG late-E neurons are activated via excitatory pathways bypassing the RTN central chemoreceptors. We recapitulate these results in our computational model.

Disclosures: **W.H. Barnett:** None. **Y.I. Molkov:** None. **E. Lemes:** None. **B. Falqueto:** None. **E. Colombari:** None. **A.T. Takakura:** None. **T.S. Moreira:** None. **D.B. Zoccal:** None.

Poster

233. Respiratory Rhythm and Pattern Generation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 233.11/GG1

Topic: E.08. Respiratory Regulation

Support: NIH HL104101

Title: Adenosine inhibits activity of chemosensitive neurons in the retrotrapezoid nucleus

Authors: *S. JAMES[1], V. E. HAWKINS[1], B. FALQUETTO[2], L. M. OLIVEIRA[4], A. T. TAKAKURA[5], T. S. MOREIRA[3], D. K. MULKEY[6]
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Abstract: The brain regulates breathing in response to changes in tissue CO_2/H^+ via a process termed central chemoreception. Neurons and astrocytes in a brainstem region known as the retrotrapezoid nucleus (RTN) function as respiratory chemoreceptors. The role of astrocytes in this process involves CO2/H+-dependent release of ATP to enhance activity of chemosensitive RTN neurons. Considering that in most brain regions extracellular ATP is rapidly broken down to adenosine by ectonucleotidase activity, we wondered whether adenosine signaling contributes to RTN chemoreceptor function. To explore this possibility, we pharmacologically manipulated activity of adenosine receptors in the RTN under control conditions and during high CO2 both in vitro and in awake and sedate rats. At the cellular level, slice-patch recordings from RTN chemoreceptors show that bath application of adenosine (1 µM) inhibited neural activity under control conditions and during high CO2. Bath application of an adenosine receptor blocker (8-

PT; 10 μM) increased basal activity (0.45 ± 0.1 Hz) and caused a modest increase in the firing response to CO2. Adenosine-mediated inhibition of chemorecpetor activity was also blunted by prior incubation with an A1 receptor antagonist 8-Cyclopentyl-1,3-dipropylxanthine (DPCPX; 30nM). In voltage clamp (Vhold=-60 mV, TTX 1μM) adenosine had no measurable effect on holding current or conductance, suggesting the effects of adenosine are mediated by synaptic rather than intrinsic mechanisms. In urethane-anesthetized rats we found bilateral RTN injection of adenosine (25 mM - 100 nl) blunted the effects of CO_2 on inspiratory activity [diaphragm frequency (8.5 ± 3 vs. vehicle: 40 ± 2%) and diaphragm amplitude (107 ± 4 vs. vehicle: 193 ± 13%)] and expiratory activity measured as abdominal frequency (33±3 vs. vehicle: 50 ± 1 bpm). Respiratory responses of anesthetized rats to exogenous adenosine were blunted by RTN injections of 8PT (100 μM) or DPCPX (5 μM). Further, in conscious rats, bilateral RTN injections of adenosine (10 mM -100 nl) also attenuated the CO2 ventilatory response (1168 ± 34 vs. vehicle: 1437 ± 16 ml/kg/min). These results identify adenosine as a potential negative regulator of RTN chemoreceptor function.

Disclosures: S. James: None. **V.E. Hawkins:** None. **B. Falquetto:** None. **L.M. Oliveira:** None. **A.T. Takakura:** None. **T.S. Moreira:** None. **D.K. Mulkey:** None.

Poster

233. Respiratory Rhythm and Pattern Generation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 233.12/GG2

Topic: E.08. Respiratory Regulation

Support: CIHR

National Sanitarium Association

Title: Regulators of G-protein signaling regulate opioid-induced respiratory depression

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Abstract: Opioid medications are widely used in pain management but may be misused or abused. These medications can cause severe side-effects, including respiratory depression, that can be potentially lethal with overdose. Although the side-effects of opioid medications are highly prevalent, there are currently no treatments to prevent respiratory depression without reducing the analgesic properties of opioid drugs. Indeed, the development of new therapies has been hindered by the lack of knowledge on how opioid medications alter brain and breathing activities. Opioid medications depress breathing by directly activating μ-opioid receptors

(MOR). We recently identified the neural sites in the medulla mediating an important component of respiratory depression and found that the preBötzinger Complex, a neural site of the medulla essential to generate breathing, plays a considerable role. We also identified that G-protein-inwardly rectifying potassium (GIRK) channels regulate MOR inhibition in the brainstem. Activation of GIRK channels by MOR is regulated by various second messengers including a class of proteins called regulators of G-protein signalling (RGS). RGS proteins slow down the kinetic of GIRK channel activation and therefore reduce inhibition by MORs. The role of these RGS proteins in respiratory inhibition by opioids is not known. Combining in vivo recordings in anesthetized rats and perfusion of drugs into medullary respiratory circuits, we investigated the role of RGS proteins in opioid-induced respiratory depression. The RGS4 inhibitor CCG-50014 (20 µM) applied alone to the medulla (in the region of the preBotzinger Complex) significantly reduced breathing rate (n=8), suggesting that RGS4 attenuates respiratory inhibition by endogenous ligands. Interestingly, CCG-50014 further reduced respiratory depression by the MOR agonist DAMGO (5 µM), showing that RGS4 proteins specifically attenuate MOR inhibition. These results suggest that RGS proteins may be potential targets for the development of new therapies to prevent opioid-induced respiratory depression without reducing opioid analgesia. Further work will aim at over-expressing RGS proteins in the medulla to determine whether RGS proteins could have a preventive effect on respiratory depression by opioids.

Disclosures: G. Montandon: None. **J. Danaf:** None. **H. Liu:** None. **R.L. Horner:** None.

Poster

233. Respiratory Rhythm and Pattern Generation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 233.13/GG3

Topic: E.08. Respiratory Regulation

Support: U01 NS 090414

Title: The effect of 5-HT_2 and 5-HT_7 receptor antagonists on baseline breathing and the hypercapnic ventilatory response in mice *In vivo*

Authors: R. J. LECHTENBERG, C. A. MASSEY, *G. B. RICHERSON
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Abstract: Background: Central chemoreceptors within the brainstem have the intrinsic ability to respond to changes in CO_2 and transduce a signal to components of the respiratory network. Serotonergic (5-HT) neurons in the medullary raphe are believed to be a subset of these central chemoreceptors based on a variety of *in vitro* and *in situ* experiments. *In vivo* studies have shown a 50% reduction in the hypercapnic ventilatory response (HCVR) after deletion or inhibition of 5-HT neurons. We sought to further define the role of 5-HT neurons as central chemoreceptors

by *in vivo* treatment of adult C57Bl6 mice with 5-HT_{2A} and 5-HT_7 receptor antagonists. **Methods:** Alzet mini osmotic pumps and brain infusion kits were used for continuous intracerebroventricular (ICV) delivery of a 5-HT_{2A} receptor antagonist (MDL 11,939) or a 5-HT_7 receptor antagonist (SB 258719). Osmotic pumps with saline, or a combination of saline and ethanol, were first used for sham treatment. Plethysmography was conducted with the following gases: 0% CO_2, 5% CO_2 and 7% CO_2, all with 50% O_2 and balance N_2. Saline pumps were then switched to pumps delivering SB 258719 at 0.75 or 7.5 ug/hr (n=6), and ethanol/saline pumps were switched to pumps delivering MDL 11,939 at 0.59 or 5.9 ug/hr (n=6). Plethysmography was then performed as above 24 hours later. Additional experiments were conducted with intra-peritoneal (IP) injections of ketanserin. Plethysmography was conducted before injection and then again 15 minutes following injection of 3 (n=3) or 10 mg/kg (n=5) ketanserin. Plethysmography was performed as previously described. A two-way ANOVA was used for statistical analysis. **Results:** ICV infusion of SB 258719 resulted in a dose-dependent reduction in the HCVR. Administration at 0.75 ug/hr resulted in reduction of minute ventilation at 7% CO_2 ($p=0.04$), while administration at 7.5 ug/hr had significant reduction in minute ventilation at 5% CO_2 ($p=0.004$) and 7% CO_2 ($p=0.0001$). The HCVR was decreased by 37% at 7% CO_2 at the higher dose. MDL 11,939 infusion showed no significant reduction in the HCVR with either 0.59 ug/hr or 5.9 ug/hr. Ketanserin injection at 10 mg/kg showed a reduction in baseline minute ventilation ($p=0.03$), as well as significant reduction in minute ventilation at 5% and 7% CO_2 ($p<0.0001$). **Conclusions:** Dose-dependent reduction in the HCVR, seen with SB 258719 and ketanserin, adds further support to the theory that 5-HT neurons of the medullary raphe have a role as central chemoreceptors, acting in part on 5-HT_7 receptors. Further data will be gathered with ketanserin at 3 mg/kg, as well as with SB 269970 (another 5-HT_7 receptor antagonist).

Disclosures: R.J. Lechtenberg: None. **C.A. Massey:** None. **G.B. Richerson:** None.

Poster

233. Respiratory Rhythm and Pattern Generation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 233.14/GG4

Topic: E.08. Respiratory Regulation

Support: NIH R01 HL130249

BCM McNair Scholar Program

March of Dimes Basil O'Connor Research Award

Parker B. Francis Fellowship

Dunn Collaborative Research Award

CJ Foundation for SIDS

American Heart Association

Title: Adrenergic receptors β1 and β2 are not required for maintenance of baseline ventilation or for the hypercapnic and hypoxic reflexes in adult mice

Authors: *J. SUN, R. RAY
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Abstract: β-adrenergic receptors (β-ARs) mediate the effects of epinephrine and norepinephrine throughout the brain and body and modulate a wide range of autonomic physiological processes, including cardiovascular, respiratory, metabolic, and reproductive function. While drugs that target these receptors are widely used in cardiopulmonary medicine, the basic mechanisms of how they work and the role of each receptor subtype (β1-3) in specific physiological conditions and disease states are still unclear. Given the major role of β-ARs in autonomic control, we sought to test the respiratory consequences of loss of β1- and β2-ARs in adult mice using whole-body plethysmography. Previous studies suggest that homozygous β1-/β2-$AR^{-/-}$ double knockout mice (JAX 003810) have remarkably normal basal heart rate, blood pressure, and metabolic rate, while exercise stress reveals deficits in metabolic pacing. Here, we assayed homozygous β1-/β2-$AR^{-/-}$ and heterozygous β1-/β2-AR-/+ mice and wildtype sibling controls for respiratory function under baseline ventilation (21% O_2/79% N_2) as well as in two respiratory stress conditions: hypercapnia (5% CO_2/21% O_2/74% N_2) and hypoxia (10% O_2/90% N_2). Parameters measured include respiratory rate, tidal volume, minute ventilation, oxygen consumption, and minute ventilation normalized to oxygen consumption. We found that loss of both β1- and β2-ARs had minimal impact on basal respiratory and metabolic parameters as compared to heterozygous and wildtype sibling controls. We also observed no differences between the three groups under either hypercapnic or hypoxic ventilatory conditions. In conclusion, this data suggests that β1- and β2-ARs are not required for proper respiratory maturation of basal rhythm generation as well as the hypercapnic and hypoxic ventilatory reflexes.

Disclosures: J. Sun: None. **R. Ray:** None.

Poster

233. Respiratory Rhythm and Pattern Generation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 233.15/GG5

Topic: E.08. Respiratory Regulation

Title: Mechanism of D-serine release from caudal brainstem astrocytes

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Abstract: Central chemoreception is important for brain CO_2 and H^+ homeostasis. Astrocytes play a key role as chemosensory interoceptors in the brainstem. They can release ATP and D-serine (D-ser) in response to hypercapnia (increased levels of CO_2). D-Ser is an endogenous agonist with high affinity for the glycine-binding site of the N-metil-D-aspartate glutamate receptor (NMDAR). Although activation of the NMDAR is not essential for the generation of the respiratory rhythm, it activation contributes to central chemoreception, but the mechanisms are poorly understood. In the present work, we evaluated the mechanisms through which cultured astrocytes from the caudal brainstem are able of releasing D-Ser. Two days old CF1 mouse neonates were anesthetized (3% isoflurane) and decapitated; their brains were extracted, disaggregated, and cultured in DMEM-F12 medium equilibrated with air containing 5% CO_2 at 37°C for 2 weeks. During experiments, DMEM-F12 medium was replaced by artificial cerebrospinal fluid, and astrocytes were exposed to 5% CO_2 for 30 min (basal condition), followed by 10% CO_2 for 30 min (hypercapnic acidosis), returned to 5% CO_2 at 37°C, and finally exposed to 50mM K^+. Samples were collected at 5, 15 and 30 min at basal and hypercapnic conditions. The concentrations of D-Ser were measured using liquid chromatography-tandem mass spectrometry (LC-MS/MS) analysis. We evaluated the effects of zero mM extracellular Ca^{2+} (aCSF without Ca^{2+}, with Mg^{2+} and EGTA) and gap junctions hemichannels blockers (probenecid and carbenoxolone) on the hypercapnia-induced D-Ser release. Our results reveal that medullary astrocytes release D-Ser in response to hypercapnia and suggest that this release is mediated likely by pannexin1. We found that carbenoxolone and probenecid also blocked the high K^+-induced release of D-Ser, which also supports the involvement of pannexin-1.
Acknowledgment: Fondecyt 1171434 (JE), Fondecyt 1131645 (RvB), Fondecyt 1141132 (GZ) and Conicyt 21140669 (MJO).

Disclosures: M.J. Olivares: None. **S. Beltrán-Castillo:** None. **R. Contreras:** None. **G. Zuñiga:** None. **R. von Bernhardi:** None. **J. Eugenín:** None.

Poster

233. Respiratory Rhythm and Pattern Generation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 233.16/GG6

Topic: E.08. Respiratory Regulation

Support: the Agence Nationale de la Recherche (ANR12-BSV4-0011-01) to MTB

Title: Role of KCC2a in mammalian respiratory at birth

Authors: *M. THOBY BRISSON[1], P. UVAROV[2], M. MARKKANEN[2], M. S. AIRAKSINEN[2], J. SIMMERS[1]
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Abstract: The developmental emergence of functional neural circuits requires the appropriate establishment of synaptic connections between their constituent neuronal elements. In central respiratory circuitry, although synaptic excitation is responsible for synchronizing neuronal activity involved in the different respiratory rhythm phases, inhibition is important for shaping the respiratory pattern. The neuronal specific potassium chloride co-transporter KCC2, serving to maintain intracellular Cl^- at low concentrations and thus rendering chloride-mediated synaptic signaling inhibitory, exists in two isoforms, KCC2a and KCC2b. The expression of KCC2 is necessary for the generation of respiratory activity at birth, but the specific role of the KCC2a isoform in this process remains unknown. In the present work we addressed this issue by investigating at birth the respiratory phenotype of transgenic mice with KCC2a deleted. First, immunostaining demonstrated that KCC2a is expressed at P0 in wild-type mouse brainstem regions where the respiratory oscillators, the preBötzinger complex and the parafacial respiratory group, are located and also in brainstem motoneuronal groups including the hypoglossus nucleus. Second, *in vivo* plethysmographic recordings performed at P0 revealed that KCC2a-deleted mutants exhibit a low breathing rate and an abnormally high occurrence of apneas. Correspondingly, in reduced *in vitro* preparations (isolated brainstem or transverse brainstem slices), a 'fictive' eupneic respiratory rhythm was generated at a lower frequency compared to that recorded in control wild-type preparations, although pauses in neural activity corresponding to apneas observed in the mutant *in vivo* were not detected. This indicated that the source of apneas is not originating from the respiratory rhythmogenic networks while anomalies in respiratory frequency are due to their inherent dysfunction. Thus, our results show that the KCC2a isoform is importantly involved in generating breathing activity at the time of birth, with the survival of mutants lacking KCC2a being probably due to a compensatory contribution of the KCC2b isoform also expressed in brainstem regions associated with control of breathing.

Disclosures: M. Thoby Brisson: None. **P. Uvarov:** None. **M. Markkanen:** None. **M.S. Airaksinen:** None. **J. Simmers:** None.

Poster

233. Respiratory Rhythm and Pattern Generation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 233.17/GG7

Topic: E.08. Respiratory Regulation

Support: FONDECYT 1171434

MECESUP USA1555

Title: D-serine, a novel component in the central chemosensory control of breathing

Authors: *S. BELTRAN-CASTILLO[1], M. J. OLIVARES[2], I. LLONA[3], R. VON BERNHARDI[4], J. EUGENIN[5]
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Abstract: We have reported that D-serine (D-ser), an endogenous co-agonist for NMDAr in CNS, modulates fictive respiration in *in vitro* preparations from mouse neonates. Now, we have evaluated the effects of D-ser in breathing modulation i*n vivo* and the role of medullary brainstem astrocytes in hypercapnic response mediate by D-ser. Modulation of respiratory rhythm by D-ser in unrestrained and conscious CF1 adult mice was evaluated using whole-body plethysmography after a single intraperitoneal (i.p.) or after stereotaxic injection within raphe nucleus (RN) performed through a pre-implanted guide cannula. D-ser (250 mg/kg i.p.) increased the minute volume (V_E) and the respiratory frequency (fR) reaching up to 141.8 ± 14.0% and 124.8 ± 5.4%, respectively, 60 min post-injection. When 30-300 µM D-ser were applied directly into the RN, the increase in fR reached up 142.7 ± 12.5% of basal, two min after injection. The i.p injection of MET-phen (9 mg/Kg) reduce the basal fR, four-hour post injection (from 4.5 ± 0.1 Hz to 4.0 ± 0.1 Hz) and significant reduced the fR increase induced by hypercapnia, 2 (from 130.4 ± 2.6% to 111.9 ± 2.3%) and 4 hours (from 136.5 ± 4.2% to 118.2 ± 3.3%) after injection. To link astrocytes function with D-ser release during hypercapnia, we evaluate the hypercapnia response during impairment of astrocyte functions using fluoroacetate (FA) in glutamine-supplemented caudal medullary slices. The hypercapnia-induced respiratory response on glutamine-supplemented slices was similar to that observed in slices superfused with no-supplemented aCSF. In contrast, addition of 5 mM FA to glutamine-supplemented slices during 30 min impaired the respiratory response to hypercapnia (from 142.6% ± 8.8% to 111.7% ± 4.6%) and reduced the hypercapnia-dependent release of D-ser (from 168.8% ± 29.4 to 112.4% ± 15%). Interestingly, 50 M D-ser treatment restored the hypercapnia-induced respiratory response (149.3% ± 12.3%) in fluoroacetate treated slices. Our results confirm the existence *in vivo* of a novel role for D-ser as that described *in vitro* where astrocytic release of D-ser induced by hypercapnia mediates the respiratory response in caudal medullary chemosensory nuclei.

Disclosures: S. Beltran-Castillo: None. **M.J. Olivares:** None. **I. Llona:** None. **R. von Bernhardi:** None. **J. Eugenin:** None.

Poster

233. Respiratory Rhythm and Pattern Generation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 233.18/GG8

Topic: E.08. Respiratory Regulation

Support: FAPESP Grant 14/22406-1

FAPESP Grant 15/23376-1

Title: Inhibition of pedunculopontine tegmental nucleus generates active expiration

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Abstract: In rodents, the parafacial respiratory group (pFRG), located in the ventral lateral medulla, has been described as a conditional expiratory oscillator that emerges mainly in conditions of metabolic challenges to increase ventilation. At resting conditions, the expiratory pFRG oscillator is synaptically suppressed during inspiratory and post-inspiratory phases. Recently, it has been demonstrated that cholinergic muscarinic transmission contributes to excitation of pFRG neurons and promotes active expiratory activity. The pedunculopontine tegmental nucleus (PPTg), located in the mesopontine region, is considered one of the major cholinergic source to the brainstem. In the present study, we further investigate whether the PPTg neurons may participate functionally in the active expiration in rats. Male Wistar rats weighing 250-400g (CEUA: 80/13) were used. For anatomical experiments, animals received retrograde tracer FluorGold (FG) injections in the pFRG (n = 4). Seven to ten days after the injections, they were perfused with paraformaldehyde and had the brains removed and sectioned for immunohistochemical procedures for choline-acetyl transferase (ChAT). For physiological experiments, urethane-anesthetized rats received bilateral injection of the GABA-A agonist muscimol (2 mM - 50 nL) injection in the PPTg region and the arterial pressure (AP) and electromyography of diaphragm (DiaEMG) and abdominal (AbdEMG) muscles were recorded. The anatomical experiments showed that there was no projections from PPTg neurons to pFRG region. Bilateral injection of muscimol in the PPTg evoked a decrease in AP (Δ = -26 ± 10 mmHg), a significant increase in the Dia_{EMG} frequency (Δ = 29 ± 8 bpm) and Dia_{EMG} amplitude (Δ = 0.2 ± 0.09 mV) and was able to generate active expiration. Our results demonstrated that PPTg does not project directly to pFRG, but its inhibition evokes active expiration, indicating that PPTg is involved with active expiration through an indirect pathway.

Disclosures: J.N. Silva: None. **T.S. Moreira:** None. **T.S.M. Moreira:** None. **A.C. Takakura:** None.

Poster

233. Respiratory Rhythm and Pattern Generation

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 233.19/GG9

Topic: E.08. Respiratory Regulation

Support: R01HL130249

BCM McNair Scholar Program

Title: Functional and anatomical mapping of amygdalar circuitry in breathing

Authors: *V. MARTINEZ[1], J. SUN[2], R. RAY[2]
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Abstract: The amygdala has been shown to be involved in respiration, and amygdalar functional deficits are associated with respiratory disorders such as Central Congenital Hypoventilation Syndrome (CCHS) and Obstructive Sleep Apnea (OSA). Human amygdala studies and electrical and pharmacological animal studies showed alterations in respiratory output. Together, these findings implicate amygdalar involvement in respiration under a number of conditions. However, it remains unclear how the amygdala is integrated into the central respiratory circuitry and how this might contribute to respiratory dysfunction. Here, we aim to functionally and anatomically characterize brainstem respiratory network projections into the amygdala. To begin anatomically and functionally mapping local and long-range amygdalar circuits involved in respiratory control, we used both local (lenti) and retrograde (CAV2) Cre expressing viruses to target the amygdala in mice. Our early studies using a unilateral application of CAV2-Cre virus in the amygdala of a Cre reporter strain shows retrograde ipsilateral and contralateral Cre activity in several brainstem and other regions associated with respiratory control, demonstrating the utility of CAV2 to genetically access neurons projecting to the amygdala that may play a role in breathing. Next, we utilized two Cre responsive DREADD mouse lines (derivative lines of intersectional double Cre and Flp recombinase responsive DREADD alleles developed in our lab; *RC::FP_hM4De* and *RC::FP_hM3D*), to either acutely silence (*RC::P_hM4De*) or activate (*RC::P_hM3D*) the amygdala by bilateral lenti-Cre application or the amygdala and amygdala afferents with bilateral CAV2-Cre applications. Mice were subsequently assayed by whole-body barometric plethysmography to determine the effect of DREADD silencing or activation under room air ($21\%O_2/79\%N_2$) and hypercapnic ($5\%CO_2/21\%O_2/74\%N_2$) conditions. Preliminarily, local (lenti-Cre) perturbations produce a distinct respiratory hypercapnic phenotype as compared to local and afferent (CAV2-Cre) perturbations, suggesting that amygdalar projecting neurons may target additional respiratory network components. In future studies, we aim to use the parental dual recombinase strains to intersectionally divide both local and afferent amygdalar circuitry in respiratory control.

Disclosures: **V. Martinez:** None. **J. Sun:** None. **R. Ray:** None.

Poster

234. Spinal Cord Injury: Posture and Locomotion

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 234.01/GG10

Topic: E.09. Spinal Cord Injury and Plasticity

Support: NIH NS055976

Title: Interneuronal activity in spinal felines treated with BDNF delivered intrathecally to the lumbar spinal cord

Authors: *M. A. LEMAY, F. MARCHIONNE, A. J. KRUPKA
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Abstract: We have shown that neurotrophins delivered via cellular means or intrathecal pump to either the injury site of lumbar spinal cord promotes plantar weight-bearing stepping in cats spinalized at the thoracic level, effectively replacing or supplementing locomotor training. Our modeling work suggests that neurotrophins promote recovery by augmenting activity in the lumbar locomotor center, thus compensating for the loss of the tonic descending drive. We measured multinunit interneuronal activity in the lateral grey matter of the L3-L7 lumbar spinal cord in animals transected at the T11-T12 level 5 weeks prior to our recordings. Activity of interneurons located at depths ranging from 0-3000μm and of 14 hindlimb muscles were acquired during air-stepping trials induced by perineal stimulation.
Recordings were conducted in six spinal animals, three that received saline delivered intrathecally for the 5 weeks following spinalization, and three that received Brain-Derived Neurotrophin (BDNF, 50 ng/day). As in previous studies, we found that animals receiving BDNF recovered consistent plantar weight-bearing at speeds up to 0.8 m/s, while the saline treated animals did not. We found locomotor activity to be superior in the BDNF treated animals during the terminal recordings, with 2/3 BDNF treated animals spontaneously locomoting for part of the session and all exhibiting locomotion bouts lasting approximately 50 secs/episode with perineal stimulation. Induced locomotor bouts were shorter in 2/3 saline treated animals and none displayed spontaneous air-stepping. Interneuronal activity analysis has been completed for one saline and one BDNF treated animals that both exhibited good locomotor activity. Results show similar to superior number of interneurons active during the locomotor bouts in the saline treated animal, with similar connection “strengths” between interneurons. Connection “strengths” were estimated using a generalized-linear-model (GLM) approach to calculate the influences between spike trains. Analysis of the interneuronal activity in the “poor” walkers is on-going and will hopefully demonstrate a positive correlation between interneuronal activity and locomotor behavior.

Disclosures: **M.A. Lemay:** None. **F. Marchionne:** None. **A.J. Krupka:** None.

Poster

234. Spinal Cord Injury: Posture and Locomotion

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 234.02/GG11

Topic: E.09. Spinal Cord Injury and Plasticity

Support: Wings for life

NIH R01 NS095366

Title: Spinal cord injury alters synaptic inputs and serotonergic modulation of Shox2 neurons in mouse

Authors: ***D. GARCIA-RAMIREZ**, S. BIBU, N. HA, L. YAO, K. J. DOUGHERTHY
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Abstract: Neural circuitry generating locomotor rhythm and pattern is located in the thoracolumbar spinal cord. Most spinal cord injuries (SCI) occur above rhythm and pattern genereting networks; therefore, these neuronal circuits are a target for improving motor function after SCI. Despite being relatively intact below the injury, locomotor circuitry undergoes substantial plasticity due to the loss of descending inputs, including changes in cellular excitability, strength of synaptic connections, and receptor expression. Rhythm generating interneurons (INs) are an obvious entry point for studying SCI and treatment. We reported previously that rhythm generating Shox2 INs from chronic SCI mice more frequently showed persistent inward currents and spontaneous bursting, properties which are typically under strong neuromodulatory control. The main objectives of the present study are to identify SCI-induced plasticity of afferent inputs to the Shox2 INs and further to determine SCI-induced changes in the serotonergic modulation of Shox2 INs. Complete thoracic spinal transections were performed on adult Shox2::Cre;Rosa26-lsl-tdTomato mice. Whole cell patch clamp recordings targeted Shox2 INs in lumbar spinal slices with dorsal roots attached for afferent stimulation from uninjured and chronic SCI mice. 5-HT produced a depolarization and an increase in the firing frequency of Shox2 INs from uninjured mice. These effects were also evident in SCI mice but required 10- to 100-fold lower concentrations of 5-HT. Primary afferent-evoked excitatory postsynaptic potentials (EPSPs) in Shox2 INs required lower intensities of dorsal root stimulation in SCI mice compared to uninjured controls. However, afferent-evoked EPSPs in Shox2 INs were strongly depressed in the presence of 5-HT. In summary, synaptic inputs and sertonergic control of Shox2 INs are altered following SCI. Although 5-HT increases Shox2 IN excitability, evoked EPSPs are reduced, suggesting differential modulation at presynaptic and postsynaptic levels, likely by different receptor subtypes.

Disclosures: **D. Garcia-Ramirez:** None. **S. Bibu:** None. **N. Ha:** None. **L. Yao:** None. **K.J. Dougherthy:** None.

Poster

234. Spinal Cord Injury: Posture and Locomotion

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 234.03/GG12

Topic: E.09. Spinal Cord Injury and Plasticity

Support: NINDS Grant 1R01 NS089972

DOD Award # SCI140238

Title: Deep brain stimulation of the mesencephalic locomotor region in freely moving vs. anesthetized minipigs

Authors: *I. OPRIS[1], S. CHANG[1], F. D. BENAVIDES[1], F. J. SANCHEZ[1], L. M. VILLAMIL[1], A. J. SANTAMARIA[1], Y. NUNEZ-GOMEZ[1,2], J. P. SOLANO[2], J. D. GUEST[1,3], B. R. NOGA[1,3]
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Abstract: **Objective**: Neuromodulation strategies to improve locomotion following spinal cord injury (SCI) or Parkinson's Disease (PD) are under active investigation. Deep brain stimulation (DBS) of the mesencephalic locomotor region (MLR) of the Yucatan minipig is a promising model for assessing neuromodulation, and planning human translation. However, a quantitative assessment of the evoked electromyographic (EMG) activity is lacking. **Methods**: DBS was applied to putative MLR sites using bilateral Medtronic electrode arrays. EMG activity was quantitatively evaluated during implantation and in freely moving minipigs. Patterns of muscle activation in select agonist/antagonist muscles of all four limbs were recorded using intramuscular EMG electrodes. Physiological parameters, including heart rate (HR) were collected during MLR stimulation. EMG signals were rectified and band-pass filtered. Circular statistics were used to determine coordination of flexor and extensor activity from EMG recordings. Phase relationships during stance and swing of each limb were evaluated before and after stimulation. **Results**: DBS elicited rhythmic motor patterns and HR changes in both chloralose anesthetized and freely moving animals. In anesthetized animals, flexor and extensor muscles within each limb were typically co-active, lacking reciprocal inhibitory circuits. Interlimb patterns varied, with co-activation or alternation of forelimbs and hindlimb muscles bilaterally. Synchronous, trot-like and pace-like patterns were observed. In open field tests, MLR stimulation evoked normal locomotion. When the stimulation current was increased there was a significant change in the EMG activity, reflected by the increased speed of locomotion.

Spontaneously-generated activity observed under each condition was similar to that observed during DBS indicating that the evoked pattern of activity is state-dependent. **Conclusion**: An accurate, practical method has been developed to target the minipig MLR. This approach may be instrumental in the design of brain machine interfaces and neuroprosthetics for SCI or PD patients.

Disclosures: I. Opris: None. **S. Chang:** None. **F.D. Benavides:** None. **F.J. Sanchez:** None. **L.M. Villamil:** None. **A.J. Santamaria:** None. **Y. Nunez-Gomez:** None. **J.P. Solano:** None. **J.D. Guest:** None. **B.R. Noga:** None.

Poster

234. Spinal Cord Injury: Posture and Locomotion

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 234.04/GG13

Topic: E.09. Spinal Cord Injury and Plasticity

Support: European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie COFUND grant agreement No 665735

Title: Locomotor activity facilitated by chemogenetic activation of grafted serotonergic neurons in paraplegic rats

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Abstract: Purpose: Cell replacement therapy to recover locomotor capability is a promising avenue of treatment for spinal cord injury. Grafting embryonic serotonergic neurons below the lesion of spinal cord injury in a paraplegic rat has been successful in the recovery of locomotion, yet needed additional exteroceptive stimulation to observe the effect. A method to regulate the activity of the grafted cells is still lacking. We applied chemogenetic technology through the use Designer Receptors exclusively Activated by Designer Drugs, (DREADDs) that are only expressed in specific cell types to selectively activate the grafted serotonergic (5HT) neurons. **Methods:** A complete transection was done at the level of T9/T10 in Sprague Dawley rats. One week after the transection a graft was placed below the level of the lesion at T12/T13. The grafts were derived from embryonic (E14) neurons from the B1-B3 area of the brainstem of the offspring of floxed DREADD mice (CAG-LSL-Gq-DREADD -acquired from Jackson labs) crossed with ePet-Cre mice, so that the CAG promotor-driven excitatory DREADD (HA-hM3Dq-pta-mCitrine) was expressed in all 5HT neurons. EMG electrodes were implanted into the soleus and tibialis anterior muscles of right and left hind limbs 7-8 weeks after spinalization. Locomotion was observed on a treadmill with EMG and video recordings. The

pharmacologically inert DREADD ligand, Clozapine N-oxide (CNO), was given i.p in doses from 0.05 - 1 mg/kg and locomotor behavioral changes were monitored at different intervals from 2 minutes to 4 hours after injection. In a stereotaxic frame the rats were immobilized and decerebrated to allow for monitoring of fictive locomotion without afferent input and to observe changes in reflexes before and after CNO administration. Bipolar electrodes were used to monitor activity from the common peroneal and tibial nerves as well as from the dorsal surface of the spinal cord near the area of the graft. The rats were transcardially perfused and fixed, their spinal cords harvested for immunohistochemistry processing. **Results:** Behavioral experiments on the treadmill showed an improvement in locomotor ability after the administration of CNO. Spontaneous air stepping appeared, spontaneous stepping on the treadmill occurred, and the intensity of the exteroceptive stimulation required to elicit plantar stepping was decreased. In the decerebrate preparation periodic episodes of spontaneous fictive locomotion were observed after CNO administration. **Conclusion**: Locomotor ability can be facilitated in paraplegic rats by chemogenetic activation of grafted DREADD-bearing 5-HT neurons.

Disclosures: M. Nazzal: None. **U. Slawinska:** None. **L.M. Jordan:** None.

Poster

234. Spinal Cord Injury: Posture and Locomotion

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 234.05/GG14

Topic: E.09. Spinal Cord Injury and Plasticity

Support: NIH NS097781

PPG HD32571

VA-RR&D: B2316 & B9249

the Rebecca F Hammond Endowment

Title: Changes in inhibitory force feedback pathways following lateral hemisection in cats

Authors: *E. KAJTAZ[1,2], M. A. LYLE[3], K. A. CHEFFER[5,6], D. R. HOWLAND[7,6], T. R. NICHOLS[4]
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Abstract: It is well established that sensory feedback regulates the mechanical properties of limbs, particularly when the limbs interact with the environment. This is accomplished at a reflex

level through length feedback from muscle spindle receptors and inhibitory force feedback from Golgi tendon organs. Briefly, length feedback from muscle spindle receptors increases limb stiffness, and intermuscular, inhibitory force feedback from Golgi tendon organs reduces limb stiffness. Inhibitory force feedback, a widely-distributed system which links cross-joint extensor muscles, has shown remarkable task dependent modulation by descending pathways. Thus, inability to modulate this reflex pathway properly after spinal cord injury [SCI], could be a critical barrier limiting recovery during rehabilitation. Previous research has shown that the magnitude of inhibitory force feedback appears to be an important control variable in the modulation of limb stiffness during locomotion. Here, we report preliminary evidence suggesting that disruption of supraspinal pathways running in the ventral funiculi of the spinal cord alters the strength and intermuscular distribution of force feedback drastically and chronically. In cats with lateral T9 hemisection, the strength of force feedback from both distal and proximal muscles onto ankle extensor muscles - notably feedback from flexor hallucis longus and vasus muscles onto soleus, plantaris and gastrocnemius - is greatly amplified compared to control animals. While decerebrate, control animals exhibit various profiles of force feedback distribution, the convergence of inhibition onto ankle extensors in cats with spinal cord damage seems to be a consistent pattern across SCI cats studied. Further analysis is under way. These findings, in combination with parallel gait studies in these cats (see companion poster Cheffer et al.), will elucidate the inhibitory force feedback contributions to deficiencies in weight support and stability post-SCI.

Disclosures: E. Kajtaz: None. **M.A. Lyle:** None. **K.A. Cheffer:** None. **D.R. Howland:** None. **T.R. Nichols:** None.

Poster

234. Spinal Cord Injury: Posture and Locomotion

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 234.06/GG15

Topic: E.09. Spinal Cord Injury and Plasticity

Support: VA-RR&D: B2316, B9249

NIH NS097781

NIH - HD32571

The Kentucky Spinal Cord and Head Injury Trust

Rebecca F Hammond Endowment

Title: Adapting motor strategies to the demands of slopes and steps post-SCI

Authors: *K. A. CHEFFER[1,2,3,5], E. KAJTAZ[6], M. A. LYLE[6], W. A. O'STEEN[1,3,5], T. R. NICHOLS[6], D. R. HOWLAND[1,2,3,4,5]
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Abstract: Adapting to changes in walking surface demands is critical for successful navigation in different environments. Although the neural requirements of each gait task vary based upon the motor features required for successful execution, all use a combination of concentric and eccentric contractions. Due to disruption of force feedback (FFB) mechanisms responsible for intralimb coordination post-spinal hemisection (Hx; see companion poster, Kajtaz et al.), the current study is focused on gait tasks in which eccentric contractions are more prominent. These contractions, in which tension increases as a muscle lengthens, are particularly active during the braking motions that occur when walking downhill or going down stairs. Project goals include 1) understanding how intact animals adapt gait patterns in response to slopes (0°, -10°,-26°) and down stairs (traditional and platform) and 2) characterizing changes in these patterns acutely and overtime post-spinal cord injury (SCI). Cats are conditioned to a food reward and baseline performance captured using a motion analysis system (*Vicon*). Post-T9 Hx, gait is tested across 12 weeks and after the final gait capture, a terminal FFB study is conducted to assess interactions among hindlimb (HL) muscles (see Kajtaz et al. for FFB). Histology is used to verify extent of SCI. Single and multi-joint angular data show that in the intact cat, adaptations to changes in slope are most apparent in the distal HL joints. After Hx, these adaptations are disrupted and stability of the hip pattern is affected. Further, on declines, fore-hindlimb coordination shows a shift towards in-phase stepping of the ipsilateral forelimb and HL. During stair negotiation, a consistent leading limb is apparent. Prior to injury, cats lead with a single forelimb followed by a specific HL. Post-injury limb preference is influenced by lesion side with the ipsilateral HL becoming the leading HL. Left-right symmetry, apparent during level and decline walking, is absent on stairs. Trailing limb excursion is reduced along with yield reflecting a change in limb stiffness. Combined, gait and FFB studies will further our mechanistic understanding of gait in the normal state and following SCI and support development/refinement of rehabilitation strategies.
Supported by: VA-RR&D: B2316, B9249, NIH NS097781&HD32571,The Kentucky Spinal Cord and Head Injury Trust, and the Rebecca F Hammond Endowment.

Disclosures: K.A. Cheffer: None. **E. Kajtaz:** None. **M.A. Lyle:** None. **W.A. O'Steen:** None. **T.R. Nichols:** None. **D.R. Howland:** None.

Poster

234. Spinal Cord Injury: Posture and Locomotion

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 234.07/GG16

Topic: E.09. Spinal Cord Injury and Plasticity

Title: Locomotor adaptation in persons with incomplete spinal cord injury during split-belt treadmill walking

Authors: *Y. THIBAUDIER, D. M. PETERS, K. BOVA, S. GARDON, H. GOESCH, S. HARTFORD, L. SMITH, T. M. KESAR, R. D. TRUMBOWER
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Abstract: Persons with chronic incomplete spinal cord injury (iSCI) often face life-long struggles with overground walking, due in part to altered spatiotemporal gait patterns. Despite clinical efforts to improve gait symmetry after iSCI, treatment strategies specifically targeting spatiotemporal interlimb symmetry remain quite limited. Thus, there is need to develop novel therapies can restore gait symmetry in persons with iSCI. Locomotor adaptation paradigms that capitalize on error-augmentation have been shown to improve gait symmetry using error-driven feedback in response to gait perturbation. Split-Belt Walking (SBW) is an established paradigm shown to elicit beneficial motor adaptation through perturbations of spatial and/or temporal gait symmetry in persons with stroke. Provided there is ample sparing of neuromotor pathways necessary for motor adaption, similar SBW interventions may also enhance gait symmetry in persons with chronic iSCI; however, this possibility has not yet been studied. Thus, the purpose of this study was to test the hypothesis that SBW locomotor adaptation is preserved during SBW in persons with iSCI. Five persons with chronic iSCI (AIS D) and age-matched neurologically-unimpaired individuals participated in 15-minutes of SBW with a 2:1 belt speed ratio to exaggerate spatial asymmetry. Able-body controls performed the SBW protocol at their iSCI matched speed. Bilateral step length and step time were measured using a Motion Analysis system. To quantify motor adaptation, interlimb symmetry was compared between early and late SBW periods (Wilcoxon Test, $p<0.05$). Our results demonstrate locomotor adaptation in persons with chronic[SG1] iSCI. Specifically, persons with iSCI exhibited significant motor adaptation ($p=0.016$) in step length asymmetry but not in step time asymmetry ($p=0.173$). Similar trends for motor adaptation in step length ($p=0.076$) but not in step time ($p=0.917$) asymmetry were observed in able-body controls. Consistent with our hypothesis, SBW induced motor adaptation of spatial asymmetry in persons with iSCI. The lack of adaption of temporal asymmetry may reflect the specificity of the protocol, which targeted spatial asymmetry. Adaptation is a key process underlying motor learning and rehabilitation, and evaluation of locomotor adaptation in iSCI will help design innovative, targeted, and individualized gait rehabilitation treatments to improve gait in persons with iSCI.

Disclosures: Y. Thibaudier: None. **D.M. Peters:** None. **K. Bova:** None. **S. Gardon:** None. **H. Goesch:** None. **S. Hartford:** None. **L. Smith:** None. **T.M. Kesar:** None. **R.D. Trumbower:** None.

Poster

234. Spinal Cord Injury: Posture and Locomotion

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 234.08/DP07/GG17 (Dynamic Poster)

Topic: E.09. Spinal Cord Injury and Plasticity

Support: The Grainger Foundation

National Institutes of Health (NIH) National Cancer Institute (NCI) K99CA214523

Partial support was provided by the Russian Science Foundation (RSF grant No. 15-15-20036)

Title: Functional ultrasound (fus) imaging of vascular changes evoked by spinal cord electrical stimulation and spinal cord transection

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Abstract: Abstract In this experiment we used ultrafast microvessel imaging-based functional ultrasound (fUS) to evaluate structural and functional microvasculature response to epidural stimulation (ES) of the spinal cord (SC) on a healthy swine model across lumbar segments. We also used fUS to monitor real-time vascular changes in SC post implantation of intraspinal micro-stimulation (ISMS) electrodes into the ventral horn as well as SC transection.
Methods: Domestic white swine and Sprague Dawley rat of both genders were used for this study. After lumbar laminectomy, SC-fUS was performed over the lumbar segments of the exposed SC (Fig. 1a) with a Verasonics Vantage ultrasound system and a L22-14v linear array transducer (Verasonics Inc., Kirkland, WA). fUS employed ultrafast compounding plane wave imaging (5-angle compounding) to acquire 200 ensembles at a 500 Hz pulse-repetition-frequency (PRF, 33.3 kHz PRF before compounding) per second. Simultaneously, EMG signals were recorded from tibialis anterior and medial gastrocnemius muscles.
Results: During ES at 40Hz, SC-fUS was acquired with a sagittal imaging plane (Fig. 1 c). SC-fUS showed significantly increased (~40%) SC blood volume (SCBV) in dorsal blood vessels (Figs. 1b and c) during ES (15 s duration with a 5s delay to the starting time of fUS), while the ventral blood vessels showed little or no stimulation effect. We also tracked vascular damages during ISMS electrode implantation and immediately following SC transection. SC-fUS showed no significant change of SCBV post ISMS electrode implantation, while the SC transection showed approximately 10% decrease of SCBV in regions close to the site of incision 20 minutes post injury.

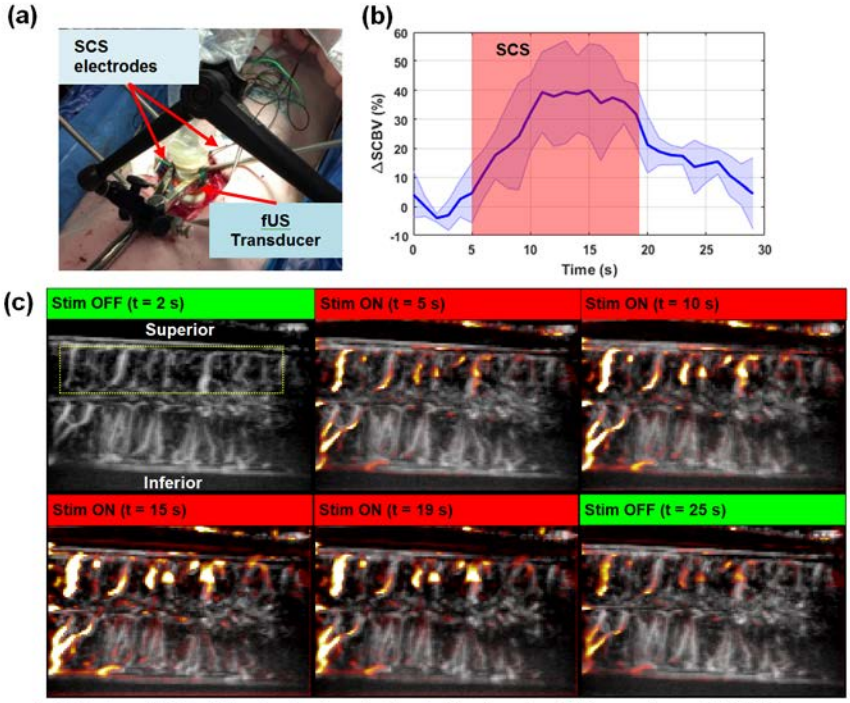

Figure 1: (a) Setup of fUS epidural spinal cord stimulation in swine (ES) experiment. (b) fUS measured superior (dorsal) spinal cord blood volume (SCBV) change in response to ES. The center line indicates mean value from 4 repeated ES experiment, and the shaded area indicates 1 standard deviation. (c) 2D fUS maps of epidural ES-induced SCBV change. The SCBV change (color map) is superimposed on the microvessel power Doppler images.

Conclusion: This pilot study demonstrated that SC-fUS has adequate spatial and temporal resolutions to investigate microvascular hemodynamics response to ES and evaluate vascular damages post SC injury.

Disclosures: P. Song: None. **R. Islam:** None. **C. Cuellar:** None. **P. Grahn:** None. **K. Lee:** None. **S. Chen:** None. **I. Lavrov:** None.

Poster

234. Spinal Cord Injury: Posture and Locomotion

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 234.09/GG18

Topic: E.09. Spinal Cord Injury and Plasticity

Support: The Broccoli Foundation

The Christopher and Dana Reeve Foundation

The Grainger Foundation

Jack Jablonski BEL13VE in Miracles Foundation

Craig H. Neilsen Foundation

Mayo Clinic Transform The Practice

Mayo Clinic Rehabilitation Medicine Research Center

Title: Subfunctional neural connections in motor complete paralysis and implications for their role in epidural stimulation enabled motor function

Authors: *J. S. CALVERT[1], I. LAVROV[1], P. GRAHN[1], D. SAYENKO[2], M. VAN STRAATEN[1], M. GILL[1], J. STROMMEN[1], D. DRUBACH[1], L. BECK[1], M. LINDE[1], A. THORESON[1], C. LOPEZ[1], D. VEITH[1], Y. GERASIMENKO[2], R. EDGERTON[2], K. ZHAO[1], K. LEE[1]
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Abstract: Patients chronically paralyzed due to spinal cord injury (SCI) have shown the ability to generate volitional movements in the presence of epidural electrical stimulation (EES). According to the current hypothesis, EES enhances previously subfunctional signals that traverse the injury via spared fibers. However, it is unknown which spinal tracts are facilitated during EES to enable volitional movement. We set out to characterize the transmission of signals across the injury site in two motor and sensory complete SCI patients (ASIA-A). Participants were tested upon enrollment, after six months of physical therapy, and following surgical recovery of EES system implantation. To test connectivity across the injury, external stimuli were applied to various locations above the injury to activate specific spinal tracts that could condition the excitability of sublesional spinal circuitry. The conditioning stimuli applied were: transcranial magnetic, galvanic vestibular, audio, ulnar, and cervical stimulation, with the intent to activate the corticospinal, vestibulospinal, reticulospinal, propriospinal, and general descending motor tracts, respectively. Stimuli delivered to the lumbosacral spinal cord were paired to these conditioning stimuli to evaluate spinal circuitry excitability. Spinal circuitry excitability was examined by recording electromyography (EMG) bilaterally from six muscles within the lower limbs to evaluate amplitudes of spinal-evoked motor responses. In Subject 1, there was no substantial change in connectivity tests across the course of the trials, despite regaining volitional motor control in the presence of EES. However, in Subject 2 there was modulation of the EMG response in multiple tests corresponding with muscles that showed a discomplete profile. The opposing outcomes in the two subjects indicate that identification of the remaining neural substrates from which SCI subjects can volitionally control movement in the presence of EES needs to be studied further as the heterogeneity of the disease may result in patients displaying different patterns of recruitment in the connectivity tests. Overall, these connectivity tests could be used to identify pathways through which motor function is facilitated in SCI patients prior to and following EES.

Disclosures: J.S. Calvert: None. **I. Lavrov:** None. **P. Grahn:** None. **D. Sayenko:** None. **M. van Straaten:** None. **M. Gill:** None. **J. Strommen:** None. **D. Drubach:** None. **L. Beck:**

None. **M. Linde:** None. **A. Thoreson:** None. **C. Lopez:** None. **D. Veith:** None. **Y. Gerasimenko:** None. **R. Edgerton:** None. **K. Zhao:** None. **K. Lee:** None.

Poster

234. Spinal Cord Injury: Posture and Locomotion

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 234.10/GG19

Topic: E.09. Spinal Cord Injury and Plasticity

Support: The Grainger Foundation

Russian Science Foundation 15-15-20036

Title: Engaging hindlimb central pattern generators via lumbosacral epidural stimulation to induce stepping in healthy adult rodents

Authors: *C. A. CUELLAR[1], R. ISLAM[1], B. KNUDSEN[1], J. SILVERNAIL[1], T. E. RICCELLI[2], J. S. CALVERT[3], H. WEN[4], P. J. GRAHN[1], K. H. LEE[1], I. A. LAVROV[1,5]
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Abstract: The generation of locomotion involves rhythmic and coordinated activation of muscles driven by spinal circuits commonly termed central pattern generators (CPGs). The basic definition of CPGs involves rhythmic motor activation that can be driven via exogenous stimuli even in the absence of supraspinal control or afferent input. In spite of the extensive literature describing different features of CPGs, the majority of these studies in mammals have been done in acute experiments in anesthetized or paralyzed animals or in vitro spinal cord preparations. In these previous studies, rhythmic motor output (i.e. fictive pattern) was facilitated using drugs that enhance the excitability of the spinal networks. Moreover, studies providing additional information of the CPGs during actual stepping in animals are still missing. Evidence of CPG activation during electrical epidural stimulation (EES) enabling motor activation in spinal rats and in humans after spinal cord injury supports the notion of the importance of afferent feedback as a determinant contribution to produce motor output. However, until now, it was not clear if hind limb CPGs can be activated in awake, spinally intact animals. Additionally, the role of sensory information in modulating intact spinal cord motor outputs has not been defined. In this study, EES was delivered at the first sacral spinal cord segment (S1) in rats (n=7, female) with two electrodes (one placed on dura mater and the second electrode at the same spinal level above the vertebra). EES frequencies ranged between 1 and 250 Hz (0.5 ms pulse duration). Voltage intensities above the threshold to elicit monosynaptic responses were used. Intramuscular

electromyography (EMG) was recorded from hind limbs. A body weight support system (Islam et al. SfN abstract 2017) was used during stepping on a treadmill at different speeds (9, 11, 13 and 15 m/min) and during open field testing. Kinematics were analyzed before (control) and during EES. Our results show that during stepping on a treadmill, EES at S1 drives performance of the hind limbs, leading to increased stepping speed beyond the fixed rate of the treadmill, which the rodent had been volitionally stepping at the same pace. This EES drive CPG activation was characterized by an increase in amplitude of EMG and acceleration. During open field test, hind limb stepping was facilitated with EES as well primary when animals receive sensory input during stepping and not during standing or sitting. These results support our hypothesis that EES can facilitate the spinal circuitry in awake intact spinal cord and emphasize the importance of sensory input in control of CPG in the central nervous system.

Disclosures: C.A. Cuellar: None. **R. Islam:** None. **B. Knudsen:** None. **J. Silvernail:** None. **T.E. Riccelli:** None. **J.S. Calvert:** None. **H. Wen:** None. **P.J. Grahn:** None. **K.H. Lee:** None. **I.A. Lavrov:** None.

Poster

234. Spinal Cord Injury: Posture and Locomotion

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 234.11/GG20

Topic: E.09. Spinal Cord Injury and Plasticity

Support: The Grainger Foundation

Partial support was provided by the Russian Science Foundation (RSF grant No. 15-15-20036)

Title: Integrated system for evaluating behavior and locomotion during neuromodulation therapy in rodents

Authors: *R. ISLAM[1], B. FELMLEE[1], C. CUELLAR[1], J. SILVERNAIL[1], T. RICCELLI[1], H. WEN[3], B. KNUDSEN[1], J. CALVERT[2], P. GRAHN[2], K. LEE[1], I. LAVROV[1]
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Abstract: Behavioral and kinematic analyses are crucial assessment tools to evaluate neurologic dysfunctions in rodent models. Classical tests, like open field analysis, are generally missing important information on motor performance such as gait analysis of locomotive patterns, electromyography (EMG) analysis and others. Therefore, establishing an integrative system for evaluation of behavior and motor functions is essential for future studies of spinal cord injury (SCI), stroke, Parkinson’s disease, and other neurologic conditions with motor impairment. To

this end, we have developed a system that allows simultaneous evaluation for the open field, independent kinematic assessment, EMG evaluation, and evoked responses, alone or in combination with locomotor training. Mechanical properties of the BWS were tested to validate it's suitability to assess rodent behavior.
The proposed system (Figure 1: a & b) consists of the following major components: (1) Body Weight Support (BWS) system (2) camera-based motion analysis (3) open field tracking system (4) electrophysiological assessment unit(5) force and torque transducer (6) motorized treadmill (7) electrical stimulator. Adult healthy and SCI female Sprague Dawley rats were used to validate system performance.
Figure 1: (a) Proposed behavioral assessment system (b) Zoomed view of the central part of the BWS
Static and dynamic frictional forces of the BWS system were found to be within comfort range by healthy and SCI rats. In a series of experiments we found the system to be capable of running simultaneous open field, kinematic assessment and to be able to provide evaluation of the field trajectory, stick diagram reconstruction
to display joint trajectories and joint angles, together with EMG and evoked responses analysis. We performed kinematic and electrophysiology assessment during locomotion on a treadmill in healthy and in SCI rats while applying epidural electrical stimulation over the lumbosacral spinal cord and/or also after injecting 0.3 mg/kg of serotoninergic agonist (quipazine). The open field, kinematic and electrophysiology properties were then compared to determine the sensitivity of the system in assessing outcome of these neuromodulation therapies. We have successfully demonstrated that new system is capable of collecting multiple modalities of assessment encompassing cognitive, locomotor and electrophysiological tests.
Current results support feasibility of collecting multiple modalities for evaluation of motor performance in one system which will aid in understanding the links between neurologic impairment and loss of locomotion and mechanisms of neuromodulation therapies.

Disclosures: R. Islam: None. **B. Felmlee:** None. **C. Cuellar:** None. **J. Silvernail:** None. **T. Riccelli:** None. **H. Wen:** None. **B. Knudsen:** None. **J. Calvert:** None. **P. Grahn:** None. **K. Lee:** None. **I. Lavrov:** None.

Poster

234. Spinal Cord Injury: Posture and Locomotion

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 234.12/GG21

Topic: E.09. Spinal Cord Injury and Plasticity

Support: Canadian Institutes of Health Research

Wings for Life

Title: Functional contribution of the mesencephalic locomotor region to locomotor recovery after spinal cord injury

Authors: *M. ROUSSEL, N. JOSSET, D. LAFRANCE-ZOUBGA, M. LEMIEUX, F. BRETZNER
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Abstract: Recently, electrical stimulation of the mesencephalic locomotor region has been shown to improve locomotor recovery after spinal cord injury (SCI). Although this region was initially identified as the cuneiform nucleus (CnF), a cluster of glutamatergic neurons, and the pedunculopontine nucleus (PPN), a cluster of glutamatergic and cholinergic neurons, its anatomical correlate is still a matter of debate. Here, we propose to identify and characterize functional contributions of these neuronal populations to locomotor control and recovery after SCI.
Using transgenic mice expressing opsin in either glutamatergic (Glut) or cholinergic (CHAT) neurons, we photostimulated (or photoinhibited) Glut+CnF or PPN or CHAT+PPN neurons before and after SCI.
Among all neuronal populations tested, only long photostimulations (20Hz, 1s, 10ms pulses) of Glut+CnF neurons initiated locomotion in control and SCI mice.
During locomotion, short photostimulations (10ms) of either Glut+CnF or Glut+PPN neurons evoked motor responses. Whereas Glut+CnF evoked excitatory motor responses in flexor and extensor muscles, Glut+PPN neurons evoked inhibitory responses in extensor muscles during their active phase and excitatory responses during their relaxation phase. In contrast, CHAT+PPN neurons did not evoke any motor responses but increased the burst duration of extensor muscles. Analysis of data after SCI is still in progress.
Long pulses (100ms) or trains of photostimulations (20Hz, 1s, 10ms pulses) of Glut+CnF neurons accelerated the locomotor rhythm and elicited transitions towards running gaits, whereas photostimulations of Glut+PPN or CHAT+PPN neurons slowed down the locomotor rhythm, thus giving rise to slow-walking gaits in control and SCI mice. Interestingly, whereas photoinhibition of CHAT+PPN neurons had almost no effect, photoinhibition of Glut+CnF or Glut+PPN neurons decelerated the locomotor rhythm or stopped locomotion, thus supporting that Glut+PPN neurons contribute to slow-walking gaits in control and SCI mice.
In summary, although all neuronal populations contribute to locomotion, our results argue that the Glut+CnF neurons would likely be a better neurological target to improve functional locomotor recovery following SCI.

Disclosures: M. Roussel: None. **N. Josset:** None. **D. Lafrance-Zoubga:** None. **M. Lemieux:** None. **F. Bretzner:** None.

Poster

234. Spinal Cord Injury: Posture and Locomotion

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 234.13/GG22

Topic: E.09. Spinal Cord Injury and Plasticity

Title: Examining sensorimotor integration in the trunk motor cortex in adult rats

Authors: *B. NANDAKUMAR[1], G. H. BLUMENTHAL[2], K. A. MOXON[3]
[1]Sch. of Biomed. Engin. and Hlth. Sci., Drexel Univ. Sch. of Biomed. Engin. Sci. and Hlth. Systems, philadelphia, PA; [2]Sch. of Biomed. Engineering, Sci. & Hlth. Systems,, Drexel Univ. Sch. of Biomed. Engin. Sci. and Hlth. Systems, Philadelphia, PA; [3]Biomed. Engin., Univ. of California Davis, Davis, CA

Abstract: While there exists extensive information about sensorimotor integration in the forelimb, hind limb and barrel cortex, little is known about details of trunk cortex. Since volitional control of trunk musculature is essential for postural stability and weight supported locomotion, understanding sensorimotor integration in the trunk cortex is useful for studies of neurological injury or disease where the somatotopic organization of cortex changes. The trunk is especially important for the impact of mid-thoracic spinal cord injury where reorganization of the trunk motor cortex is necessary for recovery of function. In order to understand sensorimotor integration in the trunk cortex, we first assessed the extent of trunk motor representation using intracortical micro stimulation (ICMS). Then, we examined somatosensory representation in the trunk motor cortex by recording evoked responses to peripheral electric stimulation of forelimb, hind limb and trunk (T10 level) . **Methods:** Naïve Sprague Dawley rats were anesthetized and a craniotomy over the medial post Bregma area (MPBA) and the caudal forelimb area (CFA) exposed most of the motor cortex. EMG electrodes were implanted in the trunk muscles at different levels of the vertebral column along with hind limb and forelimb muscles. Low impedance Tungsten electrode was slowly lowered to layer 5 of the cortex, in predefined locations with a 250 micron resolution. Movement representations were evaluated at the minimum current required to elicit movement/EMG response. Neuronexus probes were then inserted into fixed locations spanning the motor cortex. Evoked responses to peripheral electric stimulation of limbs and trunk were measured. **Results:** Activation of trunk muscles in response to ICMS at threshold current extended from +0.5 to -1mm rostrocauadally and from 1.25 to 2.5mm medial from Bregma. However, exclusive activation of trunk musculature was found in only 40% of the animals and the location was not consistent across animals. More likely, the trunk motor representation contained 3 distinct coactivation zones: ‘synergistic trunk’, characterized by unilateral synchronous activation of the forelimb & the hindlimb; ‘hindlimb trunk’, characterized by co-activation of the hindlimb & trunk musculature and ‘forelimb trunk’, characterized by co-activation of forelimb and trunk muscles. Evoked responses to both

forelimbs and hind limbs were found in the trunk motor cortex, suggesting there is extensive sensorimotor integration within the trunk motor cortex. **Conclusion:** This knowledge from normal animals can be used for greater insight into reorganization of the trunk motor cortex after spinal cord injury.

Disclosures: B. Nandakumar: None. **G.H. Blumenthal:** None. **K.A. Moxon:** None.

Poster

235. Neuromodulation and New Approaches in Monitoring Vocal Learning

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 235.01/GG23

Topic: F.01. Neuroethology

Support: NIH Grant NINDS R01 NS084844

NSF Grant 1456912

Title: The role of dopamine in sensorimotor adaptation in songbirds

Authors: *V. SARAVANAN, L. A. HOFFMANN, A. L. JACOB, S. J. SOBER
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Abstract: Sensorimotor learning is ubiquitous in complex motor behaviors. However, the neural mechanisms driving behavioral plasticity are not well understood. Dopamine has been implicated in reinforcement learning, i.e., learning driven by rewarding or aversive external cues. However the role of dopamine in sensorimotor adaptation, wherein an organism learns through evaluation of its sensory feedback rather than from external reward or punishment, has not been well characterized. We have developed learning paradigms to study these two types of sensorimotor learning in Bengalese finches (*Lonchura striata var. domestica*). Male Bengalese finches spontaneously produce songs containing complex sequences of vocal gestures (syllables). Our reinforcement learning paradigm delivers aversive auditory stimuli (blasts of white noise) contingent on the pitch of the birds' song (Tumer and Brainard, 2007). The birds learn to shift the pitch of their song away from those frequencies that trigger the aversive stimulus. We have previously shown that depleting dopamine in a song-specific basal ganglia nucleus (Area X) impairs this type of reinforcement learning (Hoffmann et al 2016). Here, we evaluated the hypothesis that dopamine mediates sensorimotor adaptation in a similar manner. To test this hypothesis, we used the same dopamine depletion paradigm mentioned above in conjunction with a sensorimotor adaptation paradigm in which the pitch (fundamental frequency) of a bird's auditory feedback is manipulated in real time through custom-built headphones, a manipulation that robustly drives sensorimotor adaptation (Sober and Brainard, 2009). Our preliminary results

suggest that dopamine may be involved in active maintenance of the desired pitch of birdsong in sensorimotor adaptation.

Disclosures: V. Saravanan: None. **L.A. Hoffmann:** None. **A.L. Jacob:** None. **S.J. Sober:** None.

Poster

235. Neuromodulation and New Approaches in Monitoring Vocal Learning

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 235.02/GG24

Topic: F.01. Neuroethology

Support: NIH R01 NS084844

NSF Grant 1456912

Title: Dopaminergic input to Bengalese finch song system nuclei

Authors: *A. L. JACOB, A. N. WOOD, S. J. SOBER
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Abstract: During learned behaviors, the brain uses sensory information to maintain and correct motor performance. Dopaminergic neurotransmission is thought to play a role in sensorimotor learning; however, studying the effects of dopamine has been difficult due to its involvement in multiple behaviors and the complexity of basal ganglia circuitry. Bengalese finches provide an excellent model system to study the role of dopamine in motor learning and error correction due to the presence of the song system, a network of sensorimotor nuclei dedicated to learning and producing song. The song system contains two parallel pathways that both begin at premotor nucleus HVC: the motor pathway and the anterior forebrain pathway (AFP). The motor pathway generates and coordinates the patterns of muscles activation necessary for song production, while the AFP, a cortical-basal ganglia-thalamic-cortical loop, mediates song learning and plasticity but is not required for adult song production. Previous studies have shown that multiple song system nuclei in both the motor pathway and AFP receive dopaminergic input and that dopamine input to the AFP is crucial for adult vocal learning and performance error correction. However, it is currently unknown whether individual dopamine neurons convey distinct dopaminergic signals to downstream neurons or if dopaminergic neurons project to multiple song system nuclei. Here, using neuroanatomical tracers combined with tyrosine hydrolase immunostaining, we describe the organization of dopaminergic projections to multiple song system nuclei.

Disclosures: A.L. Jacob: None. **A.N. Wood:** None. **S.J. Sober:** None.

Poster

235. Neuromodulation and New Approaches in Monitoring Vocal Learning

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 235.03/GG25

Topic: F.01. Neuroethology

Support: NS084844

F31NS089406

IOS-1457206

IOS-1451034

R01DC014364

Title: Cerebellothalamic and thalamostriatal projections in a songbird

Authors: *D. A. NICHOLSON[1], T. F. ROBERTS[3], S. J. SOBER[2]
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Abstract: Songbirds provide a model system for understanding how the brain learns and produces motor skills. The cerebellum plays a critical role in many motor skills, and in mammals communicates with the cortex and the basal ganglia. It remains unclear if in songbirds the cerebellum interacts with the song system, the network of brain regions required for learning and producing song. It also remains unclear if thalamus projects to the basal ganglia in the song system. Previous work in songbirds has shown the cerebellar nuclei (CbN) project to dorsal thalamus, raising the possibility that they target thalamic nuclei of the song system. We investigated this projection in Bengalese finches, first mapping out the cerebellar-recipient regions of dorsal thalamus (DT_{Cb}) with standard neuroanatomical tracers. We went on to map thalamic song system nucleus DLM in Bengalese Finches by injecting tracers in Area X. Our results show that DLM and DT_{Cb} occupy adjacent regions of dorsal thalamus. To determine whether these regions of dorsal thalamus project to the basal ganglia, we used a viral vector that specifically labels presynaptic axon terminals. We determined whether labeled thalamostriatal axon terminals were within the song system nucleus of the basal ganglia, Area X, by labeling Area X with parvalbumin antibodies. We found that thalamic song system nucleus DLM projects to Area X, as does DT_{Cb} immediately adjacent to DLM. The more medial and posterior regions of DT_{Cb} project to medial striatum outside Area X. DLM as expected also projects to LMAN, and DT_{Cb} appears to project to nidopallium outside LMAN. In conclusion, our results suggest reciprocal projections between Area X and DLM, as well as input to Area X from cerebellar-

recipient thalamus. Future studies can take advantage of the songbird model system to further our understanding of the thalamostriatal system.

Disclosures: D.A. Nicholson: None. **T.F. Roberts:** None. **S.J. Sober:** None.

Poster

235. Neuromodulation and New Approaches in Monitoring Vocal Learning

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 235.04/GG26

Topic: F.01. Neuroethology

Support: NSF Grant 1456912

NIH R01 NS084844

Title: Somatosensory-driven vocal learning in adult songbirds

Authors: *J. N. MCGREGOR[1], P. I. JAFFE[3], M. S. BRAINARD[4], S. J. SOBER[2]
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Abstract: Complex, skilled behaviors are acquired through a process of sensorimotor learning, wherein the brain uses sensory feedback to adjust motor output to improve behavioral performance. Adult Bengalese finches (*Lonchura striata var. domestica*) repetitively perform a learned, skilled behavior (song) consisting of a sequence of individual elements (syllables). Much research has focused on the importance of auditory feedback for song performance. While it is well understood that the brain receives input from and relies upon multiple sensory modalities to guide behavior, it is unknown whether songbirds can use non-auditory feedback for the purposes of vocal learning. We therefore developed a novel learning paradigm in songbirds by delivering a pitch-contingent, aversive somatosensory cue (electric stimulation) during singing. We found that this non-auditory stimulus reliably drove significant adaptive shifts in pitch of the targeted syllable. Importantly, our preliminary analysis indicates that electrical stimulation does not evoke any acute effects on vocal pitch, supporting the view that the vocal learning observed was non-auditory. This new learning paradigm allows for further interrogation of neural circuitry important for songbird sensorimotor learning.

Disclosures: J.N. McGregor: None. **P.I. Jaffe:** None. **M.S. Brainard:** None. **S.J. Sober:** None.

Poster

235. Neuromodulation and New Approaches in Monitoring Vocal Learning

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 235.05/GG27

Topic: F.01. Neuroethology

Support: NIH Grant 5R01NS094667-02

PEW Biomedical Scholar

Klingenstein Fellowship in the Neurosciences

Title: Basal forebrain sends performance error signals to VTA in singing birds

Authors: *A. PODURY, R. CHEN, P. A. PUZEREY, K. MAHER, J. H. GOLDBERG
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Abstract: Motor performance is not evaluated against a fixed target but against personal benchmarks that change with learning. Evaluating your tennis forehand relative to your past forehands is more useful than comparing it to your target of swinging like Federer. Zebra finches learn to sing by imitating a tutor song, suggesting they have a 'target' they aspire to learn. Yet song syllables are not simply evaluated against a fixed target. Instead, recent recordings suggest that syllables are evaluated against syllable-specific performance benchmarks updated during recent practice. Specifically, ventral tegmental area (VTA) dopamine neurons exhibited phasic suppressions following distorted auditory feedback (DAF) during singing, consistent with a worse-than-predicted outcome. They also exhibited phasic bursts at the precise time-step of a syllable when a predicted distortion did not occur. Burst magnitude depended on distortion history, consistent with an error signal scaled by the predicted syllable quality. Upstream circuits that compute this error signal are unknown. Here we combine lesions, electrophysiology, distorted auditory feedback (DAF), and viral tract tracing, to identify the VTA-projecting part of the basal forebrain (BFvta) as a major hub for error processing. Juvenile birds with excitotoxic lesion to BFvta failed to imitate tutor song compared to sham-lesioned siblings. Distinct subtypes of antidromically identified BFvta neurons encode auditory error and predicted syllable quality. Other BF cell types encode precise song timing, gross movement, and singing state. Using viral tracing we identified novel projections to BF from: (1) the HVC-projecting part of the motor thalamus (Uva), a source of precise song timing information; (2) the VTA-projecting part of auditory cortex (AIV), a source of fast auditory error information; and (3) the Area X projecting part of VTA, a source of modulatory prediction error. We present a simple model in which BF microcircuits integrate these three inputs to compute a syllable-specific performance benchmark, dependent on error history, against which auditory feedback is compared during singing. Because the BF-VTA projection is conserved among vertebrates, BF routing of performance-

related signals to VTA in singing birds may generalize to mammalian and even human skill learning.

Disclosures: **A. Podury:** None. **R. Chen:** None. **P.A. Puzerey:** None. **K. Maher:** None. **J.H. Goldberg:** None.

Poster

235. Neuromodulation and New Approaches in Monitoring Vocal Learning

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 235.06/GG28

Topic: F.01. Neuroethology

Support: NIH Grant R01DC014364

NSF Grant 1457206

NSF Grant 1451034

Klingenstein-Simons Fellowship

Alpha Omega Alpha Fellowship

Title: Ventral tegmental area to basal ganglia pathway bi-directionally guides skill learning

Authors: *L. XIAO[1], G. CHATTREE[2], F. GARCIA-OSCOS[2], M. CAO[2], T. F. ROBERTS[2]
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Abstract: Reinforcement mechanisms mediated by dopaminergic projections from the ventral tegmental area (VTA) are theorized to enable learning of ethologically relevant skilled motor behaviors, but direct tests of this core idea are lacking. Here, we test the role of VTA projections to the vocal basal ganglia (vBG) in singing zebra finches, a songbird species that learns to produce a stereotyped multi-syllabic courtship song during development. We optogenetically manipulate VTA-vBG terminals in singing birds contingent on how the pitch of individual song syllables are naturally performed. We find that optical excitation and inhibition of VTA terminals have opponent effects on future performances of targeted song syllables. These manipulations are sufficient to bi-directionally guide learned changes in the pitch of targeted syllables, consistent with the VTA-vBG pathway encoding positive and negative reinforcement of performance outcomes. Moreover, learned changes in song are spectrally and temporally specific. Optogenetic manipulations do not elicit direct (motor) effects on song performance and changes to future performances are confined to only the targeted syllables and only to the pitch of those syllables. Together, our findings demonstrate that VTA inputs to the basal ganglia are

sufficient to direct learning of a naturally produced skilled motor behavior and define a central role for reinforcement mechanisms in learning vocalizations.

Disclosures: L. Xiao: None. **G. Chattree:** None. **F. Garcia-Oscos:** None. **M. Cao:** None. **T.F. Roberts:** None.

Poster

235. Neuromodulation and New Approaches in Monitoring Vocal Learning

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 235.07/GG29

Topic: F.01. Neuroethology

Support: 1R01-NS-099288

Title: Imaging basal ganglia activity associated with learned vocalizations

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Abstract: The basal ganglia (BG) play a key role in initiating, coordinating and modifying complex motor sequences. Songbirds learn to sing complex and stereotyped vocal sequences, a process that requires the activity of a song-specialized BG region, known as Area X. The dedicated nature of Area X to singing provides a rare opportunity in which BG neuronal activity can be directly linked to a readily quantifiable and complex learned behavior, namely birdsong. To better understand how BG activity correlates with singing, we combined viral expression of GCaMP6s and endoscopic calcium imaging to monitor Area X neuron activity in singing zebra finches. We found that Area X neurons with small cell body diameters suggestive of medium spiny neurons were phasically active during singing but largely inactive during periods of silence. Notably, the timing of peaks in singing-related calcium transients could vary across song renditions. In contrast, neurons in the medial striatum immediately adjacent to Area X did not show singing-related activity but were active during other movements, consistent with the idea that Area X plays a specialized role in singing. Longitudinal imaging of BG neuron activity has the potential to identify the activity signatures and population codes that underlie the acquisition and maintenance of a complex learned behavior.

Disclosures: J. Singh Alvarado: None. **M. Ben-Tov:** None. **M.G. Kearney:** None. **R.D. Mooney:** None.

Poster

235. Neuromodulation and New Approaches in Monitoring Vocal Learning

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 235.08/GG30

Topic: F.01. Neuroethology

Support: F32NS098634

Title: The cholinergic projections from basal forebrain to vocal motor cortex is required for song learning but not vocal babbling in juvenile birds

Authors: *P. A. PUZEREY[1], K. MAHER[1], N. PRASAD[1], J. H. GOLDBERG[2]
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Abstract: The basal forebrain cholinergic system (BFCS) is critical for sensory and cognitive functions, yet its role in motor learning remains poorly understood. Our current understanding of BFCS function comes largely from studies in which animals learn new behaviors to obtain food or juice rewards. However, many human behaviors, like speech or playing piano, are not learned in pursuit of tangible rewards, but instead are learned to match behavior to internal goals. Songbirds provide a tractable model system to study internally guided motor learning. Zebra finches learn to sing through trial and error by matching vocalizations to the memory of a tutor song, and have a cholinergic projection from the BF to a motor cortical nucleus RA that is homologous to the BF-motor cortical projection in mammals. Here we combine chronic, local pharmacology with in vivo circuit mapping to test how the BF-RA cholinergic pathway contributes to song learning and production. First, infusion of cholinergic receptor antagonists into RA of singing juvenile birds did not significantly affect the production of vocal babbling. Chronic blockade over weeks resulted in species-atypical long syllables and dramatically impaired song learning. Using in vivo circuit mapping, we show that antidromically identified RA projecting BF (BFra) neurons may receive functional connections from RA, motor thalamus and Area X. These preliminary results demonstrate that cholinergic inputs to vocal motor cortex are required for song learning and receive functional inputs from cortical, thalamic and basal ganglia nuclei important for song learning.

Disclosures: **P.A. Puzerey:** None. **K. Maher:** None. **N. Prasad:** None. **J.H. Goldberg:** None.

Poster

235. Neuromodulation and New Approaches in Monitoring Vocal Learning

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 235.09/GG31

Topic: F.01. Neuroethology

Support: The Netherlands Organization for Scientific Research (NWO): Rubicon Fellowship to S.M.

NIH grant - MH55987 (AJD)

Title: Aberrant burst firing in the songbird cortical-basal ganglia circuit drives both spectral and sequential changes in learned song

Authors: *S. MOORMAN, M. H. KAO
Biol., Tufts Univ., Medford, MA

Abstract: Cortical-basal ganglia circuits are critical for normal motor and reinforcement learning, including vocal learning in songbirds, and are a major site of motor pathology. The outflow nucleus of this circuit (LMAN) actively generates and regulates variability in song output (e.g., Ölveczky et al., 2005; Woolley et al., 2014). Neurons in LMAN exhibit variable burst firing that is correlated with song variability (Kao et al., 2005), and manipulations that eliminate patterned LMAN burst firing also prevent song plasticity (Kojima et al., 2013). These findings suggest that burst firing in LMAN is a mechanism for generating behavioral variability. To causally test whether augmented or aberrant burst firing in LMAN can drive song plasticity, we chronically infused the $GABA_A$ receptor antagonist bicuculline methiodide (BMI) in LMAN to artificially drive LMAN bursting in young adult zebra finches (n=7 birds). In contrast to the stereotyped, stable songs of age-matched controls, the songs of birds with BMI infusions exhibited increased variability in the morphology of individual syllables and the temporal sequence of syllables (repeats, ellisions, mis-ordering). Acute changes in syllable structure and premature song truncation were observed as described by Hamaguchi and Mooney (2012). Notably, changes in spectral properties and sequence accumulated over many days of drug infusion. Individual syllables exhibited progressively higher spectral entropy and lower entropy variance, and an increasing number of syllables were not identifiable. Moreover, sequence consistency decreased, and syllable transition entropy increased as novel sequences appeared. These effects persisted during drug washout, suggesting plasticity either in LMAN or downstream in the motor pathway. Next we investigated the locus of plasticity - did observed song changes require acute input from LMAN? Transient pharmacological inactivation of LMAN did not fully restore song performance (n=3), suggesting consolidation of changes outside of LMAN in the motor pathway. Ultimately, song did recover gradually after cessation of pharmacological infusion (n=6/6).

Our results highlight the key role of temporally patterned LMAN activity in regulating complex motor sequences. Moreover, the same signals that drive acute song variability - variably-timed burst firing in LMAN - can also drive long-lasting changes in song and may subserve feedback-based song plasticity. More generally, they imply that timing and pattern of task-related cortico-basal ganglia activity are critical for modifying or maintaining sequenced motor skills and can inform therapies for basal ganglia motor disorders.

Disclosures: S. Moorman: None. **M.H. Kao:** None.

Poster

235. Neuromodulation and New Approaches in Monitoring Vocal Learning

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 235.10/GG32

Topic: F.01. Neuroethology

Support: NSF IOS 1354906.

Title: Shifts in auditory processing across development and in response to neuromodulatory estrogens in juvenile male songbirds

Authors: *D. M. VAHABA[1], M. MACEDO-LIMA[1,3], L. REMAGE-HEALEY[1,2]
[1]Neurosci. & Behavior Grad. Program, [2]Psychological and Brain Sci., Univ. of Massachusetts Amherst, Amherst, MA; [3]Ministry of Educ. of Brazil, CAPES Fndn., Df, Brazil

Abstract: In songbirds, the caudomedial nidopallium (NCM) is a higher-order auditory region analogous to mammalian secondary auditory cortex. In adults, communication processing in NCM is rapidly enhanced by local production of estrogens, namely 17β-estradiol (E2), and E2 levels rapidly rise in NCM during song presentation. However, E2's function in NCM during development is unknown. Developing male zebra finches undergo age-limited and experience-dependent vocal learning. In the sensory phase, non-singing birds create an auditory memory of their father's song, followed by the sensorimotor phase as birds begin to match their burgeoning vocalizations to the memory of their father's song. Peripheral E2 is elevated during the critical period, and E2 in NCM dynamically fluctuates during and following song learning. Thus, we sought to clarify E2's role in auditory processing during the critical period for song learning. We collected extracellular recordings across both hemispheres of NCM in sensory and sensorimotor aged male zebra finches (N = 26), coupled with microdialysis. Artificial cerebrospinal fluid (aCSF) or E2 was continuously infused prior to and during trials. Subjects were initially administered aCSF, followed by E2, and finally aCSF. During each trial, conspecific song stimuli were presented alongside recordings and retrodialysis. Recordings were analyzed off-line and sorted for single-units. We measured spontaneous and stimulus-evoked firing rates, as well as normalized response strength. Single-unit response properties were further analyzed using a

timing-based pattern classifier. Independent of hemisphere, auditory processing and classification accuracy were substantially higher in sensory animals as compared with older sensorimotor animals. Acute E2 treatment was associated with age- and hemisphere-dependent effects. In sensory subjects, E2 decreased firing rates in left and right NCM. Intriguingly, E2 also markedly decreased classification accuracy in right but not left NCM of sensory subjects. In sensorimotor subjects, E2 decreased firing rates in left NCM, while, conversely, E2 increased firing in right NCM, without impacting classification accuracy. These data extend our understanding of estrogen-dependent neuromodulation of auditory processing across development. They reveal robust shifts in sensory processing that precisely track experience-dependent critical period learning, and suggest that E2's modulation of auditory processing markedly shifts as juvenile males transition to overt vocal-motor learning.

Disclosures: D.M. Vahaba: None. **M. Macedo-Lima:** None. **L. Remage-Healey:** None.

Poster

235. Neuromodulation and New Approaches in Monitoring Vocal Learning

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 235.11/GG33

Topic: F.01. Neuroethology

Support: NIH/NINDS R01 35467

Title: Androgens in the anterior forebrain maintain song stereotypy in adult male canaries

Authors: *G. F. BALL[1], B. A. ALWARD[2,3]
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Abstract: During breeding contexts, male songbirds tend to produce a stable, stereotyped song that facilitates mate attraction or territory defense. However, when birds are altering their songs outside of breeding contexts, their song becomes more variable. This is especially prevalent in open-ended vocal learners like male canaries (*Serinus canaria*), which undergo enhanced song variability as adults during the non-breeding season, but produce stereotyped song during the breeding season to attract a mate. The neuroendocrine mechanisms controlling vocal variability, however, are not clear. Androgens have been shown to reduce significantly vocal variability and are high during the breeding season when song is stereotyped, but low during the non-breeding season when song is highly variable. We housed male canaries on short days (SD) to simulate non-breeding conditions. We used flutamide to bilaterally block androgen receptors (AR) in the lateral magnocellular nucleus of the anterior nidopallium (LMAN), a cortical-like brain region of the song control system that is known as a vocal variability generator. Immediately following surgery, birds were placed on long days (LD) to simulate the breeding season. We recorded song while birds were housed on SD and LD. Blocking AR in LMAN caused a significant increase in

the acoustic variability of song and this was paralleled by a substantial increase in the acoustic variability of syllables. We have previously shown that blocking AR in HVC, a sensorimotor region involved in song production, caused increased syllable usage variability and syllable sequence variability, while not affecting syllable acoustic variability. However, blocking AR in the robust nucleus of the arcopallium, a premotor brain region leads to increased syllable acoustic variability, similar to the current results of AR blockade in LMAN. Indeed, LMAN projects directly to RA and it is via this pathway that LMAN is thought to introduce variability into the song control system. These results suggest androgen signaling in LMAN is important for controlling vocal variability and highlight the pleiotropic nature of steroid hormones in controlling complex social behaviors such as birdsong.

Disclosures: G.F. Ball: None. **B.A. Alward:** None.

Poster

235. Neuromodulation and New Approaches in Monitoring Vocal Learning

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 235.12/HH1

Topic: F.01. Neuroethology

Support: NIH R01 MH53032

University of Virginia

Title: Dynamics of neuronal birth, addition, and survival in a sensorimotor circuit responsible for song production during transition into breeding condition

Authors: *R. HU[1], B. SETIJONO[1], Y. TOKAREVA[1], Y. SUN[1], E. A. BRENOWITZ[2], T. LARSON[3]
[1]Psychology, Univ. of Washington, Seattle, WA; [2]Univ. of Washington Dept. of Psychology, Seattle, WA; [3]Dept. of Biol., Univ. of Virginia, Charlottesville, VA

Abstract: Few brains show as extreme an ability to generate and add new neurons as those of songbirds. Seasonally breeding songbirds exhibit rapid changes in the rate of neurogenesis, survival of mature neurons, and as a result, total volume of brain regions that contribute to the production of song. For example, the songbird Gambel's white-crowned sparrow (*Zonotrichia leucophrys gambelli*) is capable of adding more than 68,000 neurons to a region of the brain responsible for song production called HVC (proper name), all within four days of transition to breeding conditions. Along with this addition in new neurons, these sparrows also increase song production and song quality. To identify the dynamics between neurogenesis and the addition of new HVC neurons during rapid seasonal growth, we labeled dividing neural stem cells and their progeny and quantified the incorporation of these progeny into HVC. Throughout the course of

the experiment, we recorded individual bird's song and analyzed the spectral features and stereotypy of whole songs. We assessed correlations between song stereotypy and rate, neuronal changes within HVC, and neural stem cell proliferation in the nearby ventricular zone during seasonal rapid growth. Identifying the dynamic interactions between stem cell proliferation, neuronal addition and survival, and a biologically relevant behavior will allow for further identification and testing of molecular and physiological mechanisms underlying behaviorally relevant adult neurogenesis.

Disclosures: R. Hu: None. **B. Setijono:** None. **Y. Tokareva:** None. **Y. Sun:** None. **E.A. Brenowitz:** None. **T. Larson:** None.

Poster

235. Neuromodulation and New Approaches in Monitoring Vocal Learning

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 235.13/HH2

Topic: F.01. Neuroethology

Support: NIH GRANT R01-NS-099288

NIH GRANT F30-NS-096871

Title: The songbird VTA integrates opponent evaluative signals for vocal learning

Authors: *M. G. KEARNEY[1,2,3], E. HISEY[2,1], R. MOONEY[2,1]
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Abstract: Learning complex skills depends on the brain's ability to evaluate performance and then use this evaluative information to adaptively shape behavior. How evaluative signals are integrated in the brain to shape behavior remains poorly understood. Research in rodents and monkeys indicates that the Ventral Tegmental Area (VTA) is the source of error signals that can adaptively shape behavior. However, dissociating the specific evaluative information conveyed by inputs into the VTA has proven challenging as the mammalian VTA receives a wide variety of inputs and is important to the adaptive modification of a wide range of behaviors. Songbirds resemble humans in their capacity for vocal learning and the songbird brain contains interconnected brain nuclei ("the song system") that play a specialized role in singing and song learning. Intriguingly, the song system includes a specialized subset of VTA neurons that are critical to juvenile and adult forms of song learning but not to performing other behaviors. This specialized organization may simplify the analysis of how the VTA integrates information from distinct inputs to adaptively shape a complex behavior, namely birdsong. Here we find that two anatomically distinct inputs into the songbird's VTA, originating in the ventral intermediate arcopallium (Aiv) and the Ventral Pallidum (VP) respectively, exert opposing effects on song

performance. Using closed loop optogenetic stimulation in singing adult zebra finches, we found that pairing optogenetic stimulation of Aiv-VTA terminals with certain syllable variants subsequently makes the bird less likely to sing those variants. In contrast, syllable-contingent stimulation of VP-VTA terminals subsequently makes the bird more likely to produce syllable variants paired with stimulation. These findings support a model in which anatomically distinct pathways to the songbird's VTA convey opponent evaluative signals about song performance. Indeed, a prior study (Mandelblat-Cerf et al. 2014) showed that Aiv neurons that project to the VTA might encode vocal errors, information that could be used by the VTA to negatively reinforce vocal performance. Notably, the current findings suggest that the VP transmits information to the VTA that is used to positively reinforce vocalization. Given that juvenile songbirds learn to sing by matching their own performance to a memorized copy of a tutor song, the VP or regions upstream of the VP may play a role in detecting matches between the pupil's song and that of his tutor.

Disclosures: M.G. Kearney: None. **E. Hisey:** None. **R. Mooney:** None.

Poster

235. Neuromodulation and New Approaches in Monitoring Vocal Learning

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 235.14/HH3

Topic: F.01. Neuroethology

Support: Hokkaido University`s Integrated Science Program (ISP) to C. N. Asogwa

JSPS KAKENHI 16H01261 to Kazuhiro Wada

Title: Species-specificity and individual difference of muscarinic acetylcholine receptor expression in the song circuits

Authors: *C. N. ASOGWA[1], M. SANCHEZ-VAPUESTA[1], S. HAYASE[2], C. MORI[4], K. WADA[3]
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Abstract: Receptors for acetylcholine, AChRs, abound in the CNS, and belong to functional classes that mediate neuromodulatory responses via distinct signal transduction pathways. AChRs have been proposed to play roles in learning, memory, intelligence, and motor performance. However, the functions of AChRs in neural circuits for vocal learning remain largely unexplored. Here, we report unique specialized expression of the muscarinic receptors subclass (chrm 2-5) in the song circuits for vocal learning and production in songbirds. We find

that the excitatory mAChRs (chrm 3 and 5) subunits are less expressed in the song nuclei. In contrast, two inhibitory mAChRs subunits (chrm 2 and 4) showed developmentally different expression in the premotor song nucleus HVC during the critical period of song learning. Intriguingly, chrm2 was selectively expressed in HVC to Area X and to RA projection neurons with a wide range of individual differences in the zebra finch. Individual difference of chrm2 expression in HVC was observed in the early stage of critical period before initiation of subsong singing. Furthermore, chrm2 expression in HVC exhibits species-specific expression among songbirds. These results suggest chrm2 may contribute to acquisition of species-specificity and individual difference of song patterns through the modulation of excitability and inhibitive properties of HVC projection neurons.

Disclosures: C.N. Asogwa: None. **M. Sanchez-Vapuesta:** None. **S. Hayase:** None. **C. Mori:** None. **K. Wada:** None.

Poster

235. Neuromodulation and New Approaches in Monitoring Vocal Learning

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 235.15/HH4

Topic: F.01. Neuroethology

Support: Postdoctoral Fellowship for Research Abroad

1R01-NS-099288

NSF IOS-1354962

Title: Instructive auditory experience shapes a songbird premotor cortex via midbrain dopamine neurons to guide song learning

Authors: *M. TANAKA[1], R. MOONEY[2]
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Abstract: Midbrain dopamine (DA) neurons transmit reward prediction error signals to the basal ganglia (BG) that are important to reinforcement learning of motor skills. However, the function of midbrain DA projections to other brain regions and to other forms of learning remains largely unexplored. Juvenile zebra finches memorize a tutor song in a sensory learning phase and then make a precise copy of this tutor song in a process of sensorimotor learning. The songbird brain contains a subset of midbrain DA neurons located in the ventral tegmental area (VTA) that project to a specialized part of the BG necessary to sensorimotor learning. Moreover, certain midbrain DA neurons project to the premotor cortical analogue HVC, a telencephalic brain nucleus that is essential to singing and for sensory learning. To understand a role of DA inputs to HVC in song learning, we blocked DA signaling in HVC of male juvenile zebra finches at

different stages of song learning. Permanently ablating DA axon terminals in HVC by bilateral injection of 6-hydroxydopamine (6-OHDA) into HVC of juvenile birds in the early sensory learning phase disrupted song copying, which could indicate a role for DA signaling in HVC in either sensory or sensorimotor learning phases. To determine which phase DA signaling in HVC contributes to, we used microdialysis methods to reversibly block DA receptors in HVC either during or immediately after daily tutoring sessions spanning 5 days. Blockade of D1- and D2-type receptors during tutoring sessions severely disrupted copying, whereas juveniles subjected to similar blockade immediately after tutoring exhibited little or no copying deficits. Furthermore, blocking D1 receptors during tutoring sessions was sufficient to disrupt subsequent song copying, suggesting that D1 receptors in HVC play a critical role in formation of the tutor song memory. Histological examination revealed that most of the dopaminergic efferents in HVC originate from the central gray (GCt) in the midbrain in the sensory learning phase. Tetrode recordings of GCt activity in a freely-behaving juvenile bird showed that a subset of GCt neurons were strongly activated during the juvenile's first encounter with a singing tutor. Furthermore, tetrode recordings in HVC in another juvenile revealed that HVC neurons rapidly increase bursting activity and acquire selective auditory responses to the tutor song within an hour after first hearing a live tutor. This study indicates that midbrain DA neurons that project to sensorimotor regions of the cortex play an important role in forming long lasting auditory memories that are subsequently used to guide vocal imitation.

Disclosures: M. Tanaka: None. **R. Mooney:** None.

Poster

235. Neuromodulation and New Approaches in Monitoring Vocal Learning

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 235.16/HH5

Topic: F.01. Neuroethology

Support: NSF Grant 1557499

NSF MRI 1626008

NSF - IGERT Traineeship

Title: Characterization of mating posture and modulatory nuclei in a female songbird

Authors: *A. PERKES[1], C. MESSIER[1], D. IPPOLITO[2], M. WILD[3], M. SCHMIDT[1]
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Abstract: Female birds produce a copulation solicitation display (CSD) in response to male song which invites and facilitates copulation. CSD has high potential for investigating the neural basis

of mating posture and mate choice, but lacks the foundation necessary for such an approach. Here we seek to establish the brown-headed cowbird (*Molothrus ater)* as a model system by characterizing the behavior and neuroanatomy of CSD.
Female cowbirds do not produce learned vocalizations, but selectively produce CSD to certain male songs. The highly selective nature of the behavior and the ease with which is can be observed make this species highly valuable as a model to study female sexual preference. Despite many studies using CSD, the behavior and the mechanisms of control are poorly understood. Previous studies indicate that parts of the avian song system–a set of nuclei necessary for producing learned vocalizations–are necessary for CSD selectivity. Although elements of the song system in the non-singing female have been demonstrated previously, a full characterization of the different components has never been performed in a single species. Here we identify the location and connectivity of the various nuclei that make up the song system in male birds. We show that female cowbirds possess a distinct nucleus RA (robust nucleus of the arcopallium) which is innervated by a tight cluster of neurons in LMAN (lateral magnocellular nucleus) as well as a more diffuse cluster of neurons in the location of HVC. As previously shown, RA has strong projections to the same brainstem areas as in males, including RAm (n. Retroambigualis), a multifunctional nucleus that likely drives expiration, posture and the cloaca. We plan to further characterize the spinal motor neuron targets of RAm that innervate the cloaca as well as muscles activated during CSD. We also plan to characterize auditory input structures to the song system as well as the connectivity patterns of the anterior forebrain pathway, a circuit that guides song learning and maintenance.
Correlating CSD with neural activity is challenging without a quantitative description of CSD. We use an array of cameras to record CSD with high temporal and spatial precision. We then use feature recognition to reconstruct posture, allowing for a statistical comparison of small differences in CSD. We will quantify CSD upon presentation of male song to females in breeding phase, observing intrinsic variability and whether variability in posture correlates with song preference. By developing these techniques, we can use cowbirds as a powerful model system for studying the neural correlates of copulatory posture and mate choice.

Disclosures: A. Perkes: None. **C. Messier:** None. **D. Ippolito:** None. **M. Wild:** None. **M. Schmidt:** None.

Poster

235. Neuromodulation and New Approaches in Monitoring Vocal Learning

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 235.17/DP08/HH6 (Dynamic Poster)

Topic: F.01. Neuroethology

Support: APVV-15- 0077

VEGA 2/0177/14

Title: Basal ganglia damage can cause unexpected transient alterations in a songbird`s brain

Authors: *K. LUKACOVA[1], J. HAMAIDE[2], A. VAN DER LINDEN[2], L. NIEDEROVA-KUBIKOVA[1]
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Abstract: Area X, a basal ganglia nucleus, is essential for vocal learning in young songbirds, and for song maintenance and the correct transition from one song motif to another in adult male zebra finches. Both in songbirds and humans, damage to the basal ganglia leads to similar abnormalities in learned vocal communication, including stuttering and changes in song tempo. Here we aimed to establish a spatio-temporal profile of structural neuroplastic events possibly related to alterations in song performance, that occur after induction of a neurotoxic lesion in Area X in adult male zebra finches. To this end, 12 adult male zebra finches were repeatedly scanned pre-op (baseline) and up to four months post-op using a magnetic resonance-based imaging tool sensitive to detect alterations to microstructural tissue properties in the living brain, i.e. diffusion tensor imaging (DTI). In addition, prior to each *in vivo* imaging session, the songs of the birds were recorded. We found changes in several DTI parameters, reflecting structural neuroplastic events, in the thalamic area efferent to the damaged region. Interestingly, structural changes were found also in a brain region not linked with learned vocal communication up to now, i.e. the cerebellum. Further, we also detected changes in song performance. In line with previous studies, song motif initially increased and two days after induction of the neurotoxic lesion it slowly decreased leading to a significantly lower motif length 4 months after induction of the neurotoxic lesion. Syllable length significantly decreased immediately after the damage, and kept this trend up to four months post-op. In contrast, the inter-syllable interval length/duration became longer. Syllable pitch slowly decreased by two months post-op after which it returned back to the baseline levels. Wiener entropy increased with the peak at three months post-op. Currently, we analyze if there is a relationship between structural neuroplastic brain changes and changes in the song performance. Further, we performed immunohistochemical stainings of FoxP2 and perineuronal nets to obtain a better understanding of neuroplastic changes in the brain. These analyses are in progress. Our results indicate that, similarly as in humans, a connection between basal ganglia and other brain areas such as the cerebellum exists. This provides an opportunity to further study the function of these areas in vocal learning and production.

Disclosures: **K. Lukacova:** Other; Grant support APVV-15- 0077, Grant support VEGA 2/0177/14. **J. Hamaide:** None. **A. Van der LInden:** None. **L. Niederova-Kubikova:** None.

Poster

235. Neuromodulation and New Approaches in Monitoring Vocal Learning

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 235.18/HH7

Topic: F.01. Neuroethology

Support: Howard Hughes Medical Institute, HHMI Investigator Funds

NIH Grant T32 MH089920

NIH Grant MH55987

NIH Grant 5R03NS078777-02

NIH Grant DC006636

NIH Grant DC011356 Project #00040917

Title: Cholinergic modulation of song motor control in adult songbirds

Authors: *P. I. JAFFE[1], M. S. BRAINARD[2,3,4]
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Abstract: The cholinergic neuromodulatory system alters global brain states and neuronal response properties across the forebrain. In primary visual cortex, acetylcholine alters the magnitude of sensory responses[1] and enhances response reliability[2]. However, a complementary understanding of cholinergic modulation of motor forebrain regions and motor output in any system is lacking. Here, we investigate cholinergic contributions to the production of adult birdsong, a motor skill controlled by a hierarchy of well-defined motor nuclei. Previous work has shown that the song premotor nucleus HVC receives cholinergic inputs that can drive changes to cell excitability in slices[3] and alter sensory response properties *in vivo*[4]. We investigated the contributions of cholinergic input to the production of adult song by reversibly dialyzing the cholinergic agonist carbachol into HVC of singing birds. We found that carbachol increased pitch and decreased pitch variability through muscarinic receptors, analogous to cholinergic modulation of sensory response magnitude and cholinergic enhancement of sensory response reliability. To determine the pathway downstream of HVC by which acetylcholine influenced behavior, we infused carbachol into HVC while inactivating LMAN, the output nucleus of a basal ganglia-forebrain circuit required for song learning and social modulation of song variability[5]. The increase in pitch persisted during LMAN inactivation while the reduction in pitch variability was greater than with either manipulation alone, indicating that acetylcholine acts directly on the song motor pathway to increase pitch and decrease pitch variability. Our

findings suggest that acetylcholine modulates neuronal circuits to produce conserved transformations of input-output relationships in diverse forebrain areas.

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Disclosures: P.I. Jaffe: None. **M.S. Brainard:** None.

Poster

235. Neuromodulation and New Approaches in Monitoring Vocal Learning

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 235.19/HH8

Topic: F.01. Neuroethology

Support: NIH grant NS092299

Title: Singing-related activity in an evaluative cortico-basal ganglia circuit of juvenile songbirds during sensorimotor learning

Authors: *R. C. YUAN, S. W. BOTTJER
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Abstract: Similar to speech acquisition in infants, vocal learning in juvenile songbirds requires iterative comparisons between feedback of the juvenile's variable motor output and the target tutor sounds that the juvenile is learning to imitate. In juvenile zebra finches, two parallel cortico-basal ganglia circuits are essential for vocal learning: a "motor" circuit drives vocal output, while an "evaluative" circuit is necessary for developing an accurate copy of the tutor song. Importantly, this evaluative circuit also contains distinct neural representations of the tutor song and the current version of the bird's own song. In juvenile birds only, neurons from the motor circuit send a corollary projection into a cortical target region, AId, of the evaluative circuit. AId is thus well-situated to integrate efference copy of the juvenile's vocal output from the motor circuit with information about the tutor song and/or feedback of current vocal behavior. However, whether AId neurons actually encode information about the juvenile's vocal

behavior is unknown. We investigated this question by making chronic extracellular recordings in AId of singing juvenile birds during the early sensorimotor learning period (35-50 dph). Singing episodes were defined as periods of continuous singing separated by at least one second of silence. The average firing rate of neurons across all singing episodes was greater than the firing rate during baseline periods in three sites within AId ($p < .01$). In contrast, recordings in AId of anesthetized juvenile birds during playback of various song stimuli (including each juvenile's own song, a juvenile conspecific song, and the adult tutor song) revealed no significant difference in average firing rate during song presentation compared to baseline for any song stimulus ($p > 0.05$; $n = 19$ sites across 11 birds), indicating that AId neurons do not respond to passive exposure to auditory vocal stimuli. These preliminary results suggest that AId neurons exhibit increased activity in juvenile birds only during production of song behavior as they are actively engaged in sensorimotor learning. Such singing-related activity could reflect efference copy from the motor circuit, which may be necessary for vocal learning during development: for instance, information about current vocal output could be compared against the tutor song in the evaluative circuit to direct accurate refinement of the juvenile's immature vocalizations. In addition, efference copy of active singing behavior may act as a gate to ensure that tutor song comparisons are made only against auditory feedback of self-generated vocal behavior.

Disclosures: R.C. Yuan: None. **S.W. Bottjer:** None.

Poster

235. Neuromodulation and New Approaches in Monitoring Vocal Learning

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 235.20/HH9

Topic: F.01. Neuroethology

Title: Neural specializations for audition in the spectacular tui

Authors: *P. MILLER
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Abstract: The tui (*Prosthemadera novaeseelandiae*) is a honeyeater bird endemic to New Zealand that is capable of producing over 1000 syllables and replicating complex speech, and is in many respects an auditory specialist. There are also indications that they may be producing ultrasound. Specializations for audition have been recognized in other bird species, such as barn owls, and research has shown that these specializations are accompanied by enlargements to auditory regions of their brain, such as the nucleus mesencephalus pars dorsalis (MLd). The aim of this research was to determine if the complex vocal behavior of tui is associated with enlargements to neural regions that process audition. Brains were sectioned, stained using Nissl and volumes obtained from the nucleus magnocellularis (NM), nucleus laminaris (NL), nucleus

angularis (NA), MLd, the robust nucleus of archopallium (RA), Area X and the higher vocal center (HVC). Regression models were used to assess how the volumes of tui's auditory nuclei compare to other species of birds, including other songbirds. Interestingly, results suggest that the relative size of most auditory regions in the tui are significantly smaller when compared to other birds, including galliformes (chicken like birds). Further, this was a trend found across all songbirds, which had relativity smaller auditory brain regions than other birds. Possible explanations for this include that the auditory nuclei in song songbirds do not scale with overall brain size like other birds, that the cell density is higher in songbirds, or that the cells in these nuclei are smaller. Alternatively, as a derived bird linage, songbirds may have evolved an auditory system that can achieve the necessary extra neural processing power needed for their complex song system without increasing the size of their auditory system.

Disclosures: P. Miller: None.

Poster

235. Neuromodulation and New Approaches in Monitoring Vocal Learning

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 235.21/HH10

Topic: F.01. Neuroethology

Support: Seed Fund from Big Ideas Generator (BIG) at The University of Chicago

NSF-BCS-16326465

Title: Telencephalic song nuclei of the anesthetized zebra finch brain exhibit functional homotopy in the absence of known direct white matter projections

Authors: *E. A. LAYDEN, K. E. SCHERTZ, M. G. BERMAN, S. E. LONDON
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Abstract: A number of mammals, including humans, macaques, mice, and rats, consistently exhibit strong interhemispheric functional connectivity (FC) between geometrically corresponding (i.e., homotopic) brain regions. Homotopic FC is known to develop and persist even in cases in which humans are born without a corpus callosum. Although songbirds are extensively studied as a model of vocal learning, it is unknown whether the avian brain similarly exhibits a homotopic functional organization. Notably, the adult male zebra finch (*Taeniopygia guttata*) relies on a balance of lateralized functional specialization and tightly coupled interhemispheric communication to successfully sing, yet no white matter projections are known to directly connect telencephalic song nuclei across hemispheres. Given the behavioral importance of interhemispheric communication in zebra finches, and the seeming ubiquity of functional homotopy in mammals, we sought to investigate whether this pattern of FC was also

evident in the zebra finch brain at rest. We acquired 12-minute resting-state functional MRI scans and anatomical scans using a 9.4 T Bruker scanner for two male zebra finches at days 25, 45, and 65 post-hatch, and for six female zebra finches, two at each age. After completing a standard preprocessing sequence, we computed FC between a set of bilateral song nuclei, including Area X, LMAN, RA, HVC, Auditory Forebrain (NCM, CMM), and Field L. Specifically, FC was defined as the Pearson correlation between two nuclei time series; correlations were Fisher transformed and standardized across each scan. Controlling for age and sex, we implemented a linear mixed-effects model to investigate whether connection type (homotopic, heterotopic-ipsilateral, heterotopic-contralateral) predicted nuclei-to-nuclei FC strength. Analyses revealed that homotopic connections were significantly stronger than heterotopic-ipsilateral connections (β = 1.04, $t(786) = 8.59$, $p < .001$), whereas heterotopic-contralateral connections did not significantly differ from heterotopic-ipsilateral connections (β = -0.10, $t(786) = -1.41$, $p > .15$). To our knowledge, this represents the first demonstration of functional homotopy in the avian brain, contributing to a growing list of vertebrates which exhibit this pattern. The emergence of homotopy in the absence of direct structural connectivity merits further investigation: delineation of the structural and functional pathways underlying this pattern may prove insightful for understanding interhemispheric communication in the zebra finch and may also yield potentially useful insights for human disorders of the corpus callosum.

Disclosures: E.A. Layden: None. **K.E. Schertz:** None. **M.G. Berman:** None. **S.E. London:** None.

Poster

235. Neuromodulation and New Approaches in Monitoring Vocal Learning

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 235.22/HH11

Topic: F.01. Neuroethology

Title: Monitoring of social interactions in laboratory animals by a 3D tracking opto-ultrasonic system

Authors: *A. L. VYSSOTSKI[1], D. L. VYSSOTSKI[2]
[1]Inst. of Neuroinformatics, Univ. of Zurich and ETH Zurich, Zurich, Switzerland; [2]Evolocus LLC, Tarrytown, NY

Abstract: Social interactions in animals are mediated by a large variety of signals including body movements and vocalizations. In small animals such as laboratory rodents or birds an inter-individual interaction goes through fast exchange of communicative signals of different nature. The rate of signals can be above human ability to follow events. A video record analysis can be time-consuming. Modern multi-camera tracking systems allow simultaneous monitoring of movements of several individuals, but have difficulties in tracking of small animals (~ 1 cm) at

moderate spatial scales (~ 5 m). A precise identification of a vocalizing animal in a group of closely located individuals can be done by animal-attached contact microphones (Nature Methods, 2014, doi:10.1038/nmeth.3114), but the audio records should be somehow synchronized with the video data.
To resolve problems of known methods, we have developed and tested a novel opto-ultrasonic system for three-dimensional animal tracking in laboratory conditions. A mobile device that has one infrared and one ultrasonic sensor, equipped with memory and/or radio transmitter, is attached to a moving creature. One compact stationary box is placed in the vicinity; it emits a pre-determined sequence of short infrared pulses, short ultrasonic signals and two planar, radially emitted light beams that move through the area of interest with constant angular speed in two orthogonal directions. The mobile device receives two angular coordinates in the form of two time intervals between an infrared pulse and the next two orthogonal planar beam receptions, and it receives one linear coordinate in the form of the time interval between an infrared pulse and the next ultrasonic signal reception, taking into account the speed of sound in the air. The ultrasonic emitter is driven by a pulse-width modulated signal to make it undetectable by animals. Several above-mentioned compact stationary boxes can be placed within the field of animal movements to increase robustness of tracking, or to use exclusively optical or exclusively ultrasonic signals for 3D animal tracking. To detect fine and rapid movements of the animal, as well as its body orientation, a 3D accelerometer, a 3D gyroscope and a 3D magnetic compass are installed on the mobile receiver to achieve autonomous inertial tracking. Vocalization of the animal was acquired by a contact microphone, and perceived auditory stimulation - by an ordinary animal-attached microphone. The laboratory test has demonstrated reliable 3D tracking together with body orientation and vocalization recording of several animals equipped with mobile receivers. Patents are pending in the USA and other countries.

Disclosures: **A.L. Vyssotski:** None. **D.L. Vyssotski:** None.

Poster

235. Neuromodulation and New Approaches in Monitoring Vocal Learning

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 235.23/HH12

Topic: F.01. Neuroethology

Support: NSF GRFP DGE-1256259

NSF GROW Travel Allowance

JSPS Postdoctoral Fellowship (Strategic Program)

Title: Neurotensin and neurotensin receptor 1 mRNA expression in song-control regions changes during development in male zebra finches

Authors: *D. P. MERULLO[1], C. N. ASOGWA[2], M. SANCHEZ-VALPUESTA[2], K. WADA[2], L. V. RITERS[1]
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Abstract: Vocal communication is an essential component of social signaling in many vertebrate species. Some animal groups, such as songbirds, learn vocalizations during development. Effective vocal learning therefore is crucial for proper social functioning, yet the precise mechanisms underlying this process are not entirely clear. In songbirds, dopamine and its receptors change during song learning in song-control nuclei including HVC, LMAN, Area X, and RA. The neuropeptide neurotensin (NT) and the NT receptor 1 (NTR1) strongly interact with dopamine signaling and can enhance dopamine activity by depolarizing dopamine neurons or reducing D2 receptor-mediated inhibition. Interactions between NT and dopamine could contribute to the song learning process. In the present study, NT and NTR1 mRNA expression was analyzed in song-control regions of male zebra finches in four different stages of song development: pre-subsong (25 days post-hatch; dph), subsong (45 dph), plastic (60 dph), and crystallized (130 dph). During the pre-subsong stage, NT expression was highest in LMAN, and NTR1 expression was highest in HVC, Area X, and RA. No changes were seen in other developmental stages, although NT and NTR1 showed different overall expression patterns. NT was present in HVC and LMAN, and absent in Area X and RA. NTR1 was seen in HVC, Area X, and RA, but not LMAN. Neither NT nor NTR1 was expressed in DLM. These changes in NT and NTR1 expression at crucial time points for song development are similar to changes observed in dopamine studies and may facilitate vocal learning through interactions with the dopamine system.

Disclosures: D.P. Merullo: None. **C.N. Asogwa:** None. **M. Sanchez-Valpuesta:** None. **K. Wada:** None. **L.V. Riters:** None.

Poster

235. Neuromodulation and New Approaches in Monitoring Vocal Learning

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 235.24/HH13

Topic: F.01. Neuroethology

Support: NIH Grant DC004722-18

NSF Grant 1261872

Title: Individual difference in early vocalization predicts the propensity for imitative vocal learning in zebra finches

Authors: *T. HAYASHI, D. LIPKIND, J. HYLAND BRUNO, O. TCHERNICHOVSKI
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Abstract: Young songbirds produce vocal babbling called subsong. Subsong changes gradually over development, until it resembles the song of an adult bird (tutor) that the young bird chose to imitate. We trained juvenile zebra finches to imitate song playbacks (simulating a tutor) and tested if the acoustic feature of their early subsongs (produced prior to hearing song playbacks) can predict the outcome of song imitation. We found that the distribution of one song feature, called Wiener entropy, can predict imitation fidelity (the similarity of the imitation to the song playbacks presented to the bird). Wiener entropy is a measure of the width of the power spectrum (tonality). The distribution of Wiener entropy during the subsong stage correlates strongly with later song similarity to the model song. In general, birds with subsongs of higher entropy (broader-band power-spectrum) were more likely to develop a song, similar to that of the playbacks presented to them. Thus, individual difference in early vocalization can predict vocal learning outcome.

Disclosures: T. Hayashi: None. **D. Lipkind:** None. **J. Hyland Bruno:** None. **O. Tchernichovski:** None.

Poster

235. Neuromodulation and New Approaches in Monitoring Vocal Learning

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 235.25/HH14

Topic: F.01. Neuroethology

Support: HHMI

NSF GRFP

Title: Further resolution of hypotheses on convergent brain regions for learned song in songbirds and speech in humans

Authors: *G. GEDMAN[1], *G. GEDMAN[1], A. R. PFENNING[2], M. WIRTHLIN[3], J.-N. AUDET[1], E. D. JARVIS[1]
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Abstract: Vocal learning is a rare, complex, convergent behavior seen in several independent lineages of birds and mammals, including humans, and is the basis for learned speech. To explain this convergent behavior, several competing hypotheses have been proposed for convergent song/speech brain regionts in song learning birds and humans. For example, one hypothesis proposed by Doupe and colleagues is that songbird RA and HVC of the song

production pathway are broadly analogous to human laryngeal motor cortex (LMC) and Broca's area respectively; another proposed by Jarvis and colleagues is that HVC and RA are specifically analogous to layers 3 and 5 of LMC, whereas the songbird LMAN vocal learning nucleus is analogous to layer 3 of Broca's area. Recent transcriptome analyses using microarrays from our group supported the hypothesis that RA is analogous to layer 5 of human LMC, but findings for HVC were inconclusive; in contrast, recent brain cooling experiments from the Long lab concluded that HVC was more similar to Broca's area than to LMC. These inconclusive and alternative results for HVC may be attributed to not having profiled genes of the cell populations surrounding HVC, limited genes on microarrays, computational tools that prevented mapping of two or more avian brain regions to one region in humans with multiple cortical layers. To test these alternatives, we conducted RNA-seq experiments of all four major song nuclei and surrounding cell populations of the zebra finch (a songbird), and compared them with human (column specific) and macaque (cortical layer specific) microarray brain data from the Allen Institute for Brain Science, with new hypothesis-driven computational tools that allowed for cortical layer specific analyses within the same region. These new studies strongly confirmed that RA has a specialized molecular profile most similar to the human LMC and layer 5 neurons of primate primary motor cortex (PMC). HVC was found to have a specialized profile similar similar to LMC, more so than to Broca's area, and specifically to layer 3 neurons of primate PMC. The arcopallium motor pathway cells adjacent to RA and the nidopallium cells adjacent to HVC (as well as LMAN) also shared significant molecular specializations with layers 5 and 2/3 of the PMC. These new findings with many more genes and more brain regions support the hypothesis that RA and HVC are analogous to different cortical layers of human LMC, as well as support the broader nuclear-to-layer hypothesis of avian and mammalian brain cell type homologies.

Disclosures: G. Gedman: None. **A.R. Pfenning:** None. **M. Wirthlin:** None. **J. Audet:** None. **E.D. Jarvis:** None.

Poster

235. Neuromodulation and New Approaches in Monitoring Vocal Learning

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 235.26/HH15

Topic: F.01. Neuroethology

Support: F32NS062609

P60AA010760

Title: The effect of alcohol on activation of zebra finch vocal control circuitry

Authors: *C. R. OLSON[1], S. R. FRIEDRICH[2], A. E. RYABININ[3], C. V. MELLO[4]
[1]Dept. of Physiol., Midwestern Univ., Glendale, AZ; [2]Behavioral Neurosci., Oregon Hlth. & Sci. Univ., Portland, OR; [3]Dept. of Behavioral Neurosci., Oregon Hlth. and Sci. Univ., Portland, OR; [4]Dept. of Behavioral Neurosci., Oregon Hlth. and Sci. Univ. Sch. of Med., Portland, OR

Abstract: Speech impairment is a widely-known cognitive effect of alcohol consumption, however the neural mechanisms underlying alcohol-induced speech impairment remain unknown. This gap in understanding exists because invasive techniques are not appropriate for use in human subjects, and most traditional model organisms lack robust, learned vocal behaviors that mirror human speech. Yet zebra finches, a songbird species, learn their vocalizations from tutors, a process analogous to how humans acquire speech. They also readily drink alcohol and have altered song while under the influence. Thus, zebra finches are particularly well-suited to examine the neural effects of alcohol on a learned vocal behavior. We used the immediate early gene *EGR1* (a.k.a. ZENK) as a proxy for neural activity to investigate how alcohol may affect the forebrain vocal circuitry of zebra finches. We assessed nuclei of the posterior pathway (RA, HVC), which is involved primarily in vocal-motor control, and of the anterior pathway (LMAN, and Area X), involved mostly in vocal learning and plasticity. We examined both adults, where song is stable, and juveniles during the vocal learning period. In adults, we found singing-related *EGR1* expression in all nuclei examined in both drinking and non-drinking birds, although *EGR1*-positive cell counts were not significantly different between groups. Alcohol exposure revealed a trend for lower *EGR1* expression within vocal-motor nucleus RA. In contrast, we found significantly decreased expression in juveniles. This effect was most evident in the anterior pathway, including Area X and X-projecting cells of HVC. These observations point to a possible age-related mechanism by which alcohol alters vocal learning, and suggests that the vocal circuitry of adults may be less vulnerable to the actions of alcohol.

Disclosures: C.R. Olson: None. **S.R. Friedrich:** None. **A.E. Ryabinin:** None. **C.V. Mello:** None.

Poster

236. Microbiota, Immunity, and Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 236.01/HH16

Topic: F.04. Stress and the Brain

Support: IOER funds

Title: Effects of stress on the human gut microbiome

Authors: J. JOHNSON[1], A. SHOSKES[1], Z. REHMAN[1], *L.-L. YUAN[2]
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Abstract: The central nervous system (CNS) and gastrointestinal (GI) tract interact via bidirectional communication, and the microbiota of the gut play an important role in mediating this signaling. Our interest lies in the effect of stress on GI microbiota and the role the microbiome plays in coping with stress. We intend to investigate the relationship between chronic stress and the gut microbiota in our own medical students, by comparing the taxonomic composition present in fecal samples before and after various amount of time in medical school. Incoming first-year medical students were recruited (n=31) for the study. Using stress/anixety surveys and physiological measures such as blood cortisol levels, we evaluate their levels of stress before their first year starts and at two additional time points (October and December) throughout their first semester. Additionally, GI microbiome samples are taken to assess gut microbial populations at each time point. Initial findings suggest that the level of depression at the mid-term was elevated comparing with the beginning of the semester. This elevation was accompanied with a significant increase in the ratio of *firmicutes*: *bacteroidetes (F: B)*, the largest phyla in human gut microbiome. Increased F: B ratio has been linked with poorer health/obesity in humans. Additional data analysis of gut microbial changes to stress and depression is underway. Results yield from this study, once it is completed, may shed light on potential treatment to reduce stress/anxiety in general, as well as to promote wellbeing of our future health care providers and physicians.

Disclosures: J. Johnson: None. **A. Shoskes:** None. **Z. Rehman:** None. **L. Yuan:** None.

Poster

236. Microbiota, Immunity, and Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 236.02/HH17

Topic: F.04. Stress and the Brain

Support: NIH Grant 5R21MH108156-02

Title: Investigating the gut-immune-brain axis in stress and depression

Authors: *C. P. ADDINGTON[1], I. A. MARIN[2], J. KIPNIS[1], A. GAULTIER[1]
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Abstract: In 2016, 1 of every 15 adults in the U.S. suffered an episode of major depressive disorder; 10-30% of which are resistant to treatment, leaving many questions about the cause of depression unanswered. We and others have previously shown that mice exhibiting depressive

behavior present with changes to their gut microbiome. Specifically, we observed a decrease in *Lactobacillus* in the gut of mice subjected to the unpredictable chronic mild stress (UCMS) model of depression compared to naïve. Additionally, we have recently reported that depressive behavior following UCMS can be corrected by administering *L. reuteri*, a species of the *Lactobacillus* genus. These findings led us to ask what systemic players may be involved in translating changes within the gut microbiome to the brain to mediate depressive behavior. Given the intimate relationship between the gut and the immune system, we looked towards immune cell populations as messengers along the gut-brain axis during depression. Using flow cytometry, we have observed that UCMS-induced changes in the gut microbiome correlate with drastic changes in immune cell populations within the gut. Moreover, this dysfunction of the gut immune compartment in stressed mice can be corrected by administration of *L. reuteri*. By both flow cytometry and mass cytometry (CyTOF), we have observed that immunity is also significantly altered in the lymph nodes (inguinal and deep cervical) of stressed mice compared to naïve. Thus, the immune compartment represents a candidate messenger within the gut-brain axis during stress and depression. Ongoing work is further characterizing the effects of stress and depression on central nervous system lymphatics and identifying the mechanism(s) of immunomodulation within the gut and lymphatics. These findings begin to illustrate a role for the immune system in mediating the effects of gut microbiome changes on mental health. Importantly, defining the role of a gut-immune-brain axis in mental health creates an opportunity for developing the gut microbiome as a novel, minimally invasive therapeutic modality.

Disclosures: C.P. Addington: None. **I.A. Marin:** None. **J. Kipnis:** None. **A. Gaultier:** None.

Poster

236. Microbiota, Immunity, and Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 236.03/HH18

Topic: F.04. Stress and the Brain

Support: SFI/12/RC/2273

SFI/12/RC/2272

Title: Depression associated alterations in the maternla microbiome during pregnancy: Implications for infant gut microbiome assembly

Authors: *K. L. TOGHER[1], A. S. KHASHAN[2], L. C. KENNY[3], C. STANTON[4], I. CARAFA[5], K. MURPHY[5], G. W. O' KEEFFE[1], C. A. RYAN[6], J. CRYAN[1], T. G. DINAN[4], G. CLARKE[7]
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Abstract: Background: The experience of maternal distress during pregnancy is associated with adverse obstetric and infant outcomes. Preclinical investigations suggest inappropriate remodelling of the microbiome during pregnancy and subsequent vertical transmission of a suboptimal microbiome at birth may be a potential mechanism underpinning this association. This study aimed to assess this theory in a clinical population. Methods: Nulliparous pregnant women enrolled in the IMPROvED study at Cork University Maternity Hospital, Ireland, completed the Edinburgh Postnatal Depression Scale (EPDS) and provided fecal samples in their second (N=46) and third trimesters (N=33). Vaginal swabs were collected prior to delivery. Fecal samples were acquired from infants at 1, 2 & 3 weeks, 3 & 5 months old. Microbial community structure was analysed by 16S rRNA gene sequencing. Results: The mean EPDS scores were 5.77 ± 4.40 and 5.66 ± 4.64 in the second trimester and third trimester respectively. The diversity (Chao1 Index) of the gut microbiome in mid pregnancy was correlated with depressive symptoms (B = -6.0, 95% CI [-12.414, -40.402], p = 0.066) in the second trimester. The effect of second trimester depressive symptoms on the diversity of the gut was reduced by the third trimester (B = -2.6, 95% CI [-8.943, 3.601], p = 0.391). The diversity of the vaginal microbiome was not correlated with maternal depressive symptoms, in the second (B = -0.53, 95% CI [-7.035, 15.972], p = 0.870) or third (B = -0.73, 95% CI [-8.897, 7.423], p = 0.856) trimester. In contrast, maternal depressive symptoms in mid pregnancy correlated with the diversity of the infant gut at 1 week old (B = -1.192, 95% CI [-2.445, 0.061], p = 0.062) but not at later ages. When stratified based on depressive symptoms (Low, EPDS ≤ 8; High EPDS ≥ 9), infants (1 week old) born to women in the high depressive group had reductions in the abundance of the dominant Bifidobacteriaceae (Low 31.7%; High 22.5%) and Lactobacillaceae (Low 2.6%; High 0.05%). Conclusion: The experience of depressive symptoms in mid pregnancy is associated with marked alterations in the maternal gut microbiome that do not persist into late pregnancy. The composition of the infant gut microbiome may be associated with 2nd trimester depression-associated maternal microbiome alterations rather than direct vertical transmission. Further studies are required to clarify the implications of these depression associated maternal microbiome alteration during pregnancy for obstetric outcomes and infant neurodevelopment.

Disclosures: K.L. Togher: None. **A.S. Khashan:** None. **L.C. Kenny:** None. **C. Stanton:** None. **I. Carafa:** None. **K. Murphy:** None. **G.W. O' Keeffe:** None. **C.A. Ryan:** None. **J. Cryan:** None. **T.G. Dinan:** None. **G. Clarke:** None.

Poster

236. Microbiota, Immunity, and Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 236.04/HH19

Topic: F.04. Stress and the Brain

Support: Ontario Brain Institute

Brain Canada

Title: Brain volume changes in germ free mice

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Abstract: Scientists have established a link between gut bacteria and anxiety-like behaviours in animal models and with emotional brain regions in healthy people. This emerging area of research has scientists and the public starting to take notice of microbes and the mind. Animals with altered commensal intestinal microbiota, whether germ free mice, or conventionally housed animals either treated with probiotics and/or antibiotics or infected with pathogenic bacteria, all indicate that rodent behavioral responses are impacted when the bacterial status of the gut is manipulated. Research from our laboratory and others shows that germ free (GF) mice, lacking exposure to any microbes, have reduced anxiety-like behaviour and related molecular changes in the CNS. This study used MRI to examines brain volume differences in male and female GF mice, GF mice conventionalized by exposure to feces from SPF mice at 5 weeks of age and specific pathogen free (SPF) C57Bl/6 mice. Brains were perfused at 9 weeks of age and imaged using a 7.0-T MRI scanner. Anatomical images were analyzed as previously reported (Lerch et al, 2008, 2011). Total brain volume was significantly smaller in GF compared to SPF mice of both sexes. Reduced relative hippocampal volume and reduced relative dentate gyrus volume was observed in GF mice compared to SPF mice. Interestingly, previous work by our group has shown elevated levels of stress hormones in GF mice that may contribute to the observed reduction in hippocampal volumes. In contrast, both male and female GF mice had increased relative cortical volumes compared to SPF mice. Initial analysis shows that GF mice conventionalized with SPF microbiota at 5 weeks of age had reduced hippocampal and dentate gyrus volume. Ongoing analysis of additional brain regions will provide insight into the role of microbiota in brain development.

Disclosures: S.L. Thompson: None. **J. Ellegood:** None. **K. McVey Neufeld:** None. **J.A. Foster:** None. **J.P. Lerch:** None.

Poster

236. Microbiota, Immunity, and Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 236.05/HH20

Topic: F.04. Stress and the Brain

Support: EU-JPI Grant 15/JP-HDHL/3270

SFI Grant 12/RC/2273

Title: Targeting the gut microbiome to reverse age-related deficits in learning and stress-induced immune priming

Authors: *M. BOEHME[1], M. VAN DE WOUW[1], K. V. SANDHU[1], A. V. GOLUBEVA[1], K. A. SCOTT[1], C. STANTON[2], T. G. DINAN[1], H. SCHELLEKENS[1], J. F. CRYAN[1]
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Abstract: Background Ageing is associated with increased neuroinflammation and a decline in brain function, including cognitive impairment. Gastrointestinal microbiota has emerged as key factors in the communication between the gut and the brain. It has been shown that the gut microbiota profile is altered in ageing. Along with their regulatory role on the immune system, microbiota may alter microglia activation state and cognition in ageing. Prebiotics, non-digestible fibres fermented by colonic bacteria, affect microbiota diversity and may thus influence immune cell priming, microglia activation and cognitive function throughout life. **Objective** To determine if chronic administration of prebiotics affects age-related changes in immune function, stress and behaviour along with alterations in gut microbiota diversity. **Methods** Male young adult (8 weeks) and middle-aged mice (10 months) received chow enriched with 10% Oligofructose-enriched Inulin (OE-Inulin: mixture of 92±2% Inulin and 8±2% Fructooligosaccharide, Orafti®Synergy1; Beneo/Belgium) or control chow for 12 weeks. After 3 weeks of diet, mice underwent tests to determine the effects of diet on cognition, stress and anxiety-like behaviour. Peripheral immune cell activation and microglia activation were investigated by flow cytometry. **Results** Caecum size, as an indicator for the rate of microbial fermentation was increased in the OE-Inulin-treated groups of both young adult and middle-aged mice. Dietary intake of OE-Inulin decreased anxiety-like behaviour and improved learning in young adult mice only. Although OE-inulin administration did not have profound changes on behaviour in middle-aged mice, OE-Inulin counteracted stress-induced peripheral immune cell activation in middle-aged mice, suggesting an immunoregulatory effect of prebiotics on immune cell priming in response to stress. In addition, middle-aged OE-Inulin-treated mice showed decreased visceral fat mass in line with a decreased food intake. Correlation data suggest a potential link between visceral fat mass, immune priming and cognition in male mice. **Conclusion** Our data suggest a role of prebiotics in regulating cognitive behaviour in adulthood and stress-induced peripheral immune cell priming in ageing.

Disclosures: **M. Boehme:** None. **M. van de Wouw:** None. **K.V. Sandhu:** None. **A.V. Golubeva:** None. **K.A. Scott:** None. **C. Stanton:** None. **T.G. Dinan:** None. **H. Schellekens:** None. **J.F. Cryan:** None.

Poster

236. Microbiota, Immunity, and Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 236.06/HH21

Topic: F.04. Stress and the Brain

Support: NIH Grant P50DA037844

SFI Grant 12/RC/2273

Title: Sex differences in the rat microbiome and addiction-related behaviors

Authors: *V. L. PETERSON[1,2,3], J. B. RICHARDS[5], P. MEYER[6], R. CABRERA-RUBIO[7,2], O. POLESSKAYA[8], A. CHITRE[8], J. A. TRIPI[6], F. CRISPIE[7,2], T. G. DINAN[2,4,1], P. D. COTTER[7,2], A. A. PALMER[8], J. F. CRYAN[3,1,2]
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Abstract: Extensive research has identified multiple factors that contribute to addiction, including environmental (eg. socioeconomic status), heredity, sex, and psychological comorbidities such as anxiety and depression. Sex differences exist in addiction-related behaviors, such as risk taking, and in the likelihood of illicit substance abuse. Recent studies have revealed that gut microbiota is a key regulator of brain and behavior especially in the context of the stress response, anxiety, and depression. However, there is limited information regarding the relationship between the microbiome and addiction or how potential sex differences in the microbiome may contribute to behavior. Therefore, this study sought to investigate sex differences in the gut microbiota in relation to addiction-related behaviors. Outbred male (N=100) and female (N=101) rats underwent a battery of behavioral tests consisting of: locomotor activity, delay discounting, light reinforcement, Pavlovian conditioned approach/reinforcement, cocaine conditioned place preference, and choice reaction time. Caecal microbial composition was assessed with 16S sequencing. Statistically significant differences in both behavior and microbiota were seen between males and females. Significant correlations between behavioral measures and genus-level bacteria were seen in tests of light reinforcement, delay discounting, reaction time, conditioned reinforcement, and locomotor activity (Spearman, $p<0.05$), many of which were explained by sex differences. Further analysis found that behavior and microbiome clustered significantly by cage mate, generation, and sex (Adonis, $p<0.001$). These results would indicate that microbiota composition may contribute to behavioral sex differences. Additionally, sex, generation, and cage mate are significant factors contributing to microbiome composition.

Disclosures: **V.L. Peterson:** A. Employment/Salary (full or part-time):; APC Microbiome Institute. **J.B. Richards:** None. **P. Meyer:** None. **R. Cabrera-Rubio:** A. Employment/Salary (full or part-time):; APC Microbiome Institute. **O. Polesskaya:** None. **A. Chitre:** None. **J.A. Tripi:** None. **F. Crispie:** None. **T.G. Dinan:** A. Employment/Salary (full or part-time):; APC Microbiome Institute. **P.D. Cotter:** A. Employment/Salary (full or part-time):; APC Microbiome Institute. **A.A. Palmer:** None. **J.F. Cryan:** A. Employment/Salary (full or part-time):; APC Microbiome Institute.

Poster

236. Microbiota, Immunity, and Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 236.07/HH22

Topic: F.04. Stress and the Brain

Support: SFI Grant 12/RC/2273

Title: Stress gone viral: Chronic social stress induces marked changes in the gut virome in mice

Authors: *J. CRYAN[1,2,3], V. L. PETERSON[2,3], A. BUROKAS[2], L. DRAPER[2,4], M. DALMASSO[2], R. CABRERA-RUBIO[2,6], F. CRISPIE[2,6], P. D. COTTER[2,6], T. G. DINAN[2,5], C. HILL[2,4]
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Abstract: In every gut, there are billions of organisms that live with the host and contribute to digestion, metabolism, immune function, and stress response. Current research now indicates that the microbiome-gut-brain axis plays a critical role in mood and behavior. Changes in gut bacteria are seen during chronic stress, hypothalamic-pituitary-adrenal (HPA) axis dysfunction, and psychiatric disorders such as anxiety and depression. Research into the role of gastrointestinal microbiota in health focuses almost exclusively on bacteria yet the number of commensal viruses, most notably bacteriophage, vastly outnumber bacteria in the gut. This study sought to investigate changes in viral gut composition following chronic social stress. Stress animals were exposed to 3 consecutive weeks of chronic unpredictable social stress. Faecal and caecal samples from control and stress animals were sequenced for bacteria (16S) and viruses (metagenomic). Following chronic social stress, stressed animals had significant increases in immobility time during the forced swim test, basal corticosterone, and cytokine IL-6 compared to non-stressed controls. Bioinformatic analysis revealed marked differences in bacteriome and virome between control and stressed animals. Moreover, viral species richness increased in the stress group alongside reductions in bacterial richness. This is the first study to investigate changes in virome in relation to the microbiota-gut-brain axis. Findings from this research

further elucidates the impact of psychological stress on the microbiome and suggests that viruses may play a role in HPA axis function.

Disclosures: **J. Cryan:** A. Employment/Salary (full or part-time):; APC Microbiome Institute. **V.L. Peterson:** A. Employment/Salary (full or part-time):; APC Microbiome Institute. **A. Burokas:** None. **L. Draper:** A. Employment/Salary (full or part-time):; APC Microbiome Institute. **M. Dalmasso:** None. **R. Cabrera-Rubio:** A. Employment/Salary (full or part-time):; APC Microbiome Institute. **F. Crispie:** None. **P.D. Cotter:** A. Employment/Salary (full or part-time):; APC Microbiome Institute. **T.G. Dinan:** A. Employment/Salary (full or part-time):; APC Microbiome Institute. **C. Hill:** A. Employment/Salary (full or part-time):; APC Microbiome Institute.

Poster

236. Microbiota, Immunity, and Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 236.08/HH23

Topic: F.04. Stress and the Brain

Support: Science Foundation Ireland (Grant Number 12/RC/2273)

Brain and Behaviour Research Foundation (NARSAD Grant Number 20771)

Title: The microbiome and transcriptional regulation of amygdala-dependent fear recall

Authors: *G. CLARKE[1,2,3], A. E. HOBAN[4], R. M. STILLING[4,2], G. MOLONEY[4], F. SHANAHAN[2], T. G. DINAN[3,2], J. F. CRYAN[4,2]
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Abstract: Background: The amygdala is a key brain structure in the acquisition and expression of fear and anxiety-related behaviours. It is increasingly appreciated that the host intestinal microbiota has the capacity to alter behaviours relevant to anxiety and stress responses. Germ-free (GF) animals, deficient of any microbial exposure throughout life, have provided unique insights into the importance of the host microbiome for neurodevelopment. In particular, the presence of the host microbiome critically regulates morphology and transcriptional programming within the amygdala. However, the role of microbiome in specific fear-related behaviours is unclear. **Methods:** Due to the well characterized and reproducible findings in relation to anxiety-related behaviours in these mice, we aimed to investigate the importance of the host microbiome for more amygdala dependent behavioural readouts using the cued fear conditioning paradigm. We also assessed, using a whole transcriptome profiling approach, the changes in both the transcriptional and post-transcriptional landscape in the amygdala of naïve

and stimulated GF C57BL/6J mice, after a fear retention stimulus. **Results:** Our results reveal that GF mice display reduced freezing ($P<0.001$) during the cued memory retention test when compared to conventionally (CON) raised mice. Our results further indicate that naive GF mice display an altered transcriptional profile with a marked increase in immediate-early response genes (such as *Fos, Egr2, Fosb, Arc*) as well as genes implicated in neural activity, synaptic transmission, monoamine transport, nervous system development and neurogenesis (e.g. *Drd2, Ngfr, Adora2a, Chat, Crh, Egr1/2*). Moreover, GF mice exposed to a fear recall test displed a unique transcriptional response. Assessing the post-transcriptional expression profile of the amygdala in these mice revealed a predicted interaction between mRNA and certain miRNAs that are differentially regulated in GF naïve mice and after stimulation. Colonised GF mice (exGF) were behaviourally comparable to CON mice in the cued memory retention test. **Conclusions:** Thus we demonstrate, for what is to our knowledge the first time, that the presence of the host microbiome is crucial for the appropriate behavioural response to amygdala-dependent memory retention and its associated gene expression patterns in the amygdala. Our data indicate that the microbiome may be a promising new therapeutic target for developing psychobiotic approaches for fear-related disorders.

Disclosures: **G. Clarke:** 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.; Science Foundation Ireland, Brain and Behaviour Research Foundation. **A.E. Hoban:** None. **R.M. Stilling:** None. **G. Moloney:** None. **F. Shanahan:** 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.; Science Foundation Ireland. **T.G. Dinan:** 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.; Science Foundation Ireland. **J.F. Cryan:** 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.; Science Foundation Ireland.

Poster

236. Microbiota, Immunity, and Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 236.09/HH24

Topic: F.04. Stress and the Brain

Support: Science Foundation Ireland Grant 12/RC/2273

Title: A gut feeling about autism: Alterations across the microbiota-gut-brain axis in a mouse model of autism spectrum disorders

Authors: *E. SHERWIN[1], A. GOLUBEVA[2], S. JOYCE[2], G. MOLONEY[3], A. BUROKAS[2], S. ARBOLEYA[5], K. MURPHY[5], K. REA[2], N. P. HYLAND[4], C. STANTON[5], G. CLARKE[2], C. GAHAN[2], T. G. DINAN[2], J. CRYAN[2]
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Abstract: The role of the gut microbiome in health and disease is becoming increasingly recognised. The gut microbiota have been shown to regulate the host's stress and immune responses as well as brain function and behaviour. The BTBR T^{+} *Itpr3*^{tf}/J mouse is a widely used animal model of autism spectrum disorder, however, there is limited information on whether microbiota-gut-brain axis signalling contributes towards the autistic-like phenotype of this strain. In this study, we investigated behaviour, circulating and central markers of hypothalamic pituitary adrenal (HPA) axis activation, gut physiology and intestinal microbiota composition in BTBR relative to control C57BL/6 male mice. Here we show that BTBR mice display robust impairments in social interaction, and increases in repetitive and anxiety-like behaviours relative to C57BL/6 mice. Moreover, alterations in circulating concentrations of the neuropeptide, oxytocin, were noted in BTBR mice, which may contribute towards the observed behavioural deficits in this strain. BTBR mice also exhibited elevated basal and stress-induced corticosterone secretion following exposure to an acute stressor, indicating heightened activation of the HPA axis. This corresponded with increased hippocampal expression of the glucocorticoid receptor (GR) in BTBR mice, further indicating dysregulation to the HPA axis in this strain. These behavioural deficits and heightened stress responses in BTBR mice were associated with gastrointestinal abnormalities with impairments in intestinal barrier function and delayed intestinal transit observed. 16S sequencing of the caecal microbiota of both strains revealed a pronounced decrease in bacterial diversity and changes in short chain fatty acid production in BTBR mice suggesting dysregulation to the gut microbiota. Together, these data provide insight into how the microbiota-gut-brain axis is affected in an animal model of autism spectrum disorders and suggest that novel microbiota-based interventions may be effective in alleviating the behavioural, stress and gastrointestinal symptoms of this neurodevelopmental disorder

Disclosures: **E. Sherwin:** None. **A. Golubeva:** None. **S. Joyce:** None. **G. Moloney:** None. **A. Burokas:** None. **S. Arboleya:** None. **K. Murphy:** None. **K. Rea:** None. **N.P. Hyland:** None. **C. Stanton:** None. **G. Clarke:** None. **C. Gahan:** None. **T.G. Dinan:** 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.; Mead Johnson, Cremo, 4D Pharma, Suntory Wellness, Nutricia. **J. Cryan:** 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.; Nutricia, Suntory Wellness, Cremo, Mead Johnson, 4D Pharma.

Poster

236. Microbiota, Immunity, and Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 236.10/HH25

Topic: F.04. Stress and the Brain

Support: Ontario Brain Institute

Ontario Graduate Scholarship

NSERC

Title: Host genetic effect on intestinal barrier function and microbiome composition

Authors: *R. G. HORNE, J. ST. PIERRE, S. ODEH, J. A. FOSTER
Psychiatry & Behavioural Neurosci., McMaster Univ., Hamilton, ON, Canada

Abstract: Bidirectional communication between gut microbiota and components of gut-brain axis is critical to brain function. Alterations in gut microbiome have been shown to affect gut barrier function, behaviour, immune response as well as expression of gene regulating molecules including microRNA (miRNA). Impairment of the gastrointestinal barrier has been mechanistically linked to many diseases including psychiatric disorders. Work by our laboratory shows that host genetics influences brain structure, behaviour and gut microbiota composition and diversity. In this study, adult female mice (BALB/c and C57Bl/6) were administered broad-spectrum antibiotics or sterile water for 2 weeks, n=6 per treatment per stain. Profiling of 16SrRNA gene was carried out using a modified bar coded Illumina sequencing method. The taxonomic profile showed significant differences in relative abundance of clinically relevant commensals including *Bifidobacterium, Lactobaccilus, Alistipes,* and *Prevotella.* Strain related microbiome differences in both alpha and beta diversity were also observed, with a principal coordinate analysis showing distinct clustering separated by strain. Intestinal permeability was assessed by gavaging unconjugated FITC and measuring recovery in the serum. Differences were observed for intestinal permeability in strains and in response to antibiotic treatment, with BALB/c demonstrating increase permeability as compared to C57Bl/6. nCounter miRNA Nanostring analysis revealed strain related differences in expression of miRNA in intestinal epithelial cells as well as differences in fecal miRNA expression. Expression of tight junction mRNAs and miRNAs linked to barrier function in small intestine is ongoing. Exploring the relationship between host genetics, microbiome, and barrier function will help elucidate the role of the microbiota-brain communication in psychiatric disorders.

Disclosures: R.G. Horne: None. **J. St. Pierre:** None. **S. Odeh:** None. **J.A. Foster:** None.

Poster

236. Microbiota, Immunity, and Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 236.11/HH26

Topic: F.04. Stress and the Brain

Support: Ontario Brain Institute

Brain Canada

Canadian Foundation For Innovation

Canadian Institute of Health Research

Title: An integrated analysis of microbiota composition on brain structure and social behaviour in mice

Authors: *C. FRANCELLA[1], J. ELLEGOOD[2], J. K. Y. LAI[1], K. C. RILETT[1], B. DARWIN[2], J. P. LERCH[2], J. A. FOSTER[1]
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Abstract: Recent findings from animal and clinical studies have demonstrated an important role for gut microbiota in brain function and behaviour. Microbiota composition and diversity is influenced by host genetics, diet, and other environmental factors. The current work integrates analysis of the microbiome with behaviour and brain structure in several mouse models to better understand how gene-environment interactions during development influence brain structure and behaviour. In the current study, male and female mice from several strains (Balb/C, C57Bl/6, FVB, CD1) and genetically-modified mice including, T cell receptor knock out mice (*TCRβ-/-δ-/-*) and Fragile X mice (*Fmr1* KO) were exposed to early life stressors including lipopolysaccharide injection on postnatal day 3 (P3) and/or overnight maternal separation on P9. Behavioural testing of social preference was conducted at 24 days of age using the three-chamber test. Fecal samples were collected at the time of behavioural testing. 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 an in-house pipeline. Brains were perfused at 4 w of age, and then imaged using a 7.0 Tesla MRI scanner. Strain, genotype, and sex difference in social preference were evident. Preliminary analysis shows distinct microbiota profiles in different strains of mice and analysis is ongoing to determine if specific bacteria are associated with social preference. Previously, we have used structural imaging to examine neuroanatomical circuits in mouse models of autism (Mol Psych 2015 20:118) and our current analysis extends this work to consider how these circuits are influenced by genetic

background, early life stress and microbiota composition. By understanding the neuroanatomy underlying differences in social behaviour and integrating an understanding of how microbiota can influence the development of these behaviours, our analysis will provide a better understand of the etiology of neurodevelopmental disorders that are associated with deficits in social behaviour.

Disclosures: C. Francella: None. **J. Ellegood:** None. **J.K.Y. Lai:** None. **K.C. Rilett:** None. **B. Darwin:** None. **J.P. Lerch:** None. **J.A. Foster:** None.

Poster

236. Microbiota, Immunity, and Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 236.12/HH27

Topic: F.04. Stress and the Brain

Support: Ontario Brain Institute

Brain Canada

Canadian Foundation for Innovation

Title: Host genetics influence on microbiota composition and behaviour

Authors: *J. A. FOSTER[1], J. LAI[1], K. RILETT[1], A. BHARWANI[2], J. ELLEGOOD[3], J. LERCH[3]
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Abstract: Much of our knowledge of microbiota-brain interactions has been generated from rodent studies that manipulate the composition and diversity of the gut microbiota. Our results revealed that germ-free mice showed reduced anxiety-like behaviour in the elevated plus maze, a well established behavioural test that examines approach and avoidance behaviour in mice, in comparison to specific pathogen free (SPF) mice. The low anxiety-like behavioural phenotype observed in germ-free mice was accompanied by long-term changes in plasticity-related genes in the hippocampus and amygdala (Neufeld et al., 2011). Different mouse strains show natural differences in anxiety-related behaviour and therefore, using different strains of mice provides a good naturalist approach to examine the link between microbiota, brain, and behaviour. Our ongoing work has focused on how the interaction between microbiota and host genetics influence brain structure and behaviour. Bacterial community profiling of 16SrRNA gene was carried out using a modified bar coded Illumina sequencing method in the McMaster Genome Center in male and female Balb/C, C57Bl/6, and FVB mice. Strain-specific differences in microbiota diversity were observed with reduced alpha diversity in Balb/C mice compared to

C57Bl/6 and FVB. Beta diversity analysis revealed strain-specific differences in microbiota composition; principal coordinates analysis (PCoA) showed 3 distinct clusters separated by strain. The taxonomic profile of the microbiota showed significant strain differences in relative abundance of clinically relevant commensals such as *Bifidobacterium, Lactobaccilus, Alistipes,* and *Prevotella.* We also examined whole brain structure using high resolution ex vivo magnetic resonance imaging to determine the association of microbiota and brain structure in different strains of mice. Initial analysis of several significant strain differences in normalized brain volume in several key brain regions implicated in stress-related behaviour. Our results show that microbiota and host genetics influence behaviour and brain structure - deciphering the molecular mechanisms involved is necessary to advance the use of microbiota-targeted therapies for use in clinical populations.

Disclosures: J.A. Foster: None. **J. Lai:** None. **K. Rilett:** None. **A. Bharwani:** None. **J. Ellegood:** None. **J. Lerch:** None.

Poster

236. Microbiota, Immunity, and Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 236.13/HH28

Topic: F.04. Stress and the Brain

Support: Science Foundation Ireland SFI/12/RC/2273

Science Without Borders 11601-13-2

Title: Social and cognitive deficits induced by early-life microbiota-gut-brain axis disruption are reversed by co-housing with control mice

Authors: *L. H. MORAIS[1,4], A. VENTURA-SILVA[4], S. ARBOLEYA[4,5], P. D. COTTER[4,5], C. STANTON[4,4,2], T. DINAN[4,2], J. F. CRYAN[4,3]
[2]Dept. of Psychiatry and Neurobehavioural Sci., [3]Neurosci. & Anat., [1]Univ. Col. Cork, Cork, Ireland; [4]APC Microbiome Institute, UCC, Cork, Ireland; [5]Teagasc Food Res. Centre, Moorepark, Fermoy, Cork, Ireland

Abstract: Mounting evidences points to the importance of the gut microbiome in all aspects of health including brain health. Early-life is a critical developmental window where microbiota acquisition coincides with neurodevelopment. Thus perturbations to the microbiota colonization during early life have been shown to affect development and behaviour in mouse models of neurodevelopmental disorders. The first major contact with bacteria happens during the birth process while the infant emerges through the birth canal and vaginal microbiome are passed on from their mothers to the infant. However, birth by Caesarean-section (CS) results in a different

pattern of microbiota seeding rewiring the entire microbiota-gut-brain axis. Recently, we have demonstrated that CS-delivered mice present with enduring behavioural and physiological phenotype in addition to changes in microbiota diversity and complexity. While the microbiota signature is different between individuals, it can be shared between co-housing groups. Therefore, we investigated whether co-housing CS with vaginally born mice (VB) in adolescence prevented CS-mediated effects in behaviour.
At weaning (Postnatal day 21), animals were divided into four different groups: VB, CS or co-housed (VB or CS) mice. Social and anxiety-like behaviour and subsequent immune HPA-axis and microbiota parameters were assessed in adulthood. CS-born offspring exhibited deficits in social memory and cognitive tasks, and an increase in anxiety-like behaviour as compared to VB controls. Co-housing CS-deliverd mice with VB attenuated the deficits in social and working memory, but not anxiety-like behaviour.
In conclusion, using co-housing as a strategy to manipulate the microbiota of CS-born mice, we were able to selectively reverse social and working memory effects induced by the delivery mode. These findings reinforce the importance of the microbiota in regulating CS-induced changes across the microbiota-gut brain axis. We further demonstrate that the adolescent phase is an important developmental window where restoration of microbiota can reverse some, but not all, behavioural responses due to microbiota alterations in early life.

Disclosures: L.H. Morais: None. **A. Ventura-Silva:** None. **S. Arboleya:** None. **P.D. Cotter:** None. **C. Stanton:** None. **T. Dinan:** None. **J.F. Cryan:** None.

Poster

236. Microbiota, Immunity, and Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 236.14/HH29

Topic: F.04. Stress and the Brain

Support: NIMH award R01MH062044

Brains and Behavior Fellowship

Next Generation New Scholars Fellowship

Lallemand Health Solutions

Title: Effects of probiotic and antibiotic treatment on the behavioral response to social defeat stress in Syrian hamsters

Authors: *K. A. PARTRICK, L. Q. BEACH, D. C. CHOI, B. CHASSAING, K. L. HUHMAN
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Abstract: Social stress contributes to several disabling neuropsychiatric disorders. The gut-brain-axis, which allows bi-directional communication between the central nervous system and gastrointestinal tract, may modulate physiological and behavioral responses to social stress. Our laboratory has recently demonstrated that mild social stress can cause significant alterations in intestinal microbiota composition in male Syrian hamsters. Of note, we also found that some members of the baseline microbiota were correlated with winning or losing a subsequent agonistic encounter. The purpose of the present study was to test the hypothesis that manipulating specific bacteria alters behavioral responses to social defeat stress. Hence, we tested whether treatment with a probiotic or with an antibiotic decreases or increases, respectively, the social avoidance response in defeated hamsters. Subjects were given drinking water with either a probiotic containing *Lactobacillus helveticus* and *Bifidobacterium longum* (Lallemand; 3g/30ml), live organisms thought to have anxiolytic effects, an antibiotic (enrofloxacin; 100mg/L) used to deplete gut microbes, or a placebo for one week prior to experimentation. Hamsters were then exposed to 9 defeats with novel aggressors across 6 days during which they continued probiotic or antibiotic treatment. Defeat-induced avoidance behavior was assessed and fecal samples were collected 24hr after the initial and the final defeats. To verify that the treatments altered gut microbiota in the expected directions, we performed quantitative polymerase chain reaction on fecal samples. We found no effect of either treatment on the time that hamsters spent avoiding a novel conspecific, despite significantly increased *L. helveticus* and *B. longum* in probiotic-treated animals compared to placebo. Both bacteria were reduced in placebo-treated animals exposed to defeat compared with levels prior to defeat, replicating our earlier finding that social stress causes a reduction in these bacteria. Surprisingly, *L. helveticus* increased in defeated hamsters that were treated with antibiotic compared to placebo. One possibility is that enrofloxacin depletes other microbes, which in turn allows *L. helveticus* to proliferate. It will be important to determine whether this antibiotic effectively reduces total gut microbiota in hamsters and if there is an alternative antibiotic that can be used in hamsters that will reduce *Lactobacillus*. These data do suggest, however, that increasing these particular gut microbiota, alone, is not sufficient to alter the behavioral response to defeat in Syrian hamsters.

Disclosures: K.A. Partrick: None. **L.Q. Beach:** None. **D.C. Choi:** None. **B. Chassaing:** None. **K.L. Huhman:** None.

Poster

236. Microbiota, Immunity, and Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 236.15/HH30

Topic: F.04. Stress and the Brain

Support: DAFM/FIRM No 10FDairy

Title: Disturbances to the microbiota-gut-brain axis in early life leads to an increase in monocyte trafficking to the brain

Authors: *E. MORELLI[1], M. BOEHME[2], L. H. MORAIS[2], R. O'CONNNOR[2], T. M. BECKER[2], B. CHRUSCICKA[2], C. STANTON[3], T. DINAN[2], J. F. CRYAN[2]
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Abstract: The gut microbiota is vital for maintaining homeostasis of several physiological processes such as the host immune response. Moreover, accumulating evidence suggests that the gut microbiota regulates brain function and behaviour. The establishment of intestinal microbiota early in life has been shown to be a crucial checkpoint to ensure normal brain development and function. Any perturbations to the microbial community can impact neurodevelopment and potentially lead to adverse outcomes later in life. The first contact of neonates with microbes is provided by the maternal microbiota. Recently, we have demonstrated that in early life (postnatal days 7-9), mice delivered via Caesarian-section have altered gut microbiota composition, intestinal barrier dysfunction and increased immune response as compared to naturally delivered animals. Based on this evidence, in the current study, we investigated whether the impaired immune response observed in Caesarian-sectioned mice triggers a neuroinflammatory state in the brain. By using flow cytometry, Ly6Chi-monocytes were found to be increased in the brains of Caesarian-sectioned mice, suggesting increased monocyte trafficking from the periphery into the brain. Moreover, CD31 was found to be decreased in the brains of Caesarian-sectioned mice, indicating that mode of delivery impacts endothelial integrity in the central nervous system. In addition, increased number of lymphocytes was observed in the brains of Caesarian-sectioned mice. Previous studies have demonstrated that the microbiota influences microglial activation. However, in the current study, microglia maturation and activation were not altered followed Caesarian-section. Ongoing studies using *ex-vivo* and *in-vitro* methods intend to assess whether increased monocyte trafficking can negatively influence neuronal function and the functional integrity of the blood brain barrier.

Disclosures: E. Morelli: None. **M. Boehme:** None. **L.H. Morais:** None. **R. O'Connnor:** None. **T.M. Becker:** None. **B. Chruscicka:** None. **C. Stanton:** None. **T. Dinan:** 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.; Mead Johnson, Suntory Wellness, Nutricia, Cremo, 4D Pharma. **J.F. Cryan:** 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.; Cremo, 4D Pharma, Suntory Wellness, Nutricia, Mead Johnson.

Poster

236. Microbiota, Immunity, and Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 236.16/HH31

Topic: F.04. Stress and the Brain

Support: DARPA W911NF1010093

Title: The gut microbiome is involved in producing vulnerability to the effects of social defeat in rats

Authors: *J. PEARSON-LEARY[1], K. BITTINGER[2], C. ZHAO[2], D. EACRET[3], C. TANES[2], S. LUZ[1], G. DAYANIM[3], S. BHATNAGAR[4]
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Abstract: Stress increases the risk of psychiatric disorders such as post-traumatic stress disorder (PTSD) and depression. However, some individuals are vulnerable while others remain resilient to its effects. In order to identify novel biological substrates mediating vulnerability and resilience to stress, we assessed the gut microbiome of adult male Sprague-Dawley rats vulnerable or resilient to the effects of repeated social defeat. Composition of fecal bacteria at the community level shifted from pre-stress baseline compared to after one week of social defeat. The class *Clostridia* significantly increased in vulnerable rats but showed no significant change in resilient rats. This is an important finding because of the known role of *Clostridia* in mediating inflammatory processes. We observed increases in pro-inflammatory cytokines and altered plasma short-chain fatty acid metabolism (SCFA), in vulnerable compared to resilient rats, consistent with our previous data showing increases in pro-inflammatory cytokines in blood and pro-inflammatory processes in the ventral hippocampus. These results were consistent with the known role of *Clostridia* in mediating SCFA metabolism and inflammation. To test whether the gut microbiome was directly involved in inducing vulnerability or resilience, we next treated naive rats with oral gavages of fecal samples from resilient, vulnerable or non-stressed control rats. These transplant recipient rats were exposed to 5 days of social defeat stress or no-stress (left in home cage following oral gavage) and tested for depression-like behaviors using the Porsolt forced swim test and anxiety-like behaviors using a social interaction tasks. Transplants from vulnerable rats decreased latencies to social defeat, indicative of passive coping during defeat, and largely showed increased depression-like and anxiety-like behaviors in rats that received transplants from vulnerable rats relative to the other conditions. We found increased expression of a microglial activation marker, Iba-1, in the ventral hippocampus of rats that received transplants from stress vulnerable rats suggesting that inflammatory processes known to

occur in the ventral hippocampus of vulnerable rats could be recapitulated by fecal transplants from vulnerable rats into naïve rats. Our data demonstrate that vulnerability and resiliency to chronic stress can be specifically mediated by the gut microbiome. Furthermore, these data suggest novel mechanisms by which the gut microbiome may mediate behavioral phenotypes.

Disclosures: **J. Pearson-Leary:** None. **K. Bittinger:** None. **C. Zhao:** None. **D. Eacret:** None. **C. Tanes:** None. **S. Luz:** None. **G. Dayanim:** None. **S. Bhatnagar:** None.

Poster

237. Circadian: Synchronization

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 237.01/HH32

Topic: F.08. Biological Rhythms and Sleep

Support: NSF IOS Grant 1257133

Title: Life in the fast lane: Exceptionally short-period circadian clocks in orb-weaving spiders

Authors: *D. MOORE[1], N. A. AYOUB[2], A. MAH[2], N. TOPORIKOVA[2], T. C. JONES[1]
[1]Dept. of Biol. Sci., East Tennessee St Univ., Johnson City, TN; [2]Biol., Washington and Lee Univ., Lexington, VA

Abstract: It is widely believed that possessing a circadian clock is adaptive because it enables organisms to schedule physiological and behavioral changes in anticipation of daily environmental events. Most endogenous circadian oscillators “resonate” with the solar cycle by expressing periods very close to the 24-hour daily period. Experimental evidence has shown that organisms with circadian clocks deviating from resonance typically have reduced fitness. Recently, we discovered that two closely related, trashline orb-weaving spider species, *Allocyclosa bifurca* and *Cyclosa turbinata*, and one spiny orb-weaving species, *Gasteracantha cancriformis*, have exceptionally short-period endogenous rhythms of locomotor activity under constant dark (DD) conditions, averaging 17.4, 18.5, and 19.0 h, respectively. These may be the shortest, or among the shortest, naturally occurring circadian periods on record and are comparable to the laboratory-generated 20- and 18-h mutants in hamsters and the 19-h per^S mutant in *Drosophila*, yet these spiders were collected from natural populations in the field. In theory, being so far out of resonance with the 24-h day, these species should not exist. Our data show that three other species of orb-weavers and two species of cobweb spiders have circadian clocks with more typical free-running periods. Further setting the short-period orb-weavers apart from all other spider species studied thus far is their pattern of entrainment to light-dark (LD) cycles. All three short-period species show a major locomotor activity peak in late scotophase (night), contrasting with the bulk of activity occurring in early scotophase in other nocturnal spiders. Experiments shifting the relative positions of the lights-on and lights-off transitions

revealed that the lights-off (dusk) transition is the primary entrainment signal. We hypothesize that entrainment is accomplished by large (5-7 h) phase delays from light exposure during the late photophase, just preceding dusk. Evidence supporting or refuting this hypothesis will be obtained by generating a phase response curve to light pulses. With respect to the possible adaptive significance of the short-period clocks, we have observed that our two trashline orb-weavers replace their webs 3-5 h before dawn (corresponding to the late-scotophase locomotor activity peak). Because our trashline orb-weavers likely descended from orb-weavers that replaced their webs at dawn, the short-period clock may have facilitated a switch from dawn to pre-dawn web-building, providing a selective advantage through a reduction in predation from diurnal predators during the early morning hours.

Disclosures: D. Moore: None. **N.A. Ayoub:** None. **A. Mah:** None. **N. Toporikova:** None. **T.C. Jones:** None.

Poster

237. Circadian: Synchronization

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 237.02/HH33

Topic: F.08. Biological Rhythms and Sleep

Title: Computational model of circadian rhythms predicts adaptive value of exceptionally short period spider clock via flexible entrainment

Authors: A. MAH[1], N. AYOUB[2], T. C. JONES[3], D. MOORE[3], *N. TOPORIKOVA[2]
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Abstract: Circadian clocks describe biological rhythms with an endogenously generated period of ~24 hours. Previous studies demonstrated clocks that resonate with the day confer higher fitness. However, the trashline orb-weaving spider, *Cyclosa turbinata*, has a circadian clock with an exceptionally short free-running period of ~19 hours. We hypothesize an adaptive benefit to *C. turbinata's* shortened period to offset the decreased fitness of a non-resonant clock. We modified previously developed computational models of circadian clocks in *Drosophila* to determine the behavior of short period clocks. Phase-response curves generated with our model predict more flexible entrainment. Furthermore, simulations of lighting conditions predict two activity peaks, rather than one, during a single day. This would be beneficial to *C. turbinate*, so that it can display both dusk predation and pre-dawn web replacement to avoid predation. Having flexible entrainment and two activity peaks may provide sufficient adaptive advantage to offset the cost of non-resonant clocks.

Disclosures: **A. Mah:** None. **N. Ayoub:** None. **T.C. Jones:** None. **D. Moore:** None. **N. Toporikova:** None.

Poster

237. Circadian: Synchronization

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 237.03/HH34

Topic: F.08. Biological Rhythms and Sleep

Support: Internal funds from a Jacob E. Nyenhuis Grant at Hope College

Startup funds from the Social Sciences Division at Hope College

Title: Behavioral effects following ablation of retinalganglion cells in diurnal grass rats

Authors: G. FOGO, *A. J. GALL
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Abstract: Light influences behavior and physiology in mammals by entraining circadian rhythms and also through direct and acute inhibition or stimulation of activity, a process called masking. Although there has been substantial progress elucidating the mechanisms responsible for the workings of the circadian system in nocturnal species, less is known about the mechanisms that support the diurnal profile of activity of mammals, especially as they relate to the retina. We recently showed that the intergeniculate leaflet (IGL) is critical for the display of normal patterns of daily activity in diurnal grass rats (Arvicanthis niloticus). Specifically, IGL lesions reverse the activity patterns of these animals such that they became night-active; this occurred through their effects on both circadian mechanisms and masking. The IGL is a thalamic structure that receives direct inputs from the melanopsin containing intrinsically photosensitive retinal ganglion cells, known as ipRGCs. Our current approach takes advantage of a diurnal mammalian model, the Nile grass rat, to test the novel hypothesis that melanopsin is critical for the expression of diurnal behavior and physiology, and is involved in masking responses to light. We will achieve this goal by injecting the immunotoxin anti-melanopsin-saporin intraocularly in grass rats and examining behavior following this experimental manipulation. Animals will be placed in various lighting conditions, including 12:12 light-dark conditions, and will be given pulses of light to test for effects of masking. We predict that controls will exhibit more general activity during the day, consistent with a diurnal species, and will exhibit increased activity following acute pulses of light. We predict that animals with the melanopsin toxin in the retina will be out of phase with controls in behavior following acute pulses of light, similar to animals with IGL lesions. Altogether, we are building a model to understand the mechanisms underlying the normal display of diurnal behavior, and we hope to add to this knowledge by examining how melanopsin contributes to the display of diurnal behavior in grass rats.

Disclosures: **G. Fogo:** None. **A.J. Gall:** None.

Poster

237. Circadian: Synchronization

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 237.04/HH35

Topic: F.08. Biological Rhythms and Sleep

Title: Low density receptor-related protein 1 influences SCN circadian clock phase shifting via NMDA receptor interactions

Authors: *J. COOPER[1], R. A. PROSSER[2]
[1]Biochem. and Cell. and Mol. Biol., [2]Dept Biochem, Cell & Mol Biol, Univ. of Tennessee, Knoxville, TN

Abstract: The mammalian circadian clock in the suprachiasmatic nucleus (SCN) exhibits daily changes in responses to glutamate: nighttime glutamate induces SCN clock phase shifts; daytime glutamate does not. LRP1 is a multifunctional membrane receptor that influences neuronal responses to glutamate. We previously demonstrated by using single unit neuronal activity recordings from mouse SCN brain slices that LRP1 is required for glutamate-induced phase resetting of the mammalian circadian clock (LRP1 inhibition blocks glutamate induced phase shifts in vitro; Cooper & Prosser, SFN 2016). LRP1 can influence neuronal responses via interactions with several proteins known to gate responses to glutamate in the SCN, including brain-derived neurotrophic factor (BNDF), TrkB, tissue-type plasminogen activator (tPA), urokinase plasminogen activator (uPA), and NMDA receptors (NMDAR). We previously found that LRP1's role does not depend on interactions with tPA. Here we assess m(ature)BDNF levels, TrkB phosphorylation, and NMDAR phosphorylation in the SCN following LRP1 inhibition. Acute coronal SCN brain slices from adult male C57BL/6 mice prepared during the day and maintained in an interface brain slice chamber were treated with 100 nM receptor associated protein (RAP; LRP1 inhibitor) at ZT16 (ZT0=lights on, ZT12=lights off) for 10 minutes (or left non-treated at ZT16 for control slices). Slices were immediately collected and frozen, and tissue lysates were analyzed via western blotting. We found that RAP does not influence mBDNF levels or TrkB receptor phosphorylation at Y706/707. LRP1 has been shown to influence NMDA receptor activity partially through controlling NMDA receptor cell surface localization. Therefore, we investigated changes in NMDAR phosphorylation at Y1472 and S1480 as indicators of potential changes in NMDAR localization. We found that RAP treatment decreases S1480 phosphorylation, while Y1472 phosphorylation is not changed, suggesting that dynamic changes in NMDAR localization may underlie LRP1's role in circadian clock phase shifting. Current studies are using cell surface biotinylation in SCN slices to assess potential changes in NMDAR and LRP1 localization following RAP +/- glutamate treatment.

Disclosures: **J. Cooper:** None. **R.A. Prosser:** None.

Poster

237. Circadian: Synchronization

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 237.05/HH36

Topic: F.08. Biological Rhythms and Sleep

Support: NIMHANS and Department of Biotechnology (DBT), New Delhi [Project No.: BT/PR 14228/MED/30/413/2010]

Title: Effect of short photoperiod regime on ventral subicular lesion-induced anxiety-like behavior in Wistar rats

Authors: *D. SUBHADEEP, B. N. SRIKUMAR, B. S. SHANKARANARAYANA RAO, B. M. KUTTY
Dept. of Neurophysiol., Natl. Inst. of Mental Hlth. and Neuro Scie, Bengaluru, India

Abstract: Neurodegeneration of the hippocampal formation is implicated in several neuropathological conditions including Alzheimer's disease (AD) and seasonal affective disorders (SAD). Individuals suffering from AD or SAD exhibit 'sundown syndrome' characterized by mood swings, confusion, and anxiety, especially during late evening (at sunset). However, it has received scant attention and only a few studies have been carried out so far indicating circadian rhythm disruption in sundown phenomenon. Further, the mechanisms underlying the emotional disturbances remain elusive. In our study, we examined the association between subiculum (a key hippocampal output structure) and anxiety-related behavior in nocturnal male Wistar rats. Our findings suggested that bilateral ventral subicular lesion (VSL) produced by administration of ibotenic acid (1µg/µl/site) results in anxiety-like behavior. In the elevated plus maze, VSL rats made lesser entries into the open arms and spent significantly more time in the closed arms. Similarly, in the light-dark exploration test, VSL rats spent significantly more time in the dark chamber and made fewer entries into the light chamber. Additionally, there was a significant increase in the weights of the adrenal glands and spleen, which highlights possible enhancement of physiological stress response following VSL. Further, we also observed significant neurodegeneration in the paraventricular, suprachiasmatic and dorsomedial nuclei of the hypothalamus, as evident by reduction in cell count following VSL. Based on this finding, we hypothesized that diurnal photoperiod manipulation will reverse the VSL-induced deficits. Seven days after sham/VSL surgery, rats were housed in short photoperiod (6/18h light-dark cycle) for 21 days after which the anxiety-like behaviors were assessed. Interestingly, short photoperiod regime (SPR) resulted in amelioration of the anxiety-like behaviors in the VSL rats. VSL rats on SPR also exhibited increased food consumption and higher rectal temperature. Furthermore, there was a reduction in weights of adrenal glands and spleen in the VSL animals.

Currently, we are evaluating the effects of SPR on affective and higher cognitive functions, structural plasticity and associated molecular and electrophysiological underpinnings in the VSL rats. A proper understanding of the efficacy of photoperiod manipulation will help in evolving strategies for the management of emotional disturbances associated with neurodegenerative and affective disorders, such as AD and SAD respectively.

Disclosures: D. Subhadeep: None. **B.N. Srikumar:** None. **B.S. Shankaranarayana Rao:** None. **B.M. Kutty:** None.

Poster

237. Circadian: Synchronization

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 237.06/II1

Topic: F.08. Biological Rhythms and Sleep

Support: U01EB02195601

R01NS09536702

F32HL133772

Title: *In vivo* circadian rhythms and light responses of VIPergic neurons of the suprachiasmatic nucleus

Authors: *J. JONES, E. D. HERZOG
Biol., Washington Univ. in St. Louis, Saint Louis, MO

Abstract: The ~20,000 heterogeneous neurons of the suprachiasmatic nucleus (SCN) synchronize daily molecular and electrical rhythms in the brain and body to local time. Although *in vitro* experiments have implicated signaling cascades in SCN photoentrainment, little is known about the roles of specific SCN cell types in this process. We hypothesized that vasoactive intestinal peptide (VIP)-containing neurons in the ventrolateral SCN mediate the response to ambient light cycles. To test this, we used *in vivo* fiber photometry to measure intracellular calcium fluorescence from VIPergic SCN neurons in freely-behaving mice. We unilaterally injected AAV9.CAG.Flex.GCaMP6s or AAV9.CAG.Flex.EGFP into the SCN of heterozygous VIP-IRES-Cre mice and subsequently implanted a fiber optic cannula immediately dorsal to the site of virus injection. After 4-5 weeks, we illuminated the SCN through a tethered fiber optic cable and recorded GCaMP6s or EGFP emission for 10 minutes per hour for up to 6 days. We found that *in vivo* calcium event frequency and baseline levels varied with circadian time in SCN VIPergic neurons from mice housed in a 12 h: 12 h light:dark (LD) cycle and in constant darkness (DD; $\tau \approx 23.8$ h). In LD, event frequency (events per minute) decreased from 1.2 ± 0.2 during the day to 0.1 ± 0.1 at night, peaking around 6 h after lights on. In DD, event

frequency decreased from 1.9 ± 0.3 during the subjective day to 0.1 ± 0.1 during the subjective night peaking around circadian time (CT) 4. Minimal events (<0.05 per minute) and no daily rhythms in event frequency were detected in EGFP control mice housed in LD or DD. We also found that 15 s light pulses evoked large calcium responses (up to 8% ΔF/F, nearly double the maximum amplitude of spontaneous events) during the late subjective day and late subjective night (CT 11.5 and 22.5), but not during mid-subjective day (CT 7.5). Evoked calcium responses were sustained for 117.5 ± 18.7 s and 27.5 ± 10.6 s after the cessation of the light pulses given at CT 11.5 and CT 22.5, respectively. These results collectively suggest that VIPergic neurons participate in the circadian activity of the intact SCN and transduce light signals to the SCN at times when light shifts SCN daily rhythms. This work is supported by NIH grants U01EB02195601, R01NS09536702 and F32HL133772.

Disclosures: J. Jones: None. **E.D. Herzog:** None.

Poster

237. Circadian: Synchronization

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 237.07/II2

Topic: F.08. Biological Rhythms and Sleep

Support: NIH F31 NS096813-02

NIH 401 GM117650

NSF GRF 0909667

Title: Using optogenetics to explore the role of VIP^+ SCN neurons in circadian rhythms

Authors: *M. TACKENBERG[1], D. G. MCMAHON[2]
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Abstract: In mammals, circadian rhythms are orchestrated by the suprachiasmatic nuclei (SCN) of the hypothalamus. The neurons of the SCN exhibit self-sustained, endogenous oscillations in gene expression, firing rate, and neuropeptide release. These daily rhythms are entrained to external light cycles through excitatory input relayed by the retina to the ventrolateral region of the SCN (vlSCN). We have demonstrated the ability to evoke action potentials within the SCN using genetically-targeted channelrhodospin-2 (ChR2) expression both *in vivo* and *ex vivo*. By refining this targeted expression of ChR2 to the vlSCN specifically using VIP::Cre-driven expression of the channel, we seek to replicate endogenous induction of firing rate brought about by retinohypothalamic signaling. Using this technique, we look to demonstrate the sufficiency of the activity within this VIPergic population of SCN neurons in setting phase, entraining the pacemaker, and responding to different day lengths using both *in vivo* and *ex vivo* preparations.

Disclosures: **M. Tackenberg:** None. **D.G. McMahon:** None.

Poster

237. Circadian: Synchronization

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 237.08/II3

Topic: F.08. Biological Rhythms and Sleep

Support: NIMH Grant R01 MH106460

NIMH Grant R01 MH077159

International Mental Health Research Organization (IMHRO)

The Brain and Behavior Research Foundation (NARSAD)

Title: Using optogenetics to determine the role of the suprachiasmatic nucleus in mood-like behaviors

Authors: *C. A. VADNIE[1], C. N. HEISLER[2], R. W. LOGAN[1], L. A. EBERHARDT[1], D. BECKER-KRAIL[1], M. A. HILDEBRAND[1], C. A. MCCLUNG[1]
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Abstract: Circadian rhythm disruptions commonly occur in mood disorders. Recent clinical findings suggest that phase delayed rhythms more commonly occur during depressive episodes, whereas phase advanced rhythms more frequently occur during manic episodes. The suprachiasmatic nucleus (SCN) synchronizes bodily rhythms with the environment, and may underlie the misaligned rhythms observed in mood disorders. Recently, disrupting molecular rhythms in the SCN was shown to cause mood-like disturbances in mice, suggesting that disrupting SCN neural activity rhythms may affect mood. Thus, our goal was to develop a model system to determine if phase-delaying and phase-advancing manipulations of SCN neural activity have differential effects on mood-like behaviors. Channelrhodopsin-2 (ChR2) was genetically introduced into the SCN by crossing mice expressing Cre recombinase in GABAergic neurons with mice expressing Cre-dependent ChR2. Optic fibers were implanted above the SCN and mice were housed in cages equipped with piezoelectric floor sensors to monitor circadian rhythms and sleep. Mice were then placed in constant darkness (DD) to observe their SCN-driven rhythms. Mice subsequently received stimulations (1 h, 10 ms pulse width, 8 Hz) every three days at times early or late into their active phase to induce phase delays or phase advances, respectively. After six stimulation sessions, mood-like behaviors were assessed. Stimulating the SCN early in the active phase induced phase delays, increasing the period of activity rhythms (24.40 ± 0.06 hr) relative to control mice (24.13 ± 0.06 hr). Stimulating the SCN late in the active phase induced phase advances, decreasing the period of

activity rhythms (23.55 ± 0.07 hr) relative to controls (23.95 ± 0.02 hr). Thus, optogenetic stimulation of GABAergic neurons in the SCN induced phase shifts in circadian activity rhythms that resembled the known effects of light pulses applied in DD. We are currently assessing the effects of the stimulation paradigms on mood-like behaviors. Importantly, we have developed a model system to determine the role of SCN-mediated phase shifts of circadian rhythms in mood regulation.

Disclosures: C.A. Vadnie: None. **C.N. Heisler:** None. **R.W. Logan:** None. **L.A. Eberhardt:** None. **D. Becker-Krail:** None. **M.A. Hildebrand:** None. **C.A. McClung:** None.

Poster

237. Circadian: Synchronization

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 237.09/II4

Topic: F.08. Biological Rhythms and Sleep

Support: Academic Research Promotion Funds, Laboratory of Community & Human Services, Rikkyo Univ

Title: A long photoperiod affects core body temperature, anxiety-like behaviors, and monoaminergic neurotransmitters in rat brains

Authors: *A. KAWATA, Y. KANEDA, M. YASUMATSU, T. ISHIWATA
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Abstract: Artificial lighting has made modern life comfortable, but has had negative effects on health, leading to an increase in prevalence of mental illnesses like depression. Neurotransmitters, like serotonin (5-HT), dopamine (DA), and noradrenaline (NA), influence activity and mental states. Studies indicate that irregular light/dark (LD) cycles change physiological indices and cause anxiety-like behaviors, but only few studies have investigated the relevant neurotransmitters. We previously reported the relationships between circadian disruption, physiological indices, anxiety-like behaviors, and levels of neurotransmitters (Matsumura et al., Chronobiology Int, 2015). These studies investigated the effects of circadian disruption, but not the effects of a long photoperiod. Here, we report how a long photoperiod affects core body temperature (T_c), anxiety-like behaviors, and 5-HT, DA, and NA levels in rat brains. Male Wistar rats were housed in 2 different LD cycles: control (CTRL) 12h:12h (n=16) or long photoperiod (LP): 20h:4h (n=16) with food/water ad libitum. After 1 month, the rats underwent open field tests (OFT) and a social interaction test (SIT), or were sacrificed. The frontal cortex, caudate putamen, preoptic area, hippocampus, amygdala (AMY), ventral tegmental area, locus coeruleus, substantia nigra, median *and* dorsal raphe, suprachiasmatic nucleus (SCN), and the paraventricular, ventromedial, and dorsomedial hypothalamus were

immediately removed after rats were sacrificed, and 5-HT, DA, and NA levels were analyzed using high-performance liquid chromatography. Temperature loggers were implanted in the intra-abdominal cavity for each group of 5 rats, and data were retrieved after 1 month. Both CTRL and LP rats synchronized with each LD cycle, which indicated that they showed different T_c rhythms. LP rats synchronized to the LD cycle in 3 weeks. Compared to the CTRL rats, LP rats showed decreased levels of NA in the SCN and 5-HT in the AMY. DA was not influenced by the LD cycle. Line crossing and time in the center of the OFT were decreased in LP rats. During the SIT, sniffing, crawling, following, and time spent in social interaction were decreased. These results suggest that the LP induced change of the T_c rhythm, neurotransmitters, and induced an increase in anxiety-like behaviors. We concluded that the LP attenuated SCN function, decreased 5-HT in the AMY, and induced anxiety-like behaviors.

Disclosures: **A. Kawata:** None. **Y. Kaneda:** None. **M. Yasumatsu:** None. **T. Ishiwata:** None.

Poster

237. Circadian: Synchronization

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 237.10/II5

Topic: F.08. Biological Rhythms and Sleep

Support: NSERC Discovery Grant to BLM, RJM and MT

AHFMR Polaris Award to BLM

Title: Misalignment of sleep and behavioral activity rhythms in a T21 light-dark phase advance paradigm

Authors: *M. TATSUNO[1], R. ROTA[1], H. W. STEENLAND[1,2], S. H. DEIBEL[1], K. ALI[1], B. L. MCNAUGHTON[1,3], R. J. MCDONALD[1]
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Abstract: Circadian rhythm misalignment has a deleterious impact on the brain and the body. In rats, acute or chronic phase advances of the light-dark cycle impairs hippocampal dependent memory. Altered sleep architecture could be a possible mechanism for the memory consolidation failure, but has yet to be assessed in the T21 phase advance paradigm in which the phase of cycle is advanced 3 hours a day (L9:D12). It has been shown that rats under the T21 paradigm could learn a spatial location in the Morris water task while experiencing circadian rhythm misalignment but could not remember the learned location at the time of retention test. In this study, continuous local field potential recordings were used to assess sleep in rats exposed to six

consecutive days of phase advances in the T21 paradigm. During the phase advances, sleep and behavioral activity remained rhythmic but were out phase with the light-dark cycle. This was evident by more activity and less sleep during the light phase of the T21 cycle. Interestingly, there were no changes in the total amount of sleep, sleep stages, or components (K-complexes, and sleep spindles), nor did there appear to be dissociation among the various rhythms assessed. We speculate that sleep that is out of phase with the light-dark cycle could impact memory by several potential mechanisms including the reduction of the hippocampal sharp wave ripples in which memory replay frequently occurs and the disruption of the dialog between the hippocampus and the cortex during the misaligned sleep.

Disclosures: M. Tatsuno: None. **R. Rota:** None. **H.W. Steenland:** None. **S.H. Deibel:** None. **K. Ali:** None. **B.L. McNaughton:** None. **R.J. McDonald:** None.

Poster

237. Circadian: Synchronization

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 237.11/II6

Topic: F.08. Biological Rhythms and Sleep

Title: Sodium lighting alters cardiovascular circadian rhythms in mouse

Authors: *X. CHEN[1], G. J. DEMARCO[2]
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Abstract: Studies in nocturnal rodents often need to be performed during the dark phase of their light cycles. Reported to be visible to humans but not rodents, low-pressure sodium light (LPSL) has been used as an alternative to complete darkness to conduct studies and animal welfare checks during the dark phase. Previous work in our laboratory has shown that LPSL impacts the circadian timing system in rodents. This study tested the hypothesis that LPSL would alter cardiovascular circadian rhythms in mouse. Heart rate, blood pressure, and locomotor activity were captured from 10 telemetry implanted male C57BL/6J naïve mice under three different 12:12-hour light cycles - white light:dark (LD), white light:sodium light (LS), and sodium light:dark (SD). Circadian parameters were quantified and results from LS and SD were compared to LD. When placed under LS conditions, heart rate, blood pressure, and activity acrophase was delayed by 2.8, 2.3, and 2.6 hours respectively and eventually demonstrated entrainment. Under LS conditions the circadian robustness for blood pressure and activity was reduced 14.3 and 10.5%, respectively, and the amplitude of the activity circadian rhythm was reduced 36.1% compared to LD conditions. Under 12:12-hour SD cycles mice did not exhibit phase shifts and showed entrainment. The robustness and amplitude of the heart rate circadian rhythm was elevated 11.2 and 13.4%, respectively, and the robustness of the activity circadian

rhythm was reduced 11% under SD conditions compared to LD. To simulate a procedure, animals were exposed to a 2-hour sodium light pulse within the dark phase under LD conditions. This treatment disrupted entrained cardiovascular circadian rhythms, delayed activity acrophase by 1.1 hours, and increased activity in the light phase. In conclusion, these data demonstrates that sodium lighting is not the equivalent of complete darkness and can influence cardiovascular circadian physiology in C57BL/6J mouse.

Disclosures: X. Chen: None. **G.J. DeMarco:** None.

Poster

237. Circadian: Synchronization

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 237.12/II7

Topic: F.08. Biological Rhythms and Sleep

Support: CONACyT 239403

PAPIIT IG200314

Title: Circadian disruption increases alcohol intake associated with ΔFosB in corticolimbic brain areas

Authors: *M. RESÉNDIZ, C. ESCOBAR
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Abstract: Modern lifestyle promotes activities at night that provides conflicting time signals and disrupts the circadian system, increasing the risk of suffering metabolic, immune and behavioral diseases. The aim of this study was to evaluate the effect of circadian disruption on alcohol intake and to identify possible changes at the level of corticolimbic structures that may favoring alcohol overconsumption.
Male Wistar rats (n=48) were housed individually in cages with food and water *ad libitum*. Rats were randomly assigned to one of the following conditions: control 12:12 h L-D cycle, constant light (LL), or forced activity during the rest phase (REST).
General activity of each animal was continuously evaluated using an automated monitoring system that allows verifying circadian patterns at the behavioral level. After 3 weeks in their corresponding conditions LL rats showed arrhythmicity, while REST rats remained rhythmic similar to controls.
After 3 weeks in their corresponding condition brains were obtained in the day and in the night via perfusion and the circadian rhythm of Per1 was evaluated. In the control group Per1 exhibited a day/night difference in the infralimbic cortex, nucleus accumbens, insula and, suprachiasmatic nucleus while in REST and LL groups no day/night difference was observed,

confirming a circadian disruption at the corticolimbic level.
Other control, REST and LL rats were exposed to a 10% alcohol drink for 16 hours daily (from ZT10- ZT 2 next day), the daily intake of water and alcohol for each animal was monitored for 12 days, followed by a deprivation period (72 hours), after which a Binge-like test was performed.
Brains were obtained after drinking alcohol in the Binge test and the number of positive cells to ΔFosB was quantified in the infralimbic cortex, nucleus accumbens, insula and, suprachiasmatic nucleus
Control and LL rats showed a similar daily alcohol intake, while the REST group showed increased alcohol intake along the 12 days. In the Binge-like test both LL and REST rats showed a higher intake than the control rats.
For REST and LL rats the number of ΔFosB positive cells in the different corticolimbic areas was consistent with the behavioral data suggesting a neuroplasticity process consistent with the behavioral data.

Disclosures: M. Reséndiz: None. **C. Escobar:** None.

Poster

237. Circadian: Synchronization

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 237.13/II8

Topic: F.08. Biological Rhythms and Sleep

Support: FDN 143337

CIHR Banting and Best Canada Graduate Scholarship

Title: Osmo and thermosensitive OVLT neurons regulate SCN vasopressin neurons in horizontal slices of mouse hypothalamus

Authors: *C. GIZOWSKI[1], C. ZAELZER[2], C. W. BOURQUE[3]
[2]Neurol., [1]McGill Univ. Hlth. Ctr., Montreal, QC, Canada; [3]Neurol., McGill Univ., Montreal, QC, Canada

Abstract: Circadian rhythms are orchestrated by the brain's master clock, the suprachiasmatic nucleus (SCN), to adapt organisms to the 24-h day-light cycle. The SCN is primarily synchronized to circadian time via light exposure, however circadian rhythms can be shifted by non-photic stimuli. For example, systemic hypertonicity and increases in core body temperature have been shown to cause shifts of circadian locomotor activity, presumably to optimize osmoregulation and thermoregulation. The mechanisms by which these stimuli alter the rhythmicity of SCN neurons remain unclear. The organum vasculosum lamina terminalis

(OVLT) is a preoptic multimodal sensory nucleus that contains neurons capable of detecting changes in both temperature and osmolality via the transduction channel dn-Trpv1. We therefore examined if OVLT neurons can modulate SCN clock neurons. To determine if OVLT neurons project to the SCN, we injected fluorescent microspheres in the SCN of mice and allowed the animals to recover for 7 days to allow retrograde axonal transport. We found retrogradely labelled neurons in the OVLT, indicating that such neurons send axons to the SCN. In a subset of these mice, hypertonic saline was injected subcutaneously 2 hours before the brain was perfused with fixative and stained to examine expression of the activity-dependent immediate early gene c-Fos. Many retrogradely labeled OVLT neurons were found to express c-Fos, indicating that such neurons could provide osmosensory information to the SCN. Indeed, single cell RT-PCR analysis of retrogradely labelled OVLT neurons confirmed the expression of dn-Trpv1, and most of these also expressed GAD65, a marker of GABAergic neurons. Preliminary results suggest GABA excites SCN vasopressin (VP) neurons during the subjective day, when electrical activity is low. Since OVLT neurons are excited by hypernatremia and heat, we hypothesized that SCN VP neurons can be excited via OVLT GABAergic neurons. Using horizontal hypothalamic slices that retain the OVLT-SCN network, we obtained whole-cell voltage clamp recordings of SCN VP neurons. In the presence of Kynurenic acid to block glutamatergic synapses, bath application of a hypernatremic solution or local heating of the OVLT caused a significant increase in the frequency of spontaneous inhibitory post-synaptic currents, indicating that a pathway arising from the OVLT can relay osmo- and thermosensory information to SCN VP neurons. The functional significance of this projection remains to be determined.

Disclosures: **C. Gizowski:** None. **C. Zaelzer:** None. **C.W. Bourque:** None.

Poster

237. Circadian: Synchronization

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 237.14/II9

Topic: F.08. Biological Rhythms and Sleep

Support: NIH Grant NS078220

NIH Grant NS092545

Title: Intracellular calcium in the suprachiasmatic nucleus and the resetting of circadian phase, a potential role for CRAC channels

Authors: *J. C. WALTON, J. K. MCNEILL, IV, A. M. ROSENHAUER, H. E. ALBERS
Neurosci. Inst. and Ctr. for Behavioral Neurosci., Georgia State Univ., Atlanta, GA

Abstract: The mammalian suprachiasmatic nuclei (SCN) of the hypothalamus function as a central circadian clock that entrains an organism's physiology and behavior to environmental light-dark cycles. Recent studies have directly linked intracellular Ca^{2+} (iCa^{2+}) rhythms to the core clock gene transcriptional-translational feedback loop, but few studies have examined the role of iCa^{2+} in circadian entrainment, and fewer have investigated the source of this iCa^{2+}. Toward this end, we investigated the effects of iCa^{2+} antagonists on photic phase resetting *in vivo* using Syrian hamsters implanted with cannula aimed at the SCN. In the early subjective night, microinjection of the iCa^{2+} antagonist 8-(Diethylamino)octyl 3,4,5-trimethoxybenzoate hydrochloride; 3,4,5-Trimethoxybenzoic acid 8-(diethylamino)octyl ester hydrochloride (TMB-8) induced phase delays that were not different from those caused by a 150 lux 15 minute light pulse. TMB-8 given in conjunction with a light pulse enhanced the phase delaying ability of the light pulse. The effects of TMB-8 do not appear to be mediated by ryanodine receptors. However, the Ca^{2+} release-activated Ca^{2+} (CRAC) channel antagonist YM58483 (BTP2) had effects similar to TMB-8 in the early subjective night. Using hamster-specific primers, the presence of the CRAC channels STIM and ORAI have been confirmed in the SCN across the day at the transcript level. To our knowledge, these data provide the first evidence of the presence of, and a role for, CRAC channels in the mammalian SCN. We are currently performing experiments to determine CRAC protein localization in the SCN, as well as investigating the potential roles of CRAC mediated iCa^{2+} in both photic and non-photic phase advances.

Disclosures: J.C. Walton: None. **J.K. McNeill:** None. **A.M. Rosenhauer:** None. **H.E. Albers:** None.

Poster

237. Circadian: Synchronization

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 237.15/II10

Topic: F.08. Biological Rhythms and Sleep

Support: MRC Grant MC_U142684173

Title: Conditional gene targeting defines dual roles for Zfhx3 in SCN development and in setting the pace of behavioural rhythms in adults

Authors: *A. G. WILCOX[1], G. BANKS[1], P. L. OLIVER[2,1], P. M. NOLAN[1]
[1]MRC Harwell Inst., Harwell Campus, United Kingdom; [2]Univ. of Oxford, Oxford, United Kingdom

Abstract: Previous work revealed an important and novel role for the transcription factor ZFHX3 in circadian biology. A dominant missense mutation in the gene resulted in a

heterozygous mutant (Short circuit; *Sci*) with shortened circadian period in constant conditions and altered sleep homeostasis. Further investigations revealed this was due, in part, to dysregulation of key circadian neuropeptides responsible for intercellular synchrony in the suprachiasmatic nucleus (SCN). However, as the constitutive knockout (KO) of *Zfhx3* is lethal, homozygous mutants have not been behaviourally characterised. Using conditional mutagenesis we have been able to circumvent the lethality of the constitutive null and generate conditional null alleles of *Zfhx3* to further our understanding of its role in circadian rhythms. Using this approach both temporally and spatially restricted homozygous knockouts of *Zfhx3* were generated.

A ubiquitously-expressed inducible Cre driver was used to delete the gene specifically in adult tissues, thus preserving its developmental expression. In wheel-running screens, KO of *Zfhx3* in adult mice in constant darkness resulted in a significantly acute shortening of circadian period from 23.7(±0.09) hrs to 22.7(±0.15) hrs in 70% of mice screened [$p<0.005$]; the remaining animals lost rhythmicity in constant conditions. Mutants also showed increased activity in the light phase following KO; however phase angle of entrainment was not significantly different. Using the SCN-enriched *Six3*-Cre line, *Zfhx3* was deleted in developing SCN during embryogenesis. These homozygous mutants were arrhythmic in all conditions and unable to entrain to a light-dark cycle. They were also unable to entrain to social cues from cagemates when group housed. Subsequent histological examination revealed that there was an apparent loss of SCN cell identity in these animals, as there was no visible dense cell nucleus present above the optic chiasm.

This work highlights the importance of *Zfhx3* in the circadian system, providing evidence that it is necessary both for maintaining stable circadian rhythms in the adult and for terminal differentiation of the SCN in developing brain.

Disclosures: **A.G. Wilcox:** None. **G. Banks:** None. **P.L. Oliver:** None. **P.M. Nolan:** None.

Poster

237. Circadian: Synchronization

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 237.16/II11

Topic: F.08. Biological Rhythms and Sleep

Support: PAPIIT-UNAM I6200314

CONACyT (239403)

Title: Effects of LD cycle after LL expossure during lactaction on the SCN and locomotor activity

Authors: *M. PALMA, I. OSNAYA RAMIREZ, C. ESCOBAR
Anat., UNAM, mexico city, Mexico

Abstract: Disruption of the circadian system during early stages of development can lead to increased propensity to disease and metabolic disorders. The present study explored the effects of circadian disruption by constant light (LL) during lactation on the circadian system and the metabolic regulation. Pups exposed to constant conditions during lactation exhibited increased body weight, loss of rhythmic behavior, increased levels of glucose and triglycerides as well as loss of the rhythm of both variables and alterations in the retina´s morphology. In the SCN we found a loss in the rhythm of VIP, AVP, PER1 and a decrease in the number of inmunopositive cells was observed in LL. Exposure to LD conditions after lactation was able to revert the effects induced by constant conditions only in locomotor activity while the peptides in the SCN did not recover neither the rhythmicity nor the total inmunopositive number of cells, the retina of LL group did not show improvements at P90, the glucose and triglycerides levels were still increased at the end of the study in the LL and DD groups. Our data show that constant conditions LL or DD during lactancy disrupt circadian and metabolic systems at short and long term. These results point out the main role played by the LD cycle during early development and the risk of altered light-dark cycles during early stages of development.

Disclosures: M. Palma: None. **I. Osnaya Ramirez:** None. **C. Escobar:** None.

Poster

237. Circadian: Synchronization

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 237.17/II12

Topic: F.08. Biological Rhythms and Sleep

Support: XDB02020005

Title: An increased hypothalamic kisspeptin signaling is associated with the non breeding to breeding season switch in free ranging adult male rhesus monkeys

Authors: *T. ANWAR[1,2], M. SHAHAB[2]
[1]Xuzhou Med. Univ., Jiangsu, China; [2]Quaid i Azam Univ., Islamabad, Pakistan

Abstract: Kisspeptin is known as one of the fundamental regulators of neuroendocrine reproductive axis. We hypothesized that the expression of hypothalamic kisspeptin, GPR54 and GnRH underlies the seasonal changes of reproduction in Rhesus monkey. We examined the expression of kisspeptin, GPR54 and GnRH (mRNA and protein levels) in the medio-basal hypothalamus (MBH) of adult male rhesus monkeys maintained under free ranging conditions during breeding (BS; January; N = 3) and non-breeding season (NBS, July; N = 3). Cerebro

spinal fluid (CSF) was collected (four samples collected at 30 min interval/animal from the lumbar vertebrae; N = 3) for the determination of kisspeptin during BS (November) and NBS (August) (N = 4) along with the determination of peripheral testosterone levels by using specific RIA's.
A significant increase during the breeding season, in the relative mRNA expression of kisspeptin ($P < 0.01$), GPR54 ($P < 0.0005$) and GnRH ($P < 0.0001$) in the MBH was observed. The number of kisspeptin cell bodies significantly increased in the arcuate nucleus (ARC) during the BS ($P < 0.0001$). The number of GnRH, GPR54 positive, GPR54 positive GnRH cell bodies and contacts between the GnRH and kisspeptin cell bodies were significantly increased ($P < 0.01$; $P < 0.01$, $P < 0.001$ and $P < 0.01$, respectively) in the BS. The CSF kisspeptin levels ($P < 0.0001$), peripheral testosterone concentrations ($P < 0.0001$) and paired testis weight ($P < 0.0001$) were also increased during the BS monkeys.

Disclosures: T. Anwar: None. **M. Shahab:** None.

Poster

237. Circadian: Synchronization

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 237.18/II13

Topic: F.08. Biological Rhythms and Sleep

Support: NIH T32 NS099578

NIH 5R01NS094211-02

Title: Jet lag induces a transient misalignment of circadian timing of sleep stages in the mouse

Authors: *R. SANCHEZ[1], I. L. BUSSI[2], M. BEN-HAMO[3], H. O. DE LA IGLESIA[4]
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Abstract: In mammals, daily rhythms of physiology and behavior are synchronized to the 24-hour light-dark (LD) cycle via retinal input to the suprachiasmatic nucleus (SCN), the master circadian clock located in the hypothalamus. The SCN is divided into two subregions, the dorsomedial SCN (dmSCN) and ventrolateral SCN (vlSCN), and relies on a GABAergic coupling mechanism to maintain neural network synchrony. Sleep is one of the most critical physiological and behavioral outputs of the circadian clock, and the SCN has been demonstrated to play an important role in sleep timing and quality. Jet lag, the malaise resulting from abrupt shifts in the LD cycle, is a common challenge to the circadian system and is characterized by severe sleep disturbances lasting several days beyond the initial shift. Although previous work

has demonstrated that normal SCN function is necessary for an animal to entrain to a new LD cycle following an abrupt shift, these studies have focused on behavioral outputs as a measure of circadian rhythmicity, leaving our understanding of how sleep architecture is altered by jet lag incomplete. Here we present a behavioral model of jet lag in which we combine locomotor activity monitoring with electrocorticographic (ECoG) and electromyographic (EMG) recordings to assess sleep-wake patterns in the mouse for one month. Mice were first subjected to a 6 hour phase delay, followed by a 6 hour advance of the LD cycle, simulating westward and eastward transmeridian flights, respectively, while ECoG/EMG data were recorded continuously. Mice were allowed to adjust to the new light cycle for 10 days before the next shift was introduced. We report that jet lag induces a transient misalignment in the circadian timing of non-rapid eye movment (NREM) and rapid eye movement (REM) sleep stages. This misalignment is of greater magnitude and takes longer to rectify following an advance jet lag paradigm. For both advances and delays, we find that the acrophase of REM sleep is slower to adjust to the new LD cycle than NREM sleep. We hypothesize that this difference in entrainment time of REM and NREM acrophases is due to differential gating of circadian sleep stage timing by the dmSCN and vlSCN, respectively. Ongoing work is testing the role of these SCN neuronal subpopulations in sleep stage timing by using genetic targeting strategies to disrupt GABAergic neurotransmission in a region-specific manner. Our work contributes to the understanding of mechanisms underlying sleep disturbance in jet lag, and provides a novel experimental paradigm for probing the circadian regulation of sleep in the mouse.

Disclosures: **R. Sanchez:** None. **I.L. Bussi:** None. **M. Ben-Hamo:** None. **H.O. de la Iglesia:** None.

Poster

237. Circadian: Synchronization

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 237.19/II14

Topic: F.08. Biological Rhythms and Sleep

Support: Pac-12 Conference Student-Athlete Health & Well- Being Grant Program, Grant Reference # 2-02 Pac-12-Colorado-McQueen-16-01

Title: Travel in collegiate varsity student athletes: Relationship to mood within season competition

Authors: *E. VILLEGAS, JR[1], M. HOLLIDAY[2], M. B. MCQUEEN[3], T. D. HERNÁNDEZ[1]
[1]Psychology and Neurosci., [3]Integrative Physiol., [2]Univ. of Colorado Boulder, Boulder, CO

Abstract: With over 460,000 students involved in NCAA college sports, there is a need for improved understanding of the health and well-being of varsity student-athletes during a typical

academic year and across their years at University. Understanding this is vital toward identifying stressors that adversely impact student-athletes, as well as best practices for sustainable athlete training, performance, long term health and well-being. It has been shown (Penn Schoen Berland, 2015) that time commitments are a perceived stressor to varsity student-athletes, including competition travel. With this in mind, the present Pac 12 funded study conducted repeated, in-season assessment of pre- and post-travel mood disturbance using the Brief Assessment of Mood (BAM) scale. Baseline assessment was compared to pre- and post-season travel across travel timepoint or "trip". In addition to analyzing the total BAM Mood disturbance score, we also analyzed individual factors within the scale such as anxiousness, fatigue and sadness. Mood disturbance appeared to be higher at Baseline compared to competition travel. Individual factors showed interesting patterns that will be discussed in terms of the broader impact of travel on varsity student-athletes, and the ways in which this varies by sport. Together, this study provides a unique means by which to track varsity student-athlete stressors over time. As well, it allows for an opportunity to create best practices to minimize the adverse impact of travel-related stressors on performance, mood, health and well-being.

Disclosures: E. Villegas: None. **M. Holliday:** None. **M.B. McQueen:** None. **T.D. Hernández:** None.

Poster

237. Circadian: Synchronization

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 237.20/II15

Topic: F.08. Biological Rhythms and Sleep

Support: NSF Award 1649717

NSF Award 1435152

Title: Spatial statistical analysis of artificial light at night in select rural and suburban wildlife

Authors: S. JOHNSON, *F. JEFFERSON
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Abstract: Natural light cycles provide critical information to organisms pertaining to its circadian cycle, visual perception, and spatial orientation. Artficial light at night (ALAN), also known as light pollution, can extensively alter normal light cycles as it is displayed at times and places in which it does not naturally occur. Moreover, pervasive use of ALAN can be regarded as a stressor on the physiologies of organisms and has adversely affected the natural daily processes of ecological wildlife systems. In this study, we evaluate spatial and temporal dimensions in our ecological analysis of the effects of ALAN in select communities of deer and

rodent populations. Data obtained from ArcGIS is used to investigate the effects of ALAN to deer and rodents over the previous 30 years. Spatial statistics is conducted to analyze data obtained from the ArcGIS subscription database. An increase in deaths, movement, and decrease in select deer and rodent populations could be attributed to growth in human population where the addition of ALAN often occurred. This data provide insights into the long-term effects to communities and deer and rodent populations following addition of ALAN. Future investigation into the sleep-wake effects is anticipated.

Disclosures: S. Johnson: None. **F. Jefferson:** None.

Poster

237. Circadian: Synchronization

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 237.21/II16

Topic: F.08. Biological Rhythms and Sleep

Title: Opioids inhibit melanopsin ganglion cell signaling via Kv1.2

Authors: *A. M. CLEYMAET[1], A. S. HOAG[2], J. VIGH[2]
[1]Clin. Sci. and Biomed. Sci., [2]Biomed. Sci., Colorado State Univ., Fort Collins, CO

Abstract: A subset of retinal ganglion cells, melanopsin-expressing intrinsically photosensitive retinal ganglion cells (ipRGCs), are exclusively responsible for photoentrainment of circadian rhythm. They do this by processing and conveying environmental light information to the body's master clock in the suprachiasmatic nucleus (SCN). We have shown that ipRGCs express μ-opioid receptors (MORs). As well, MOR specific agonists strongly diminish light-evoked ipRGC firing in whole-mount retinal preparations. We dissected the molecular events underlying this event. We enzymatically dissociated ipRGCs from the retinas of an *Opn4*::EGFP mouse line. Using electrophysiological and pharmacological techniques, we assessed the effects of the MOR specific agonist DAMGO (1 μM) on depolarization-evoked firing of ipRGCs. DAMGO decreased ipRGC excitability as evidenced by the increase in the current threshold required for the first ramp evoked spike (2.19 ± 0.83 pA, DAMGO: 5.53 ± 1.34 pA, n = 18, $p<0.001$). However, DAMGO did not alter the spike threshold (-51.40 ± 0.87 mV, DAMGO: -51.88 ± 0.96 mV, n = 18, p=0.135). Instead, DAMGO hyperpolarized the potassium current (I_K) activation threshold ($V_{0.05}$), such that, in the presence of DAMGO, I_K activation took place at the Na^+-spike initiation threshold ($V_{0.05}$ control: -39.44 ± 2.85 mV, DAMGO: -51.43 ± 3.36 mV, n = 10, $p<0.001$). DAMGO application thus resulted in a competing outward I_K that increased the depolarizing current threshold required for voltage gated sodium channel activation. Furthermore, the DAMGO-evoked I_K activation shift was absent in the presence of 4AP (2mM), suggesting that the DAMGO-sensitive I_K was blocked by 4AP ($\Delta V_{0.05}$ control vs. DAMGO: 9.93 ± 0.99 mV, n=20; 4AP vs. 4AP & DAMGO: 1.38 ± 2.06 mV, n = 7, $p<0.001$). Based on I_K

sensitivity to 2 mM 4AP, the candidate DAMGO-sensitive voltage gated K^+-channels (K_v) were $K_v1.1$ and $K_v1.2$. Immunohistochemistry revealed that ipRGCs express $K_v1.2$ but not $K_v1.1$. In conclusion, DAMGO-mediated inhibition of ipRGC signaling via $K_v1.2$ underlies opioid-induced attenuation of ipRGC light-evoked firing. Additional dissection of opioid-mediated inhibitory effects on ipRGCs may be relevant for future therapeutic mediation of circadian rhythm pathology.

Disclosures: **A.M. Cleymaet:** None. **A.S. Hoag:** None. **J. Vigh:** None.

Poster

238. Circadian: Cellular and Molecular Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 238.01/II17

Topic: F.08. Biological Rhythms and Sleep

Support: NIH K08 HD071026

Tuberous Sclerosis Alliance

William Randolph Hearst Foundation

American Sleep Medicine Foundation

NIH R01 NS058956

John Merck Fund

Nancy Lurie Marks Family Foundation

Title: Aberrant Bmal1 proteostasis underlies circadian abnormalities in tuberous sclerosis complex

Authors: *J. O. LIPTON[1], L. M. BOYLE[1], E. D. YUAN[1], K. HOCHSTRASSER[1], F. CHIFAMBA[1], F. DAVIS[2], P. TSAI[3], M. SAHIN[1]
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Abstract: Tuberous Sclerosis Complex (TSC) is a neurodevelopmental disorder characterized by mutation in either the TSC1 or TSC2 genes whose products for a critical inhibitor of the mechanistic target of rapamycin (mTOR). Loss of TSC1/2 gene function renders an mTOR-overactivated state. Clinically, TSC manifests with epilepsy, intellectual disability, autism, and sleep dysfunction. We report abnormal circadian phenotypes in mouse models of TSC. We show that mTOR regulates the proteostasis of the core clock protein BMAL1, affecting its translation,

UBE3A-mediated degradation, and subcellular localization. This results in elevated levels of BMAL1 and a dysfunctional clock that displays abnormal timekeeping in constant conditions and exaggerrated responses to phase resetting. Genetically lowering the dose of BMAL1 rescues circadian behavioral phenotypes in TSC mouse models. Our findings indicate that BMAL1 deregulation is a feature of the mTOR-activated state and suggest molecular mechanisms for mitigating circadian phenotypes in a neurodevelopmental disorder.

Disclosures: **J.O. Lipton:** None. **L.M. Boyle:** None. **E.D. Yuan:** None. **K. Hochstrasser:** None. **F. Chifamba:** None. **F. Davis:** None. **P. Tsai:** None. **M. Sahin:** None.

Poster

238. Circadian: Cellular and Molecular Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 238.02/II18

Topic: F.08. Biological Rhythms and Sleep

Title: Exploring the molecular clock in sympathetic preganglionic neurons

Authors: *C. NATHAN[1,2], J. ASPDEN[3], S. DEUCHARS[2], J. DEUCHARS[2]
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Abstract: Cardiovascular physiology exhibits a diurnal rhythm e.g. blood pressure dips at night and increases in the morning. Loss of diurnal rhythm of blood pressure is correlated to an increased risk of developing cardiovascular diseases. Blood pressure is to a large part controlled by sympathetic nervous system activity, which exhibits diurnal activity. Since sympathetic preganglionic neurons (SPNs) are the final common pathway the central nervous system influences blood pressure, this project aims to determine if SPN function could be regulated by diurnal expression of genes.
C57/Bl6 mice were terminally anesthetized and perfused with 4% paraformaldehyde. To facilitate cell sorting, immunohistochemistry was used to attempt to selectively label SPNs using cellular markers which the Allen Brain Atlas and/or Gensat project indicated were expressed only in SPNs or differentially between SPNs and motor neurons (e.g. CD44, glutathione peroxidase 3). A selective marker has yet to be found. The diurnal expression of genes encoding proteins involved in determining neuronal activity in the spinal cord and from micro-punches that include the IML, obtained at morning and evening time points, is being investigated using qPCR. Initial results indicated that mRNA levels of proteins involved in serotonergic (Htr2a), adrenergic (Adra2a), GABAergic (Gabra5) and cholinergic (ChAT) signalling, vary with time of day. Functional effects of such variations will be tested in future electrophysiology experiments.

Disclosures: **C. Nathan:** None. **J. Aspden:** None. **S. Deuchars:** None. **J. Deuchars:** None.

Poster

238. Circadian: Cellular and Molecular Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 238.03/II19

Topic: F.08. Biological Rhythms and Sleep

Support: NIH Grant 1R01NS082413 to KLG

Title: Circadian clock regulates neuronal excitability in dopaminergic neurons of the substantia nigra

Authors: *J. R. PAUL[1], L. J. MCMEEKIN[2], S. FOX[4], S. D. YATES[5], R. M. COWELL[3], K. L. GAMBLE[6]
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Abstract: Extensive research has explored circadian regulation of neuronal activity in the primary circadian pacemaker, the suprachiasmatic nucleus; however, very little is known about circadian control of excitability in other spontaneously active neurons. The dopaminergic cells of the substantia nigra pars compacta (SNc) are a population of pacemaker neurons necessary for initiating general locomotor activity through dopamine release in the striatum. Previous reports showing daily rhythms in dopamine levels in the dorsal striatum, which are absent in *Bmal1*$^{-/-}$ mice, suggest that SNc activity might be rhythmically regulated; yet the influence of circadian rhythms on the SNc physiology is still unknown. Therefore, the goal of study was to determine the role of the molecular clock in regulating SNc pacemaker activity. SN samples collected from wild-type mice during the day (ZT 11) or night (ZT 23) exhibited significant day/night differences in the mRNA levels of multiple core clock genes. Specifically, *Per 1* and *Per2* were increased during the day, whereas *Bmal1* expression was elevated at night. Furthermore, real-time bioluminescence recordings of PER2::LUC rhythms from organotypic slice cultures of the substantia nigra (but not ventral tegmental area) showed persistent oscillations for multiple cycles in the absence of external input. Whole-cell current clamp recordings from the SNc during the day (ZT 4-11) or night (ZT 13-23) revealed that dopaminergic neurons exhibited a significant day/night difference in spontaneous action potential frequency, with higher activity during the day than at night. Ablation of *Bmal1* in SNc neurons dampened the day/night difference in neuronal excitability. This effect was primarily due to increased activity at night when Bmal1 expression is typically elevated. Finally, the expression of multiple genes encoding for voltage-gated sodium channels (*Scn1a, Scn2a, Scn8a*) were elevated during the day when dopaminergic neuronal activity is higher, suggesting that sodium currents may be involved in rhythmic SNc activity. Ongoing experiments will determine if the persistent sodium current exhibits day/night

differences in SNc neurons. Given that circadian disruption and dopaminergic neuronal dysfunction are associated with Parkinson's disease, better understanding the mechanism by which the clock regulates SNc physiological rhythms could provide further insight into the etiology of the disease.

Disclosures: J.R. Paul: None. **L.J. McMeekin:** None. **S. Fox:** None. **S.D. Yates:** None. **R.M. Cowell:** None. **K.L. Gamble:** None.

Poster

238. Circadian: Cellular and Molecular Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 238.04/II20

Topic: F.08. Biological Rhythms and Sleep

Support: CIHR Grant M00204

Title: Mapping clock genes expression in dopamine receptor-bearing neuronal subtypes

Authors: *N. DE ZAVALIA, J. GOLDSMITH, S. AMIR
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Abstract: Dopamine is involved in various neural and behavioural processes such as learning, reward, motivation, and neuroendocrine control. Dysfunction of dopaminergic systems is implicated in multiple pathologies such as Parkinson's disease and addiction. Increasing evidence has highlighted interactions between the dopaminergic signaling and circadian rhythms. However, little it's known about the expression of clock genes in neuronal subsets within dopaminergic target structures. The aim of this work was to map the expression of PER1, PER2 and BMAL1 in dopaminergic targets, using drd1a-tdTomato/drd2-GFP double-transgenic mice. Regions examined included the limbic forebrain (dorsal striatum, nucleus accumbens, central amygdala, stria terminalis), hippocampus, olfactory bulb and olfactory tubercle. PER1, PER2 and BMAL1 were primarily expressed in neurons with almost no expression in glia. Almost all cells (~99%) positives for PER1, PER2 or BMAL1 were also positives for DAPI, a neuronal marker. The clock genes were homogeneously expressed in the D1- and D2- dopamine receptor neuron populations without any preferential expression. These results suggest that core circadian clocks are expressed in all neurons in the regions examined. D1 and D2-bearing neurons are distinguished by their post-receptor signaling mechanisms and behavioral functions, and further studies will be required to elucidate the role of clock genes in these dopamine-recipient neurons.

Disclosures: N. De Zavalia: None. **J. Goldsmith:** None. **S. Amir:** None.

Poster

238. Circadian: Cellular and Molecular Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 238.05/II21

Topic: F.08. Biological Rhythms and Sleep

Support: Ed and Ethel Moore Alzheimer's Research Program Grant Award #7AZ13

USF Health RISE 2017SSAE

Title: Modeling sundowning syndrome in mouse models of Alzheimer's disease

Authors: *S. NAGARAJ[1], A. YUNUS[2], D. GULICK[2]
[2]Mol. Med., [1]Univ. of South Florida Morsani Col. of Med., Tampa, FL

Abstract: Sundowning Syndrome (SS) is a significant constellation of symptoms, expressed in a circadian pattern in Alzheimer's disease (AD), which devastates patients and increases the burden on caregivers. Current treatment options are scant. Here, we use two distinct mouse models of SS to study whether an inhibitor of the circadian clock-regulating casein kinase 1 isoforms epsilon and delta (CK1ε/δ) can improve circadian rhythmicity and behavior. Our models of SS are aged (18 to 20-month-old) C57BL/6J mice, which is a model of normal aging, and 7-9-month-old amyloid precursor protein/presenilin 1 (APP/PS1) mutant mice, a model of β-amyloid deposit pathology: both models show symptoms characteristic of SS. The CK1ε/δ inhibitor PF-670462 has shown success in recovering circadian rhythmicity in mouse models. Using measurement of wheel running and water drinking patterns, we can assess the recovery of circadian activity patterns in our models. Using a series of behavioral tests at multiple times of day, we can also measure the change in anxiety and cognitive performance. Ongoing experiments are characterizing the changes in cognitive function, and changes in β-amyloid pathology, of mouse models of SS in a circadian fashion following PF-670462 administration. The results show that directly manipulating effectors of the biological clock provides a novel means of treating SS and improving the lives of AD patients as well as their caregivers.

Disclosures: S. Nagaraj: None. **A. Yunus:** None. **D. Gulick:** None.

Poster

238. Circadian: Cellular and Molecular Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 238.06/II22

Topic: F.08. Biological Rhythms and Sleep

Support: NIH Grant R01AG043972

NIH Grant T32HL105349

Title: Hippocampal circadian disruption in early senescence mouse model

Authors: *J. DAVIS[1], H. MUNIR[1], M. MOKASHI[1], D. MOUNT[1], S. D. YATES[3], D. ALLISON[2], M. YOUNG[4], K. L. GAMBLE[5]
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Abstract: Age related cognitive decline and disruptions in circadian rhythms are growing problems as the average human life span increases. Multiple strains of the senescence-accelerated mouse (SAM), derived from the AKR/J line, show reduced life span, and the SAMP8 strain in particular has been well documented to have cognitive deficits in behavior as well as impaired long-term potentiation (LTP) in hippocampus when compared to the senescence resistant strain (SAMR1). While the SAMP8 strain of mice have been shown to have a split pattern of circadian locomotor activity, little is known about circadian regulation within hippocampus of these strains of mice. We hypothesized that the cognitive deficits in these mice are due in part to altered circadian clock function in the hippocampus. To test this hypothesis, we measured protein expression of the key molecular clock components, PER2 and BMAL1, at 4-hour intervals across the 24-hour light-dark cycle in whole hippocampus isolated from SAMP8 and SAMR1 mice at 6 months of age; immunohistochemistry in the SCN was also performed. Western blot analysis revealed a normal 24-h rhythm in PER2 and BMAL1 expression in hippocampus from SAMR1 control mice (cosinor analysis, $p < 0.05$). However, despite seemingly normal PER2 immunoreactivity in the SCN in both strains (verified by immunohistochemistry), SAMP8 mice had arrhythmic expression of PER2 and BMAL1 in whole hippocampus (cosinor analysis, $p > 0.60$). Experiments are ongoing to determine whether night restricted feeding can rescue arrhythmicity of the hippocampal molecular clock. Understanding how circadian rhythms impact cognition in aging will be important for improving quality of life in elderly populations.

Disclosures: J. Davis: None. **H. Munir:** None. **M. Mokashi:** None. **D. Mount:** None. **S.D. Yates:** None. **D. Allison:** None. **M. Young:** None. **K.L. Gamble:** None.

Poster

238. Circadian: Cellular and Molecular Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 238.07/II23

Topic: F.08. Biological Rhythms and Sleep

Support: Wellcome Trust Programme Grant 08964712/Z/09/Z to SLL and BCC

Neuroendocrinology Charitable Trust Fellowship award to BCC

Title: Prolonged activation of the glucocorticoid receptor during methylprednisolone treatment results in dysregulated hippocampal clock gene expression, dysregulated sleep, and impaired memory consolidation in the rat

Authors: *M. BIRNIE, A. L. FODDER, G. R. I. BARKER, R. DEMSKI-ALLEN, B. P. FLYNN, A. PRATAP, Y. M. KERSHAW, E. C. WARBURTON, M. W. JONES, B. L. CONWAY-CAMPBELL, S. L. LIGHTMAN
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Abstract: Synthetic glucocorticoids (GCs) are widely used in the clinic due to their potent anti-inflammatory actions, but are associated with many adverse side effects. In addition to the well-characterised metabolic side effects, there are many clinical reports of sleep disturbances and memory impairments in patients undergoing chronic GC treatment. Unlike the endogenous GCs, which induce a transient 'pulsatile' transcriptional activity of GR target genes, synthetic GCs such as methylprednisolone (MPL) induce prolonged GR activation in GC target regions of the brain such as the hippocampus (HC). However the exact nature of the molecular and functional consequences of prolonged hippocampal GR activation during chronic MPL treatment is not yet fully understood. Here, we have treated 9-10 week old male Lister Hooded rats with 1mg/ml MPL in drinking water (provided *ad libitum* for 5 days). We found that this dose was able to maximally suppress the endogenous GC (corticosterone in rat) whilst inducing prolonged hippocampal GR activity throughout the circadian nadir. RNAseq of total RNA from whole hippocampus revealed significant dysregulation in circadian rhythmicity of the clock gene expression network in MPL treated rats, compared to controls. Period1, important for the maintenance of circadian rhythmicity, increased to maximal mRNA expression levels at ZT10-18 in control rats as expected. In contrast, MPL treated rats exhibited elevated and phase-shifted expression. Further dysregulation of the circadian clock was evident in Period2, Cry1, Bmal1, and Rev-erbα. At the physiological level, we found that locomotor activity and core body temperature were significantly dysregulated with MPL treatment. Hippocampal-dependent memory was significantly impaired in the object location task. MPL treated rats were able to discriminate between novel and familiar object location following a 1hr delay between sample and test phase but not after a 6hr delay. Therefore, we have used *in vivo* electrophysiological local field potential recordings of the prefrontal cortex-amygdala-hippocampus network to monitor activity during this 6hr memory consolidation phase. We have found dysregulation in sleep architecture with further analysis of these data to elucidate changes in network activity underlying memory consolidation including hippocampal-prefrontal interactions. Our data strongly supports the conclusion that MPL treatment acts centrally via GR to disrupt the molecular transcriptional clock mechanism, with consequent disturbance of sleep patterns and hippocampal-dependent memory consolidation processes.

Disclosures: **M. Birnie:** None. **A.L. Fodder:** None. **G.R.I. Barker:** None. **R. Demski-Allen:** None. **B.P. Flynn:** None. **A. Pratap:** None. **Y.M. Kershaw:** None. **E.C. Warburton:** None. **M.W. Jones:** None. **B.L. Conway-Campbell:** None. **S.L. Lightman:** None.

Poster

238. Circadian: Cellular and Molecular Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 238.08/II24

Topic: F.08. Biological Rhythms and Sleep

Support: NRF 2017R1A2A1A05001351

DGIST 2017010095

Title: MicroRNAs as modulators of circadian gene Period2 oscillation

Authors: *I. PARK[1], K. KU[1], J. KIM[2,1], D. KIM[3,1], H. CHOE[1], Y. CHOE[4], K. KIM[1,5]
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Abstract: Circadian clock controls an organism's biological rhythm and regulates physiological conditions in response to external time cues. Most of living organisms have their own time-keeping mechanism that is maintained by transcriptional-translational auto-regulatory feedback loops involving several core clock genes such as *Periods*, *Cryptochromes, Clock,* and *Bmal1*. Recent discoveries have found the relevance between changes in circadian oscillation and post-transcriptional modification by microRNAs (miRNAs). However, the specific mechanisms of miRNAs on circadian oscillation remain unclear. To understand modulatory functions of miRNAs on circadian rhythm, we first screened candidate miRNAs targeting *Period2 (Per2)* using several *in silico* algorithms and consistently identified miR-24-3p and miR-25-3p as promising candidates. Luciferase reporter assay validated that miR-24-3p and miR-25-3p repressed the expression of the luciferase reporter retaining the predicted miR-24-3 and miR-25-3p binding sites on 3' untranslated region (UTR) of *Per2* mRNA. Furthermore, real-time bioluminescence analyses using PER2::Luc mouse embryonic fibroblasts confirmed that PER2 protein oscillation patterns were sensitive to the level of selected miRNAs. Overexpression of either miR-24-3p or miR-25p-3p resulted in dampening and period lenghtening of PER2::Luc oscillation, while inhibition of either miR-24-3p or miR-25-3p caused increase in relative amplitude of PER2::Luc oscillation. Also, lentiviral overexpression of miRNAs dampened PER2::Luc oscillation in the suprachiasmatic nucleus slices *ex vivo*, similarly to *in vitro* results.

In summary, both miR-24-3p and miR-25-3p are involved in fine-tuning of circadian rhythmicity through regulating PER2 oscillation at the post-transcriptional level.

Disclosures: I. Park: None. **K. Ku:** None. **J. Kim:** None. **D. Kim:** None. **H. Choe:** None. **Y. Choe:** None. **K. Kim:** None.

Poster

238. Circadian: Cellular and Molecular Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 238.09/II25

Topic: F.08. Biological Rhythms and Sleep

Support: BK21 Plus funded by the Ministry of Education, Republic of Korea 10Z20130012243

Rural Development Administration, Republic of Korea PJ01121602

Title: Transcription of D site of Albumin promoter binding protein(Dbp) is controlled by a position dependent motif sequence

Authors: *P. K. KWON, *P. K. KWON, J. KANG, K. KIM
POSTECH, Pohang, Korea, Republic of

Abstract: Circadian rhythm depends on transcriptional regulation of clock controlled genes. Several transcriptional regulations have been identified and their contribution to circadian rhythm has been assessed. However, there are mostly focusing on well-known clock-controlled genes solely. Although Dbp (D Site of Albumin Promoter Binding protein) shows strong rhythmicity gene, transcriptional regulation of Dbp still remains little knowledge. Here, we elucidated an in-depth molecular mechanism that is involved in the transcriptional regulation of Dbp. Additionally, we identified a new role of the position effect of CT motif which can foster Dbp transcription either down regulate of transcription depending on the position from transcription start site. Here, we propose a model whrereby CT motif of Dbp plays a role in transcription modulated by position dependent manners.

Disclosures: P.K. Kwon: None. **J. Kang:** None. **K. Kim:** None.

Poster

238. Circadian: Cellular and Molecular Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 238.10/II26

Topic: F.08. Biological Rhythms and Sleep

Support: NIH grant GM10499102

UNCF/Merck Postdoctoral Fellowship

Title: Physiological role of sub-threshold Kv12-encoded K+ channels in regulating the excitability of mouse SCN neurons

Authors: *T. HERMANSTYNE[1], D. GRANADOS-FUENTES[2], E. D. HERZOG[4], J. M. NERBONNE[3]
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Abstract: Transcripts encoding the pore-forming (α) subunits of the Kv12 subfamily, Kv12.1 and Kv12.2, are enriched in the suprachiasmatic nucleus (SCN), suggesting roles in regulating daily rhythms in SCN excitability. To explore the physiological roles of Kv12.1 and Kv12.2, we generated short hairpin RNAs (shRNAs) selectively targeting Kv12.1 or Kv12.2 and used these to acutely 'knockdown' Kv12.1 or Kv12.2 expression in the adult mouse SCN. Whole-cell current clamp recordings revealed that knockdown of either Kv12.1 or Kv12.2 significantly altered nighttime excitability in SCN neurons. The mean ± SEM repetitive firing rates measured at night, for example, were significantly ($P < 0.01$) higher in Kv12.1- (4.9 ± 1.1 Hz) and Kv12.2- (3.6 ± 0.8 Hz) targeted shRNA-expressing SCN neurons when compared with WT SCN neurons (0.7 ± 0.2 Hz), whereas there were no significant differences in firing rates during the day. The mean input resistances measured at night in Kv12.1- (1.2 ± 0.3 GΩ) and Kv12.2- (1.8 ± 0.3 GΩ) targeted shRNA-expressing SCN neurons, were significantly ($P < 0.001$) higher than in WT SCN neurons (0.9 ± 0.1 GΩ). In addition, the nighttime resting membrane potentials were significantly more depolarized in Kv12.1-targeted and Kv12.2-targeted shRNA-expressing SCN neurons than in WT SCN neurons. Taken together, these observations suggest that Kv12 channels are key regulators of the nighttime hyperpolarization of the membrane potential, and the resulting decrease in the repetitive firing rates, of SCN neurons. Preliminary semi-quantitative PCR analyses revealed that the transcripts encoding Kv12.1 and Kv12.2 do not vary significantly as a function of time, suggesting that post-transcriptional mechanisms underlie the day-night differences in the functional expression of the Kv12 currents (I_{Kv12}). On-going whole-cell voltage clamp recordings in *in vitro* slices are focused on quantifying the diurnal regulation

of I_{Kv12} functional expression. This work was supported by NIH grant GM10499102 to EDH and JMN and a UNCF/Merck Postdoctoral Fellowship to TOH.

Disclosures: T. Hermanstyne: None. **D. Granados-Fuentes:** None. **E.D. Herzog:** None. **J.M. Nerbonne:** None.

Poster

238. Circadian: Cellular and Molecular Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 238.11/II27

Topic: F.08. Biological Rhythms and Sleep

Support: National High Technology Research and Development Program of China (2015AA020512)

National Natural Science Foundation of China (31571090,81371458)

the National Key Research and Development Program (2016YFC1306703)

Title: Whole-brain mapping of direct inputs of the GABAergic neurons in the parvicellular reticular nucleus

Authors: *Y. SU, X. FENG
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Abstract: The GABAergic neurons in the parafacial zone play important role in sleep-wake regulation and are identified as a sleep-promoting centre in brainstem. Previous studies have revealed the afferent projection of parvocellular reticular formation (PCRtA) in the parafacial zone with HRP and PHA-L tracing in rats. But the monosynaptic inputs of GABAergic neurons in the PCRtA are still unkown. In our study, we used the modified rabies virus-EnvA-ΔG-mCherry combined with Cre/loxP gene-expression strategy to map the direct monosynaptic inputs to the GABAergic neurons in the PCRtA. The GABAergic neurons in the PCRtA receive inputs spanning almost the entire brain. The afferent inputs were mainly from the hypothalamic area, zona incerta and parasubthalamic nucleus in hypothalamus; substantia nigra, reticular part and deep mesencephalic nucleus in midbrain, intermediate reticular nucleus, medial vestibular nucleus (parvicellular part) in pons and medulla. This cell-type-specific
neural whole-brain mapping of the PCRtA GABAergic neurons shows the underlying circuit mechanisms in sleep-wake regulation.
Support: This work was supported by the National High Technology Research and Development Program of China (2015AA020512),the National Natural Science Foundation of China (31571090,81371458), the National Key Research and Development Program (2016YFC1306703).

Disclosures: **Y. Su:** None. **X. Feng:** None.

Poster

238. Circadian: Cellular and Molecular Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 238.12/JJ1

Topic: F.08. Biological Rhythms and Sleep

Title: Extracellular plasticity in the suprachiasmatic nucleus (SCN): Investigating the acute effects of matrix metalloproteinase (MMP) inhibition on neuronal activity and synaptic adhesion molecule expression

Authors: *K. ABRAHAMSSON[1], R. A. PROSSER[2]
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Abstract: Neurons in the SCN exhibit circadian rhythms that synchronize mammalian behavior and physiology to the environment. Although signaling pathways inside SCN neurons are known to regulate circadian neuronal activity, the involvement of extracellular-matrix (ECM) molecules in SCN clock phase regulation is less clear. Day vs. night differences in extracellular proteases and glial cell morphology in the SCN set a precedent for the involvement of ECM proteins in regulating the circadian clock. Two candidate proteins, MMP-2 and MMP-9, may link the ECM to circadian rhythm production in the SCN. Classically known as ECM remodelers, MMP-2/9 can be activated when neuronal activity increases. MMP-2/9 are also involved in regulating N-methyl D-aspartate receptor (NMDAR) activity, a critical element of the photic phase shifting pathway. We have shown differential effects of BiPS, an MMP-2/9 inhibitor, on the clock: BiPS induces phase delays, advances or has no effect depending on the time of in vitro drug application. Both advances and delays induced by BiPS are inhibited by the NMDA antagonist AP5, while only BiPS-induced daytime phase advances are inhibited by treatments upstream of TrkB activation. This work highlights that the mechanism(s) of action of MMP-2/9 in the SCN are time dependent. MMP-9 activity, in particular, is highest during the early night (Zeitgeber time 16: ZT 16, where ZT 0 is lights-on and ZT 12 is lights-off) and low at ZT 23. This project aims to better understand the mechanisms underlying BiPS induced phase shifts by examining the cellular changes that occur after MMP-2/9 inhibition. Currently, I am using extracellular electrophysiology to examine if BiPS acutely affects the firing rate of SCN neurons in acute SCN brain slices prepared from C57Bl/6 male mice. It is known that MMP-2/9 activity can regulate transynaptic signaling via cleavage of synaptic adhesion molecules like β-dystroglycan and neuroligins. Thus, I am also using western blotting of SCN tissue to explore BiPS-induced changes in the expression of these scaffolding proteins. Ultimately, our goal is to determine if

changes in the extracellular matrix, synaptic structure and/or neuronal activity are regulated by MMP-2/9 in a manner that affects the functioning of the circadian clock.

Disclosures: K. Abrahamsson: None. **R.A. Prosser:** None.

Poster

238. Circadian: Cellular and Molecular Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 238.13/JJ2

Topic: F.08. Biological Rhythms and Sleep

Support: NSF IOS 1354913

NSF DBI 1450962 BRAIN

Title: Characterizing a novel circadian peptide, cerebellin-short, in the rat suprachiasmatic nucleus

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Abstract: The suprachiasmatic nucleus (SCN, the central circadian clock in mammals, has been the focus of quantitative, high-resolution peptidomic analyses that identified and characterized multiple peptides with diurnal variations (Lee et al., *Mol. Cell Proteom.* 2010, *J. Proteom. Res.* 2013, Southey et al, *J. Proteom. Res.* 2014), A number of these peptides are important for synchronizing the intrinsic rhythm among SCN cells and conveying time-of-day to other parts of the organism. Mass spectrometry of the secreted proteome revealed a major new circadian peptide, cerebellin-short (SGSAKVAFSAIRSTN) (Hatcher et al., *PNAS*, 2008). Cerebellin-short is a 15 amino acid peptide that lacks the C-terminal histidine of full-length cerebellin, a 16 amino-acid peptide enriched in cerebellum (Slemmon et al., *PNAS*, 1984). The distribution and function of cerebellin-short in the SCN, however, are unknown. Here we show that mRNA encoding Cbln1, the precursor for cerebellin, undergoes a robust daily oscillation, peaking ~ ZT 20. Tissue levels of a Cbln1 partial cleavage product also oscillate around the clock with a peak 12 h later than the mRNA. Upon synaptosomal fractioning, full-length and partially cleaved Cbln1 both are present in the cytosolic fraction (S2), but only the partially cleaved product is observed in the P2 synaptosome fraction. Immunohistochemical analysis revealed that both Cbln1 and the partially cleaved product overlap with cells positive for vasoactive intestinal peptide (VIP) or arginine vasopressin (AVP). Co-staining is not observed in cells expressing glial fibrillary acidic protein (GFAP). Exogenous cerebellin-short applied at midday and early

night advance phasing of the spontaneous firing rhythm of SCN neurons. Together these data support a role for endogenous cerebellin-short contributes a circadian regulatory function among SCN neurons.
Funding: NSF IOS 1354913, NSF DBI 1450962 BRAIN

Disclosures: J.L. Chu: None. **J.W. Mitchell:** None. **M.U. Gillette:** None.

Poster

238. Circadian: Cellular and Molecular Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 238.14/JJ3

Topic: F.08. Biological Rhythms and Sleep

Support: Czech Science Foundation Grant 16-12695S

Czech Science Foundation Grant P304/12/G069

MEYS Grant LQ1604 NPU II

ERDF and MEYS Grant CZ.1.05/1.1.00/02.0109 BIOCEV

Title: The effect of P2X7 receptor blockers on ATP release from rat hypothalamic slices

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Abstract: In mammals, circadian rhythms are driven by a pacemaker located in the suprachiasmatic nucleus (SCN) of the hypothalamus. In most species, including rat, the SCN has two subdivisions that differ in the neuronal input and the content of neuropeptides. The ventrolateral part of the SCN receives the glutamatergic inputs from the retina and produces vasoactive intestinal polypeptide, whereas the dorsomedial part does not have a direct visual input and produces arginine vasopressin. The SCN also generates a circadian rhythm in extracellular adenosine triphosphate (ATP) that negatively correlates with the neuronal activity and vasopressin secretion rhythm, indicating that ATP is primarily stored and released from non-neuronal cells, most probably astrocytes. However, the specific route for ATP release and mechanisms regulating its circadian rhythm are not well understood. In the current study, we tested a hypothesis that ATP leaks from the astrocytic cytosol through the pore of plasma membrane P2X7 receptor channels (P2X7R). ATP rhythm continues in constant darkness *in vivo* and persists in hypothalamic slices. We prepared organotypic slices from hypothalamic coronal sections (~ 250 µm thick) containing the SCN, removed from rats of 14-15 postnatal days. After

7 days of stabilization in culture, samples of the medium above slices were collected every 4 hours over a 52 hour incubation period, and ATP content in the medium was measured. Control cultures exhibited circadian rhythm in extracellular ATP accumulation with a peak between 24:00 - 04:00 h. ATP rhythm was completely inhibited by bath application of apyrase, an enzyme that hydrolyses nucleotides, and CGP, mitochondrial Na/Ca transporter blocker. It was also inhibited by AZ 10606120 and A 438079, specific blockers of P2X7R, and potentiated by GW 791343, a positive allosteric modulator of P2X7R. Carbenoxolone, which blocks pannexin-1 hemichannel, partially reduced ATP accumulation. Application of glutamate potentiated ATP release, and phase shifted ATP rhythm. Tetrodotoxin, a blocker of neuronal activity, partially inhibited ATP accumulation and disrupted its rhythmicity. GABAA and glutamate receptor blockers abolished rhythmicity without changing ATP amplitude. Electrophysiological measurements performed on acutely isolated slices showed that P2X7R blockers did not affect the electrical activity of SCN neurons and double-immunohistochemistry revealed expression of the P2X7R protein in astrocytes of the SCN. These data suggest that astrocytic P2X7R and pannexin-1 channels are involved in extracellular ATP accumulation that reflects mitochondrial ATP production controlled by SCN neurons.

Disclosures: **A. Bhattacharya:** None. **I. Svobodová:** None. **Z. Bendová:** None. **H. Zemková:** None.

Poster

238. Circadian: Cellular and Molecular Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 238.15/JJ4

Topic: F.08. Biological Rhythms and Sleep

Support: EY021222

Title: F-spondin is essential for maintaining circadian rhythms

Authors: *G. L. CARRILLO, J. SU, A. MONAVARFESHANI, M. A. FOX
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Abstract: The suprachiasmatic nucleus is the master regulator of circadian rhythms and receives direct input from the M1 class of intrinsically photosensitive retinal ganglion cells (ipRGCs). Here, we sought to identify mechanisms that regulate the targeting of M1 ipRGC axons to the SCN. Using a bio-informatic approach, we identified three candidate targeting cues enriched in the developing SCN: F-spondin (encoded by the spon1 gene), Slit1, and ALCAM. Using targeted mouse mutants, we tested the necessity of each cue for retino-hypothalamic targeting and for establishing normal circadian rhythms. All three cues appeared largely dispensable for retinohypothalamic targeting. Moreover, Slit1 and ALCAM were not required for normal

photoentrainment or the maintenance of circadian rhythms. While F-spondin-deficient mice (*spon1*$^{-/-}$) exhibited normal patterns of wheel running activity in normal light:dark conditions, they became arrhythmic in the absence of light. Moreover, behavioral analyses suggest that light masks the lack of intrinsic rhythmicity in spon1 mutants. The expression of core clock genes in the SCN appears largely unaltered in the absence of F-spondin, but VIP-expressing neurons appear mislocalized. Taken together, these results confirm the strong influence of light-derived signals in regulating innate circadian behavior and reveal a novel role for F-spondin in maintaining circadian rhythms.

Disclosures: G.L. Carrillo: None. **J. Su:** None. **A. Monavarfeshani:** None. **M.A. Fox:** None.

Poster

239. Sleep: Regulators

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 239.01/JJ5

Topic: F.08. Biological Rhythms and Sleep

Support: NIH Grant R01NS075545

Title: Arc function in sleep

Authors: *A. SUZUKI[1], R. W. GREENE[2]
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Abstract: Arc (activity-regulated cytoskeleton-associated gene) plays critical roles in synaptic plasticity in several physiological reactions. Arc is a neural protein, expressed in a neural activity-dependent manner, and involved in synaptic downscaling through reducing AMPA receptors. Neural activity also promotes Arc into nuclear translocation. On the other hand, growing evidence suggest that the most important role of sleep is involved in the maintenance of synaptic homeostasis. Awake strengthens synaptic connection but sleep eliminates excess amounts of synapses. Interestingly, mRNA and protein Arc expression is similarly increased in sleep-deprived brains. Additionally, we have reported a lack of sleep homeostasis both in NREM and REM sleep in the absence of Arc gene. Thus, Arc seems important in homeostatic sleep regulation, but its function in sleep is less understood. Here, we report that the Arc subcellular distribution was correlated to sleep/wake behavior; sleep deprivation promoted Arc nuclear translocation, and recovery sleep exported Arc from the nuclei. We further found that in sleep-deprived brain, expression of several sleep deprivation response genes was disrupted in the absence of Arc gene. These results suggest Arc plays an important role in mRNA induction of sleep response genes in the brain.

Disclosures: **A. Suzuki:** None. **R.W. Greene:** None.

Poster

239. Sleep: Regulators

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 239.02/JJ6

Topic: F.08. Biological Rhythms and Sleep

Support: Research Grant Program at Escuela de Medicina, Universidad Anáhuac Mayab

Title: Effects of histone demethylation or histone methylation inhibition in sleep in rats

Authors: *M. J. FRANCO-TORMO[1], N. BARBOSA-ROCHA[2], H. BUDDE[3], S. MACHADO[4], E. MURILLO-RODRÍGUEZ[5]
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Abstract: Reversible histone methylation has been described as a key element in epigenetic mechanisms. Histone methyltransferases and demethylases have been identified as contributing factors in the development of multiple health disturbances, especially cancer. However, the neurobiological role of histone demethylases in behaviors, such as sleep, remains unknown. Thus, we investigated the effects in sleep-wake cycle of systemic administration of the histone demethylation inhibitor GSK-J1 (0, 5, 10, 25 mg/Kg, ip) during the lights-on or lights-off period of rats. Preliminary results showed that GSK-1 when injected at the beginning of the lights-on period induced no statistical differences in total time were found in wakefulness (W), slow wave sleep (SWS) or rapid eye movement sleep (REMS). However, if administered at the beginning of the lights-off period or rats, GSK-J1 provoked a decrease in W and increased SWS as well as REMS. Next, to characterize the pharmacological effects of inhibition of histone methylation, rats received systemic injection of DZNep (0, 5, 10, 25 mg/Kg, ip) during either the lights-on or lights-off period of rats. We found that inhibition of histone methylation caused a dose-dependent increase in W as well as a decrease in SWS and REMS. Importantly, recent reports have shown that blocking demethylases by chronic administration of inhibitors resulted in depression-like phenotype. Since increase in REMS has been associated with depression, a provocative link between methylation/demethylation in sleep and mental disturbances rises as a common neuromolecular mechanism. Our study provides for the very first time, novel findings about the possible neurobiological role of histone methyltransferases and demethylases in sleep control in rodents.

Disclosures: **M.J. Franco-Tormo:** None. **N. Barbosa-Rocha:** None. **H. Budde:** None. **S. Machado:** None. **E. Murillo-Rodríguez:** None.

Poster

239. Sleep: Regulators

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 239.03/JJ7

Topic: F.08. Biological Rhythms and Sleep

Support: JSPS KAKENHI Grant Number JP16K19004

Title: Effects of ghrelin on the locus coeruleus neurons in rats

Authors: *J. KIM, D. SHIMA, Y. IKAI, T. TAJIMA, K. NAKAJIMA
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Abstract: Ghrelin, produced by peripheral organs and brain, is known as an endogenous ligand for growth hormone secretagogue receptors (GHS-Rs) which express in the some peripheral organs and also in some brain regions. Ghrelin has been known as a potent stimulator of GH secretion and feeding, and also contributes to anxiety behavior and regulation of sleep-wakefulness, but the mechanisms are not known. The locus coeruleus (LC), which involves noradrenergic neurons, participates in induction of anxiety-like behavior and arousal state. Although expression of the GHS-Rs in the LC has not been reported, recent study demonstrated that fluorescein-conjugated ghrelin, injected in the cerebrospinal fluid, accumulated in the LC together with the other brain region, which express GHS-R mRNA. However, effects of ghrelin on the LC neurons are remained unclear. Thus, we examined effects of ghrelin on the LC neurons using intracellular Ca^{2+} ($[Ca^{2+}]_i$) imaging and whole-cell patch clamp recording technique on the rat brain slice preparations. Application of ghrelin induced $[Ca^{2+}]_i$ elevation of the LC neurons in both absence and presence of tetrodotoxin, and the $[Ca^{2+}]_i$ elevation was blocked by [D-Lys^3]-GHRP-6, a specific antagonist for GHS-Rs. The $[Ca^{2+}]_i$ elevation was attenuated by inhibitor of IP_3 receptors and T-type Ca^{2+} channels, respectivery, and abolished by combination of them. Furthermore, electrophysiological study demonstrated that the LC neurons were depolarized by ghrelin. These results suggest that ghrelin induces $[Ca^{2+}]_i$ elevation on the LC neurons postsynaptically via GHS-R-like receptors with a dual $[Ca^{2+}]_i$ elevation pathway including a efflux from intracellular Ca^{2+} store and influx from extracellular solution via T-type Ca^{2+} channels, presumably activated by the depolarization. Ghrelin may contribute to the induction of anxiety-like behavior and/or the regulation of sleep-wakefulness via the excitatory effect on LC neurons.

Disclosures: **J. Kim:** None. **D. Shima:** None. **Y. Ikai:** None. **T. Tajima:** None. **K. Nakajima:** None.

Poster

239. Sleep: Regulators

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 239.04/JJ8

Topic: F.08. Biological Rhythms and Sleep

Support: CIHR

Title: Physiological characterization of a novel selective melatonin mt_1 receptor agonist

Authors: M. LOPEZ-CANUL[1], S. MIN[1], L. POSA[1], T. SASSON[1], D. DE GREGORIO[1], R. OCHOA-SANCHEZ[1], S. COMAI[2], *G. GOBBI[1]
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Abstract: Background: Melatonin is a neurohormone produced in a circadian rhythm in the pineal gland (Tan et al., 1999) which is involved in numerous physiological functions, including sleep and temperature regulation, via its G-protein coupled receptors MT_1 and MT_2 (Dubocovich and Markowska 2005). Differential localizations of MT_1 and MT_2 receptors have been found, suggesting a selective functional specificity for these receptors (Lacoste et al, 2015). The aim of this study is to investigate the role of the first selective MT_1 receptor partial agonist (pK_i=8.93) N-(2-{Methyl-[3-(4-phenylbutoxy)phenyl]amino}ethyl)acetamide (UCM871; Rivara et al., 2007) on the sleep-wake cycle, temperature modulation, and activity of the noradrenergic (NA) neurons of the Locus Ceruleus (LC) over a 24-hour period. **Methods:** Electroencephalograms (EEG) were recorded in freely-moving rats (n=7-11) during a period of 24 h (from 6 PM to 6 PM) following a subcutaneous injection of vehicle (veh) or UCM871 (3.5, 7 and 14 mg/kg), injected every 4 hours. To assess the effects of UCM871 on body temperature, rectal temperature was measured (n=9-11) every 15 minutes from 4:00 AM/PM to 9:30 AM/PM, following an injection of UCM871 (3.5, 7 and 14 mg/kg, s.c.) or veh. Given the role of the NA neurons of LC in sleep activity, *in-vivo* single unit extracellular recordings of NA neurons were performed following the administration of veh or UCM871 (3.5, 7, 10 and 14 mg/kg, s.c.) during the day and the night. **Results:** Rats treated with UCM871 at 14 mg/kg s.c. exhibited an increase in the duration (min) of rapid eye movement (REM) sleep compared to the control group (veh: 96.6±7.0; UCM871: 119.7±5.1, $p<0.05$) over 24 hours. Remarkably, UCM871 (14 mg/kg) increased REM sleep only during the dark phase (veh: 41.17±3.9; UCM871: 60.3±4.2, $p<0.05$) with no effect (veh: 55.47±4.0; UCM871: 59.41±4.7, $p>0.05$) during the light phase at the same doses. Furthermore, UCM871 at 14 mg/kg increased body temperature compared to vehicle (veh: 0.39±0.1; UCM871: 0.73±0.05, $p<0.05$) only during the dark phase and had no effect in the light phase (veh: -0.63±0.06; UCM871: -0.78±0.08, $p>0.05$). Finally, NA neurons activity in the LC was decreased in both phases with UCM871. However, the decrease was more pronounced

($p<0.01$) during the dark phase at 10 (71.3±10.3 %) and 14 mg/kg (80.5±9.9 %) in comparison with the decrease during the light phase at the same doses (10 mg/kg: 43.9±17.9 %; 14 mg/kg: 47.0±23.1 %). More neurons responded to UCM871 during the dark phase in comparison with the light phase. **Conclusion:** These data suggest that MT_1 receptors play an important role in temperature and REM regulations and adrenergic function mainly in the dark phase.

Disclosures: **M. Lopez-Canul:** None. **S. Min:** None. **L. Posa:** None. **T. Sasson:** None. **D. De Gregorio:** None. **R. Ochoa-Sanchez:** None. **S. Comai:** None. **G. Gobbi:** None.

Poster

239. Sleep: Regulators

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 239.05/JJ9

Topic: F.08. Biological Rhythms and Sleep

Support: IH/NINDS K08 NS069667

Tross Research Fund UICCOM

NIH/NINDS T32 NS007421

Title: Role of 5-HT_{2A} receptors in acidosis-induced arousal from sleep

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Abstract: Sleep is necessary for all mammals. Sleep deprivation results in decreased cognitive and motor performance, increased risk of accidents, and ultimately death. It is critical for animals to balance the need for sleep with the ability to arouse from sleep in response to life threatening stimuli. One such arousal stimulus is carbon dioxide (CO_2), as elevated CO_2 typically signifies an airway obstruction. Although arousal from sleep in response to CO_2 is relevant to diseases such as obstructive sleep apnea, sudden infant death syndrome, and sudden unexpected death in epilepsy, its underlying mechanisms remain poorly understood. Serotonin (5-HT) is necessary for arousal to CO_2 as *Lmx1b*$^{f/f/p}$ mice, which have a genetic deletion of 5-HT neurons, do not wake to increased CO_2. 5-HT modulates sleep wake regulation and central 5-HT neurons are directly chemosensitive. Systemic application of 5-HT_{2A} receptor antagonists prevents arousal to CO_2 in wild type mice, and systemic application 5-HT_{2A} receptor agonists restores arousal to CO_2 in *Lmx1b*$^{f/f/p}$ mice. However, the site of 5-HT_{2A} receptor activation remains unknown. This on-going study seeks to begin to determine the site of 5-HT_{2A} receptor activation in CO_2-induced arousal. Adult male *Lmx1b*$^{f/f}$ (phenotypically wile type) and *Lmx1b*$^{f/f/p}$ (5-HT neuron deficient) mice were implanted with EEG/EMG headmounts and microdialysis cannulae directed towards

the DRN (AP: -4.6 μm; ML: ±0.0 μm; DV: -1.8 μm). Mice were then allowed to recover from surgery and were habituated to the testing chamber. On the trial day, normal artificial cerebrospinal fluid (aCSF bubbled with 5% CO_2/21% O_2/74% N_2; pH 7.4) was perfused (45 μl/min) into the DRN. Once the mouse was asleep, the perfusate was changed to either normal aCSF, acidified aCSF (bubbled with 25% CO_2/21% O_2/54% N_2; pH 6.8), or aCSF with drug. Dialysis of the 5-HT_{2A} agonist TCB-2 (300 μM) to the DRN was not sufficient to induce arousal from sleep in *Lmx1b*$^{f/f}$ or *Lmx1b*$^{f/f/p}$ mice. Systemic (*i.p.*) application of the 5-HT_{2A} receptor antagonist MDL 11,939 (10 mg/kg) 30 min prior to perfusion of acidified aCSF in to the DRN of *Lmx1b*$^{f/f}$ mice was sufficient to prevent arousal. Systemic application of TCB-2 (10 mg/kg) 30 min prior to perfusion of acidified aCSF into the DRN of *Lmx1b*$^{f/f/p}$ mice was not sufficient to restore arousal. Perfusion of MDL 11,939 (1 mM) into the DRN of *Lmx1b*$^{f/f}$ mice concomitant with acidified aCSF did not prevent arousal. These data suggest that CO_2 induces arousal by activating chemosensitive 5-HT neurons in the DRN, which then activate 5-HT_{2A} receptors at a downstream target site.

Disclosures: C.M. Ginapp: None. **N.K. Leibold:** None. **N.M. Bode:** None. **G.F. Buchanan:** None.

Poster

239. Sleep: Regulators

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 239.06/JJ10

Topic: F.08. Biological Rhythms and Sleep

Support: VA Merit Grant (McCarley, 5I01BX001356)

VA Merit Grant (Basheer, I01BX001404)

VA Merit Grant (Strecker, I01BX002774)

NIMH R03 MH107650 (Yang)

NIMH R01 MH039683 (McCarley)

NIMH R01 MH099180 (Kalinchuk)

NINDS R21 NS079866 (Basheer)

Title: Overriding sleep homeostatic regulation by activation of basal forebrain purinergic P2 receptors

Authors: *C. YANG[1], A. KALINCHUK[1], K. A. JACOBSON[2], S. WINSTON[1], J. T. MCKENNA[1], R. W. MCCARLEY[1], R. E. STRECKER[1], R. BASHEER[1], R. E. BROWN[1]

[1]Psychiatry, Harvard Med. School/Va Boston Healthcare Syst., West Roxbury, MA; [2]Mol Recog Sec, LBC, Natl. Inst. of Diabetes and Digestive and Kidney Dis., Bethesda, MD

Abstract: The basal forebrain (BF) is a key node of the ventral ascending activating system. It is strongly implicated in sleep homeostasis due to its wake-promoting neurons and the accumulation of adenosine during prolonged wakefulness in this particular brain region. Adenosine triphosphate (ATP), an important neuro-/glio-transmitter, can act indirectly on the inhibitory purinergic P1 receptors following breakdown to adenosine. However, it can also act directly on P2 purinergic receptors (P2Rs), the sleep role of which is poorly understood. To test the effect of P2R on sleep homeostasis, adult male Swiss-Webster mice were sleep-deprived for four hours (Zeitgeber time 1-5) by 'gentle handling' including presentation of new objects into the cage and gentle touching of the animals by a brush when animals attempted to sleep. This 4 h sleep deprivation (SD) increased non-rapid-eye-movement (NREM) sleep during the following 3 h recovery period as assessed by a Repeated measures one-way ANOVA with Bonferroni post-hoc test statistical analysis (non-SD control NREM%: 55.0 ± 3.6%, ACSF infusion after SD NREM%: 69.6 ± 2.8%, $F(2,16)=15.18$, $p<0.001$, N=9), and decreased wakefulness (non-SD control wake%:36.9 ± 4.5%, ACSF after SD wake%: 24.1 ± 2.9%, $F(2,16)=9.486$, $p<0.01$). Bilateral infusion of a non-hydrolysable ATP analogue (1 mM ATP-γ-S) into BF during the 3h recovery period via reverse microdialysis significantly reversed the SD-induced NREM sleep rebound and brought the sleep amount back to the non-SD control level (ATP-γ-S after SD NREM%: 60.7 ± 3.8%; wake%: 33.6 ± 4.6%, $p<0.05$ compared to ACSF after SD and $p>0.05$ compared to non-SD control). Our data presented here suggest that the application of a selective P2R agonist into the BF attenuates recovery sleep after an acute SD, and may override the sleep-inducing effects of adenosine, presumably by direct excitation of wake-promoting neurons. These data suggest that the P2Rs on BF neurons may be interesting targets for the development of novel pharmacological agents to prevent sleepiness in sleep-deprived individuals.

Disclosures: C. Yang: None. **A. Kalinchuk:** None. **K.A. Jacobson:** None. **S. Winston:** None. **J.T. McKenna:** 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.; Merck MISP. **R.W. McCarley:** None. **R.E. Strecker:** None. **R. Basheer:** None. **R.E. Brown:** None.

Poster

239. Sleep: Regulators

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 239.07/JJ11

Topic: F.08. Biological Rhythms and Sleep

Title: Sedative effect of herbal formula on 5-HT2c Receptor binding affinity and EEG

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Abstract: Many plant materials have been used in the Asia for treating insomnia and depression. However, scientific evidence for their sedative-hypnotic activity has not been fully investigated. Thus, this study was carried out to investigate sedative-hypnotic effects of the water extracts of herbal formula YJ05. We investigated the positive effects of YJ05, a Korean herbal medicine on sleep architecture. To examine the sedative effects of YJ05 on 5-HT_{2c} receptor, we employed a 5-HT_{2c} receptor-tryptamine binding assay system based on a protein chip. Using this assay system, YJ05 was screened as an antagonistic herb against 5-HT_{2c} receptor from 32 Korean herbal medicines using a 5-HT_{2c} receptor-tryptamine binding assay system. A further attempt was made to confirm the antagonistic effect of YJ05 on 5-HT_{2c} receptor by an in vivo sleep study. YJ05 decreased wake time and increased REM and NREM sleep when compared with the normal and YJ01-treated control group based on electroencephalogram (EEG) data in rats. These findings suggest that YJ05 increases NREM sleep and decreases wake time. These results strongly suggest that the sedative effect of YJ05 against 5-HT_{2c} receptor and EEG may improve herbal drugs for insomnia.

Disclosures: S. Lee: None. **H. Lee:** None. **I. Kang:** None. **I. Shim:** None.

Poster

239. Sleep: Regulators

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 239.08/JJ12

Topic: F.08. Biological Rhythms and Sleep

Support: NIH/NINDS K08 069667 (GFB)

Tross Research Fund

Niels Stensen Fellowship (NKL)

Kootstra Fellowship (NKL)

NIH/NINDS T32 NS007421 (BSP)

Title: Dorsal raphe serotonergic neurons mediate CO_2-induced arousal from sleep

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Abstract: Sleep is an essential phenomenon that is conserved across many species. Sleep deprivation leads to cognitive, behavioral, and physiological impairment, and ultimately death. While sleep is essential, the ability to arouse from sleep in response to life-threatening stimuli is also vital. One such stimulus is hypercapnia, or elevated CO_2, which can result from airway obstruction. CO_2-induced arousal is relevant to diseases such as obstructive sleep apnea (OSA), sudden infant death syndrome (SIDS), and sudden unexpected death in epilepsy (SUDEP). How a rise in CO_2 causes arousal is not well understood. Serotonin (5-HT) neurons in both rostral and caudal sites are sensitive to CO_2/pH. Given that 5-HT neurons comprise a component of the ascending arousal system and are heavily interconnected with other arousal system components, they are an attractive candidate for mediating CO_2-induced arousal. It is known that mice that lack 5-HT neurons in the central nervous system do not arouse to inspired CO_2. While this implicates 5-HT neurons in mediating CO_2-induced arousal, this does not indicate whether rostral or caudal populations are required. Given that rostral 5-HT neurons are involved in sleep-wake regulation we hypothesized that 5-HT neurons in the midbrain dorsal raphe nucleus (DRN) mediate CO_2-induced arousal from sleep. Adult male wildtype (WT) mice, 5-HT neuron deficient (*Lmx1b*$^{f/f/p}$) mice, and mice in which 5-HT_{1A} receptors were first eliminated (*Htr1a*^{KO}) and then selectively re-overexpressed on 5-HT neurons (*Htr1a*^{RR}) were implanted with EEG/EMG headmounts and microdialysis cannulae directed toward the DRN or medullay raphe. Normal (5% CO_2, pH 7.4) or acidified (25% CO_2, pH 6.8) artificial cerebrospinal fluid (aCSF) was microdialyzed (45 μl/min) when animals were asleep. Perfusion of acidified aCSF into the DRN, but not medullary raphe, caused arousal from sleep in WT mice (n = 10). This effect was lost in *Lmx1b*$^{f/f/p}$ mice (n = 10). Inactivation of 5-HT neurons via systemic application of the 5-HT_{1A} receptor agonist 8-OH-DPAT (0.5 mg/kg, *i.p.*) prolonged the arousal latency to inspired CO_2 (7% CO_2, 21% O_2, 72% N_2) in *Htr1a*^{RR} mice (n = 6). 8-OH-DPAT did not affect the latency to arousal following exposure to hypoxia (10% O_2, 90% N_2; n = 6). The latency to CO_2-induced arousal was also prolonged in *Htr1a*^{RR} mice when 8-OH-DPAT (1 mM) was perfused directly into the DRN (n = 6). Perfusion of normal aCSF did not affect arousal latency. These data suggest that DRN 5-HT neurons are important for arousal from sleep to CO_2. Understanding the mechanism of CO_2-induced arousal from sleep may lead to improved interventions for OSA, SIDS, and SUDEP.

Disclosures: N.K. Leibold: None. **H.R. Smith:** None. **D.A. Rappoport:** None. **C.M. Ginapp:** None. **B.S. Purnell:** None. **E. Audero:** None. **C.T. Gross:** None. **G.F. Buchanan:** None.

Poster

239. Sleep: Regulators

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 239.09/JJ13

Topic: F.08. Biological Rhythms and Sleep

Support: DA031900

Title: Impact of sleep-wake activity on dopamine terminal neurotransmission

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Abstract: Dopamine (DA) has been implicated in the regulation of a variety of behavioral and physiological functions including motivation, reward, and locomotion. Further, DA systems have been demonstrated to participate in arousal including sleep/wake activity. For example, ventral tegmental area (VTA) DA neurons are strongly activated during waking and rapid-eye movement (REM) sleep while displaying low activity during non-REM sleep. In addition, several microdialysis studies indicate that DA levels fluctuate across the light/dark cycle. The dopamine transporter (DAT) is a homeostatic regulator that can undergo compensatory adaptations to control DA extracellular levels. We recently showed that DA signaling varies across the light/dark cycle, but it remains unclear whether these fluctuations are associated with time of day, light conditions, or sleep wake activity. To address these issues, we examined whether sleep-wake activity has an impact on DA terminal neurotransmission. Rats were implanted with EEG/EMG electrodes to determine sleep wake activity immediately prior to ex vivo fast scan cyclic voltammetry (FSCV) detection of DA release and uptake. We measured the maximal rate of DA uptake (V_{max}) using FSCV in the nucleus accumbens core 6 hours into the dark phase of a 12hr light/dark cycle. Under these conditions rats that were awake exhibited higher maximal DA uptake rates relative to rats that were asleep. These results suggest that sleep/wake activity, rather than time of day impacts DA uptake dynamics. Ongoing studies are currently underway to determine whether this relationship is maintained in rats exposed to constant light or dark conditions. These results will have implications concerning a wide-array of DA-dependent physiological processes including cognition, drug–associated behaviors, learning and memory, and locomotion.

Disclosures: I.P. Alonso: None. **D.L. Bernstein:** None. **R.A. España:** None.

Poster

239. Sleep: Regulators

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 239.10/JJ14

Topic: F.08. Biological Rhythms and Sleep

Support: Escuela de Medicina, Universidad Anáhuac Mayab

Title: The blocker of FAAH and the transient receptor potential cation channel subfamily V member 1, N- arachidonoyl-serotonin (AA-5-HT) promotes sleep in rats

Authors: *M. E. DE LA CRUZ DELGADO[1], E. MURILLO-RODRÍGUEZ[2], N. BARBOSA ROCHÁ[3], H. BUDDE[4], S. MACHADO[5]
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Abstract: The discovery of the endocannabinoid system, which includes anandamide (AEA), receptors (CB_1 and CB_2), enzymes that synthesize AEA as well as the inactivating enzymes (fatty acid amide hydrolase (FAAH) for AEA as well as the anandamide membrane transporter, has brought scientific interest since this complex system modulates multiple neurobiological functions, including sleep. However, the role of the blocker of FAAH and the transient receptor potential cation channel subfamily V member 1 (TRPV1), *N*-arachidonoyl-serotonin (AA-5-HT), in sleep has not been investigated. In the present study, varying doses of AA-5-HT (5, 10 or 20mg/Kg, i.p.) at the beginning of the lights-on period of rats, caused no significant changes in sleep patterns. However, a similar pharmacological treatment to animals at the beginning of the dark period induced a dose-dependent effect by decreasing wakefulness and increasing slow wave sleep (SWS) and rapid eye movement sleep (REMS). Power spectra analysis of states of vigilance during the lights-off period showed that injection of AA-5-HT diminished alpha spectrum during alertness. In contrast, delta power spectra was enhanced as well as theta spectrum, during SWS and REMS, respectively. Overall, our findings suggest that simultaneous FAAH activity and TRPV1 activation play a critical role for sleep control, which can be therefore modulated by AA-5-HT.

Disclosures: M.E. De La Cruz Delgado: None. **E. Murillo-Rodríguez:** None. **N. Barbosa Rochá:** None. **H. Budde:** None. **S. Machado:** None.

Poster

239. Sleep: Regulators

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 239.11/JJ15

Topic: F.08. Biological Rhythms and Sleep

Support: Wake Up Narcolepsy Foundation

Title: Social interaction promotes cataplexy in orexin knock out mice

Authors: *D. M. HAWRYLUK, C. E. MAHONEY, T. E. SCAMMELL
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Abstract: Narcolepsy Type 1 (NT1) is a common sleep disorder that affects about 1 in 2,000 people. Narcolepsy is characterized by excessive daytime sleepiness, poor sleep quality, and bouts of cataplexy, sudden muscle atonia with preserved consciousness. NT1 is caused by loss of the orexin/hypocretin neurons, which play an essential role in exciting other brain regions that regulate wake and REM sleep such as the locus coeruleus, tuberomammillary nucleus, and raphe nuclei. In the absence of orexins, these target nuclei are unable to sustain prolonged periods of wake and REM sleep is dysregulated, leading to fragmented sleep and episodes of cataplexy. In humans, cataplexy is triggered by strong, usually positive emotions, almost always in a social setting. Due to the strong link between social interaction and cataplexy, we hypothesized that social interaction between orexin knockout littermate mice promotes cataplexy. We first tested whether orexin knockout mice have normal social cognition using the 3-chamber social interaction test, the social novelty test and the social conditioned place preference test. Video recordings of these tests were analyzed for time spent in each chamber. Female orexin knockout mice showed similar scores to wild type mice in every test. The adult male orexin knock out mice showed less place preference on the social conditioned place preference test. We then tested our hypothesis that social interaction between littermates promotes cataplexy using a novel social reunification test, in which littermate mice were reunited after brief separation. We used group-housed male and female orexin knockout mice, both adults and juveniles. Video recordings of this behavioral assay were scored for the number of cataplexy bouts per group of mice and compared to previous control sessions when mice were housed together or housed alone. Adult and juvenile females, as well as juvenile males had about twice as much cataplexy after reunification with littermates when compared to controls. These results suggest that social signals promote cataplexy in a mouse model of narcolepsy just as is seen in people and dogs with narcolepsy. Future studies to define the circuits through which these social signals trigger cataplexy may lead to better treatments for cataplexy as well as a better understanding of the interactions of social signals and reward.

Disclosures: D.M. Hawryluk: None. **C.E. Mahoney:** None. **T.E. Scammell:** None.

Poster

239. Sleep: Regulators

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 239.12/JJ16

Topic: F.08. Biological Rhythms and Sleep

Support: National Institutes of Health grant NS083218

EpiC, the University of Kentucky Epilepsy Research Center

Scholarship support from the Higher Committee of Education in Iraq to Asmaa Ajwad

Title: Dynamic sleep modulation in mice through ambient temperature control

Authors: A. AJWAD[1], D. HUFFMAN[1], F. YAGHOUBY[1], H. WANG[1], B. F. O'HARA[2], *S. SUNDERAM[1]
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Abstract: Sleep disorders are increasingly common and can negatively impact human health. Understanding interactions between sleep and physiological processes such as thermoregulation could lead to novel strategies for the treatment of disordered sleep. As a first step toward this goal, we characterized the effect of a step change in ambient temperature (T_a) on sleep in mice, and then dynamically altered T_a to try to promote sleep quality. Following IACUC approval, ten C57BL/6 mice were instrumented for EEG/EMG monitoring. In static experiments, T_a was elevated from the baseline of 24°C to one of four levels (24, 27, 30, and 33°C) near the thermoneutral zone for mice (30°C) for six hours (11 a.m.-5 p.m.) on different days. Vigilance state was then visually scored in 4-second epochs as Wake, REM, or NREM (i.e., non-REM). Three sleep metrics (proportion, number of bouts, and mean bout duration) were computed for each state to quantify sleep architecture in each condition. Control mice exposed to elevated T_a spent more time in both NREM and REM sleep and less in Wake ($p<0.05$). There was a significant increase in NREM bout duration, but a reduction in the number of bouts. Following the static trials, a real-time classifier was used to determine instantaneous vigilance state from the EEG/EMG with 1-second resolution and estimate a sleep-wake ratio (Q) in a moving 5-minute window. A nonlinear scaling was applied to scale Q to the interval [0, 1] before using it as a measure of sleep quality and as the basis for manipulating T_a. Every 5 min, T_a was altered by ±1°C according to a simple control law to minimize the error between Q and a target value (Q*). A preliminary trial showed that mean Q over several hours of the light period tended toward a chosen target value of 0.63 corresponding to a sleep-wake ratio of 1.5:1. By comparison, T_a maintained at baseline conditions gave a mean Q of about 0.3. Thus, sleep modulation through ambient temperature control seems feasible and, if implemented correctly, may improve sleep in individuals with related disorders. One application of specific interest relates to sleep-seizure

interactions in epilepsy. In order to assess the feasibility of improving sleep and reduce seizure likelihood, we first studied the effect of static T_a on sleep in the pilocarpine mouse model of temporal lobe epilepsy. Our results showed that elevated T_a promotes sleep—as we saw in controls—but with more fragmented NREM. This suggests an opportunity to titrate sleep by regulating T_a and assessing the effect on seizure yield. To that end, we are refining our protocols for dynamic sleep modulation in controls and will apply them to epileptic animals as well.

Disclosures: A. Ajwad: None. **D. Huffman:** None. **F. Yaghouby:** None. **H. Wang:** None. **B.F. O'Hara:** None. **S. Sunderam:** None.

Poster

239. Sleep: Regulators

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 239.13/JJ17

Topic: F.08. Biological Rhythms and Sleep

Support: Hungarian Brain Research Program (KTIA_NAP_13-2014-0016)

NKFIH-K119650

Title: Temperature modulates sleep spindle frequency *In vivo* and in silico

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Abstract: Temperature dependence of cerebral activity is a very important, albeit under illuminated field of neuroscience. In our current work we examined whether parameters of sleep spindle oscillations are affected by different core body and brain temperatures under urethane anesthesia in mice. We employed a novel thermoelectrode, which we used to monitor thermal changes of thalamic nuclei while recording multiunit activity of corresponding neuronal populations. Our results indicate that spindle frequency is moderately correlated with brain temperature change. Moreover, we show that by applying heat through the thermoelectrode locally increases sleep spindle frequency. As a further contribution, we designed and evaluated a computer model of thalamic nuclei that robustly reproduces experimentally found temperature dependence of spindle frequency. This relation could be considered both as an experimental factor as well as a possible diagnostic and therapeutic tool.

Disclosures: **M. Csernai:** None. **K. Kocsis:** None. **D. Burka:** None. **S. Borbely:** None. **Z. Fekete:** None. **V. Balogh:** None. **S. Kali:** None. **Z. Emri:** None. **P. Bartho:** None.

Poster

239. Sleep: Regulators

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 239.14/JJ18

Topic: F.08. Biological Rhythms and Sleep

Support: P01HL095491

Title: Optogenetic activation of glutamatergic neurons in the PPT promotes arousal

Authors: *D. KROEGER[1], J. A. THUNDERCLIFFE[2], L. ZHU[2], E. ARRIGONI[2], T. E. SCAMMELL[2]
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Abstract: A variety of studies on different species have suggested that the pedunculopontine tegmental (PPT) region in the brainstem is a key site for the regulation of sleep/wake states - specifically REM sleep regulation. We recently showed that chemogenetic activation of glutamatergic PPT neurons promotes wakefulness for several hours. Here we used optogenetic activation of these neurons to further investigate the mechanisms and pathways through which PPT glutamatergic neurons produce wakefulness. Using vGlut2-cre mice, we transfected neurons in the PPT region with a viral vector coding for cre-dependent ChR2 tagged with fluorescent mCherry and implanted bilateral optical fibers above the PPT nuclei as well as EEG/EMG leads. Two weeks later, we administered blue laser light to activate ChR2-expressing neurons and recorded sleep/wake states. Activation of ChR2-expressing glutamatergic neurons during NREM sleep rapidly elicited wakefulness in a stimulation-frequency dependent manner, with higher frequencies producing wake more quickly and with longer duration. Random, automated stimulation for 10 s at 5 Hz over 24 h revealed that activation of glutamatergic PPT neurons reduces the latency to wake from NREM sleep by 83%, but the latency to wake from REM sleep was reduced by only 19%, suggesting that glutamatergic PPT signaling does not interfere with REM sleep. Interestingly, continuous stimulation for 5 min at 5 Hz decreased spontaneous locomotion for the first ~2.5 min, but did not impair movement when animals were prompted to move. We conclude that glutamatergic PPT neurons can potently promote arousal, probably through their projections to specific forebrain regions.

Disclosures: **D. Kroeger:** None. **J.A. Thundercliffe:** None. **L. Zhu:** None. **E. Arrigoni:** None. **T.E. Scammell:** None.

Poster

239. Sleep: Regulators

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 239.15/JJ19

Topic: F.08. Biological Rhythms and Sleep

Support: VA Merit BX001356

VA Merit BX002774

VA Merit BX001404

VA CDA BX002130

MH039683

HL095491

Title: Optogenetic excitation of parvalbumin containing GABAergic neurons in the mouse thalamic reticular nucleus: A comparison of laser protocols to induce naturalistic sleep spindles

Authors: *F. KATSUKI, J. M. MCNALLY, S. THANKACHAN, D. S. UYGUN, J. T. MCKENNA, R. E. BROWN, R. E. STRECKER, R. BASHEER, R. W. MCCARLEY
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Abstract: Sleep spindles, 8-15 Hz waxing and waning brain oscillations observed during NREM sleep, have been associated with memory consolidation. Parvalbumin (PV) containing GABAergic neurons in the thalamic reticular nucleus (TRN) may play a central role in the control of spindle generation. Although optogenetic alteration of TRN neuronal activity is an effective means to manipulate spindles, the optimal parameters of stimulation for reliably and consistently inducing cortical spindles which are indistinguishable from physiological spindles are unclear. Identification of these parameters is critical to be able to use the optogenetic approach to study the role of spindles in memory consolidation.
EEG/EMG recording was performed in PV-Cre mice, following bilateral AAV-ChR2 injection into the TRN. Optical excitation of TRN PV neurons was performed via laser illumination (473 nm) using two different protocols: 1) short single pulse (10 ms), 2) 10 Hz spindle-like-pulse (1 s), with a spindle-like waxing and waning of laser power. This analog pulse pattern was generated via a Gaussian envelope transform of a train of 100 ms half sine waves. Optical excitation was given once every 10 s only during NREM sleep via use of a threshold based NREM gate. Since preliminary data using high laser power (20 mW) showed an increase in wake, the maximum laser power for each animal was adjusted to the lowest level (0.5-1.5 mW) providing an observable change in EEG but not EMG. A custom-designed script was used to

detect NREM spindles (10-15 Hz), which were then compared between laser and control (sham laser) sessions within animals.
Both laser protocols significantly increased the number of spindles within 2 s of laser onset compared to the control. However, the single-pulse protocol (N=3) frequently produced sharp spike-like event related potential (ERP) immediately after laser onset (average latency to onset 25 ms) sometimes followed by a spindle. In contrast, the 10 Hz spindle-like-pulse protocol (N=5), produced a higher percentage of spindle-like events, and were rarely accompanied by spike-like ERP. Further, there was no change in the distribution of sleep and wakefulness between control and laser conditions.
These findings suggest that use of optical stimulation where power is modulated with a waxing and waning profile can evoke spindle-like events which are morphologically similar to physiological spindles. Use of low laser power is critical to elicit spindles without altering behavioral state. This protocol may be useful to investigate a role of sleep spindles controlled by TRN PV neurons in cognitive function.

Disclosures: **F. Katsuki:** None. **J.M. McNally:** None. **S. Thankachan:** None. **D.S. Uygun:** None. **J.T. McKenna:** 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.; Merck MISP. **R.E. Brown:** None. **R.E. Strecker:** None. **R. Basheer:** None. **R.W. McCarley:** None.

Poster

239. Sleep: Regulators

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 239.16/JJ20

Topic: F.08. Biological Rhythms and Sleep

Support: Dept. of Veterans Affairs (VA merit, I01 BX001356 to RWM & VA CDA, IK2 BX002130 to JMM), NIMH RO1 MH039683 (RWM), NHLBI HL095491 (RWM).

JTM received partial salary compensation and funding from Merck MISP, but has no conflict of interest with this work.

Title: Activation of inhibitory inputs to TRN modulates sleep spindles and NREM sleep: An optogenetic investigation into basal forebrain parvalbumin neurons role in the control of TRN parvalbumin neurons

Authors: *S. THANKACHAN, J. M. MCNALLY, F. KATSUKI, J. T. MCKENNA, R. E. STRECKER, R. E. BROWN, R. BASHEER, R. W. MCCARLEY
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Abstract: The thalamic reticular nucleus (TRN) serves as a hub of the thalamocortical circuit and plays a central role in cognition and sleep-wake behavior. Previous work showed GABAergic/ parvalbumin (PV) TRN neurons are abnormal in schizophrenia (Sz) (Bukahri et al., 2016) and may play a role in the sleep dysfunction-associated deficits in memory consolidation and cognitive performance seen in Sz patients. Of particular interest is the role of TRN in the generation of sleep spindles, 8-15Hz oscillations observed during NREM EEG, shown to be reduced in Sz. To interrogate the role of TRN in the generation of such symptoms/signs, we examined two optogenetic techniques aimed at inhibiting TRN PV neuronal activity: 1) direct-inhibition of TRN cells and; 2) indirect-inhibition of TRN cells by the activation of terminals of the basal forebrain (BF) PV neurons projecting to TRN. We then assayed their ability to modulate sensory transmission, NREM sleep, and spindles.
We injected adeno-associated virus, (AAV)-ArchT-GFP or (AAV)-ChR2-EYFP bilaterally into TRN or BF, respectively, in PV-Cre mice. These mice were implanted with optical fibers targeting bilateral TRN and EEG/EMG screw electrodes to record sleep. Histology confirmed viral-transduction and optical-fiber localization.
Direct-inhibition of TRN PV cells with ArchT (523nm; 1min/5min) over a 5hr recording period (10AM-3PM) resulted in a decrease in total NREM (-17%) and REM sleep (-16%, N=7). While direct inhibition did not inhibit spindle density, it increased the cortical response to a 40 Hz auditory click train (N=6). Indirect inhibition of TRN neurons by ChR2 excitation (473nm) of BF PV terminals in TRN (N=8) at 40Hz for 5s/min across a 6hr (9AM-3PM) recording decreased both NREM (-8%) and REM sleep (-8%). Additionally, spindle density (spindles/min) was strongly decreased during stimulation. Interestingly, the overall spindle density was higher compared to the sham condition as more spindles occurred between terminal stimulation/excitations, when the laser was off. This was due to strong rebound of spindles following repeated suppression, and appeared to subside over the course of the recording.
Our data suggest that modulation of TRN activity can impact sleep, spindle activity, and sensory transmission. Further, it strengthens evidence of BF PV neurons in control of wake and suppression of NREM sleep through inhibitory projections to the TRN PV neurons. Importantly, TRN could be a target for pharmacologic manipulation to increase spindles, as a spindle abnormality is seen in Sz associated with the memory consolidation deficit.

Disclosures: S. Thankachan: None. **J.M. McNally:** None. **F. Katsuki:** None. **J.T. Mckenna:** 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.; Merck MISP. **R.E. Strecker:** None. **R.E. Brown:** None. **R. Basheer:** None. **R.W. McCarley:** None.

Poster

239. Sleep: Regulators

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 239.17/JJ21

Topic: F.08. Biological Rhythms and Sleep

Support: NIHLB P01 HL095491

VA CDA BX002130 (JMM)

JTM received partial salary compensation and funding from Merck MISP, but has no conflict of interest with this work.

Title: Optogenetic inhibition of basal forebrain parvalbumin GABA neurons implicates these cells as a therapeutic target for treating sleep disturbance in sleep apnea

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Abstract: Arousal from sleep occurs during obstructive sleep apnea to restore breathing. However, many apnea patients have a low respiratory arousal threshold, waking too easily. These excess arousals lead to chronic sleep disruption, which increase patient risk for cardiovascular disease and cognitive impairment. To understand the neural mechanism driving unwanted arousals and, ultimately, inform the development of therapeutic interventions, the brain circuitry involved in arousal during sleep apnea must first be identified. Previous work, using a sleep apnea mouse model involving increasing concentrations of CO2 (hypercarbia), suggested that the external lateral part of the parabrachial area (PBel) of the brainstem is involved in this arousal mechanism (Kaur et al. 2011). Localized lesions of PBel reduced arousal to CO2, but did not interrupt arousal to audible tones, suggesting a specific role in hypercarbia-induced arousal. The PBel projects to the Basal Forebrain (BF), which represents the final ventral neocortex-projecting node of the ascending activating system. From the BF, parvalbumin (PV) positive GABAergic neurons (situated amongst cholinergic and glutamatergic neurons) innervate the neocortex, promoting cortical activation and behavioral arousal (Kim, Thankachan, et al., 2015). The BF is a nexus of various arousal-inducing sensory pathways. Thus, we hypothesize that inhibition of the BF will disrupt arousal to both hypercarbia and audible tones. To test this, we bilaterally injected Cre-dependent AAV-ArchT into the BF of PV-Cre mice (N = 6), allowing optical inhibition of the firing of BF PV positive GABAergic neurons. During

NREM sleep, mice were exposed to 1) increasing gradient concentrations of CO2 (from ambient levels, up to 10%); and 2) increasing volumes of audible 4KHz tones (ten second periods of 2dB, 5dB, 10dB & 30dB, plus a crescendo from silent up to 30dB; values are relative to the baseline volume of ~42dB). We then measured the latency to arousal from NREM sleep, relative to the onset of CO2 or tone stimuli. As a control, we measured latencies in the same animals without light-induced inhibition of their BF PV neurons. When the BF was optically inhibited, latency to arouse from CO2 was prolonged to 21.13 ± 1.47 seconds vs control at 10.28 ± 1.75 seconds (N=6, paired t-test, $p < 0.05$). Further, preliminary findings suggest that BF PV inhibition blocked arousal from either sensory stimulus (CO2 or tone).
These studies further define the neural pathways involved in respiratory-induced arousals, such as seen in obstructive sleep apnea. The BF is likely to be a valuable target of therapeutics designed to block unwanted arousals in sleep apnea.

Disclosures: D.S. Uygun: None. **J.M. McNally:** None. **J.T. McKenna:** 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.; Merck MISP. **F. Katsuki:** None. **R.E. Strecker:** None. **R.W. McCarley:** None.

Poster

239. Sleep: Regulators

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 239.18/JJ22

Topic: F.08. Biological Rhythms and Sleep

Support: R01-GM104948

Title: Bidirectional chemogenetic control of GABA neurons in the tail of the ventral tegmental area modulates arousal in mice

Authors: *K. VLASOV[1,3], J. PEI[1,3], N. E. TAYLOR[3,1,4], C. J. VAN DORT[3,1,4], J. A. GUIDERA[3], E. N. BROWN[1,3,4,2], K. SOLT[3,1,4]
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Abstract: Many sedative and anesthetic drugs have been hypothesized to act through endogenous sleep circuits to inhibit discrete arousal centers in the midbrain and brainstem. Recently, ventral tegmental area (VTA) dopamine neurons have been found to play an important role in promoting wakefulness and modulating sleep as well as restoring consciousness from general anesthesia. The largest inhibitory projections to this region are GABA neurons from the

tail of the VTA also known as the rostromedial tegmental nucleus (RMTg). Here, we characterize the behavioral and electrophysiological effects of bidirectional chemogenetic manipulation of RMTg GABA neurons in VGAT-cre mice (n=18).
We used a novel combination of DREADDs (Designer Receptors Exclusively Activated by Designer Drugs) virus constructs that allow for stimulation and inhibition of the same neuron population within animal with systemic injections of ligands Clozapine-N-Oxide (CNO) and Salvinorin B (SalB) respectively. We found that stimulating RMTg GABA neurons with CNO resulted in profound sedation indicated by a decrease in exploratory behavior in an open field test and impaired coordination on an accelerating rotarod. Stimulation of GABA neurons also caused an increase in anesthetic sensitivity to sevoflurane with the dose needed for loss of consciousness reduced by almost half, however inhibition of GABA neurons with SalB had no statistically significant effect compared to saline baseline. In addition, stimulation of these neurons induced high-amplitude slow delta oscillations post ligand injection, comparable to drug-free periods of natural non-REM sleep. These results show that RMTg GABA neurons modulate behavioral arousal and suggest that GABAergic sedatives and anesthetics may decrease arousal by inhibiting neighboring wake-promoting excitatory neurons in the VTA.

Disclosures: **K. Vlasov:** None. **J. Pei:** None. **N.E. Taylor:** None. **C.J. Van Dort:** None. **J.A. Guidera:** None. **E.N. Brown:** None. **K. Solt:** None.

Poster

239. Sleep: Regulators

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 239.19/JJ23

Topic: F.08. Biological Rhythms and Sleep

Support: NIH Grant R01-AA023181

Title: Developmental ethanol induced sleep fragmentation, behavioral hyperactivity, and parvalbumin cell loss are prevented by lithium co-treatment

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Abstract: Developmental ethanol exposure can lead to long-lasting cognitive impairment, hyperactivity, and emotional dysregulation among other problems. In healthy adults, sleep plays an important role in each of these behavioral manifestations. Our previous work has demonstrated that some aspects of cognitive impairment in adult mice exposed at postnatal day 7 (P7) to EtOH correlate with slow-wave sleep (SWS) fragmentation (Wilson, et al., 2016). We have also previously demonstrated that co-treatment with LiCl on the day of EtOH exposure

prevents many of the anatomical and physiological impairments observed in adults. Here we explored diurnal rhythms (activity, temperature) and slow-wave sleep in adult mice that had received a single day of EtOH exposure on P7 and saline treated littermate controls. Half of the animals also received a LiCl injection on P7. SWS and diurnal activity patterns were assessed in adults (P90) and parvalbumin (PV) cell density was assessed at P14 and P90. The results suggest that developmental EtOH resulted in adult behavioral hyperactivity and reduced SWS compared to saline controls. Both of these effects were prevented by LiCl treatment on the day of EtOH exposure. Finally, developmental EtOH resulted in decreased PV-expressing cells in cortex and hippocampus at P90. In the cortex, this decrease appeared to be partially explained by a decrease in PV expression, rather than cell loss. No decrease was observed at P14, however, suggesting a delayed maturational effect rather than a direct loss during the EtOH induced wave of cell death over the 24hrs post injection. As with sleep and behavioral activity, LiCl treatment prevented this decrease in PV expression. Together these results further describe the long-lasting effects of developmental EtOH on adult behavior, physiology and anatomy. Furthermore, they demonstrate the neuroprotective effects of LiCl co-treatment on this wide range of developmental EtOH's long-lasting consequences.

Disclosures: **M. Saito:** None. **M. Ilina:** None. **J. Betz:** None. **K. Masiello:** None. **M. Hui:** None. **D.A. Wilson:** None.

Poster

239. Sleep: Regulators

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 239.20/JJ24

Topic: F.08. Biological Rhythms and Sleep

Support: NIMH Grant 60670

Rackham Research Grant

Title: Preventing locus coeruleus silences during sleep alters learning and sleep spindle density

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Abstract: We investigated whether the cessation of norepinephrine release across sleep is essential for sleep dependent memory consolidation. The locus coeruleus (LC), actively secretes norepinephrine throughout the brain except when it falls silent during rapid eye movement (REM) sleep and sleep spindles of the transition to REM (TR) sleep state. While norepinephrine acts to strengthen synaptic connections, the cessation of norepinephrine release during these sleep periods uniquely allows synaptic weakening. We hypothesize that these transient silences

allow bidirectional synaptic plasticity necessary for the incorporation of new memories or ideas into preexisting memory circuits. Rats were trained to find food rewards on a hippocampally-dependent spatial learning task. Rats were tested on a familiar task, and then given a reversal learning task and optogenetically stimulated during subsequent sleep. Results showed that optogenetic stimulation of the LC during sleep after learning allowed sleep to proceed normally but significantly reduced spindles in TR sleep and prevented a post-learning increase in sleep spindles. Stimulation during sleep after training also significantly impaired reversal learning of reward positions in the spatial maze task. Additionally, LC stimulation during sleep altered maze strategies to utilize less accurate solutions that do not require the hippocampus. We conclude that periods of norepinephrine cessation are necessary for proper sleep-dependent memory consolidation involving tasks requiring alterations in pre-existing memory circuits.

Disclosures: K. Swift: None. **B.A. Gross:** None. **G.R. Poe:** None.

Poster

239. Sleep: Regulators

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 239.21/JJ25

Topic: F.08. Biological Rhythms and Sleep

Support: R01MH099231

P01NS083514

R01GM116916

T32 GM008962

Title: Activation of layer 1 neurogliaform cells promotes sleep slow waves

Authors: *K. PEELMAN, C. M. FUNK, W. MARSHALL, C. CIRELLI, G. TONONI
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Abstract: During slow wave sleep, cortical neurons undergo a slow oscillation characterized by a synchronous alternation between periods of high firing (ON periods) and silence (OFF periods). It has been unknown whether the generation of slow waves is due to disfacilitation or disinhibition. Recent data from our lab has shown that activation of somatostatin interneurons promotes slow wave activity (SWA) during sleep (Funk et al. BioRxiv 2017). However, it is unknown as to whether other classes of interneurons contribute to the generation of non-rapid eye movement (NREM) slow waves. Neurogliaform (NGF) cells are a major component of layer 1 of cortex and have dense horizontal axonal arborizations that span across multiple cortical columns. They are able to coordinate synchronous activity within the local circuit due to their

unique ability to initiate changes in dendritic excitability within the majority of nearby cells. Here, we studied how activation of NGF cells in layer 1 via excitatory M3 Designer Receptors Exclusively Activated by Designer Drugs (DREADD) receptors influences NREM sleep. Sleep/wake chronic polysomnographic recordings were performed in freely-moving NGF-Cre adult mice (n=4) infected in four cortical areas (bilateral frontal and parietal) with Cre-inducible AAV expressing the excitatory designer receptor hM3Dq. Animals were implanted with silicone probes spanning all cortical layers to record local field potential (LFP) activity in virus-infected areas. Clozapine-N-Oxide (CNO) was administered to animals halfway through the sleep cycle (~6 hours after lights on), and sleep SWA was analyzed for the six hours after administration. We found a significant increase in SWA after CNO administration relative to control NGF-Cre animals that had not been injected with virus and received CNO (n=4, p=0.0109). The increase in SWA with NGF activation occurred mainly in the first hour after CNO. In contrast, somatostatin interneurons show a prolonged increase in SWA lasting more than six hours after CNO administration (p = 3.6e-10), suggesting that multiple interneuron subtypes may regulate SWA to varying extents, perhaps underlying the generation of different types of slow waves.

Disclosures: K. Peelman: None. **C.M. Funk:** None. **W. Marshall:** None. **C. Cirelli:** None. **G. Tononi:** None.

Poster

239. Sleep: Regulators

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 239.22/JJ26

Topic: F.08. Biological Rhythms and Sleep

Support: NIH Grant DK105510

NSF Grant 1652060

Title: Hypothalamic arcuate nucleus neurons that regulate energy homeostasis can also influence sleep/wake behavior

Authors: N. GOLDSTEIN, K. LOY, B. LEVINE, O. MEYERSON, W. DUKE, A. JAMNIK, *M. CARTER
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Abstract: Eating and sleeping represent two mutually exclusive behavioral states that satisfy distinct homeostatic needs. Because an animal cannot eat and sleep at the same time, brain systems that regulate energy homeostasis are likely to influence sleep/wake states. Previous studies indicate that sleep/wake behavior in mammals is significantly affected by food need and availability. For example, food deprivation causes fragmentation of sleep and an increase in

wakefulness. Additionally, the orexigenic hormone ghrelin promotes wake states while the anorexigenic hormones leptin and insulin increase the duration of slow wave sleep. However, the role of neurons that centrally regulate food intake in sleep/wake behavior is unknown. The hypothalamic arcuate nucleus contains two populations of neurons that oppositely regulate energy homeostasis: agouti-related protein (AgRP)-expressing neurons detect caloric need and induce food intake behavior, while pro-opiomelanocortin (POMC)-expressing neurons induce satiety. Here, we test the hypothesis that AgRP neurons affect sleep homeostasis by promoting states of wakefulness while POMC neurons affect sleep homeostasis by promoting states of sleep. We found that optogenetic or chemogenetic stimulation of AgRP neurons in mice promoted wakefulness while decreasing the quantity and quality of sleep. Acute AgRP neuron stimulation increased sleep fragmentation and altered EEG power during slow wave sleep and rapid eye movement sleep. In contrast, stimulation of POMC neurons promoted sleep states. Taken together, these data indicate that nuclei that regulate feeding behavior can also affect sleep/wake behavior, demonstrating interplay between energy and sleep homeostatic systems.

Disclosures: **N. Goldstein:** None. **K. Loy:** None. **B. Levine:** None. **O. Meyerson:** None. **W. Duke:** None. **A. Jamnik:** None. **M. Carter:** None.

Poster

239. Sleep: Regulators

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 239.23/JJ27

Topic: F.08. Biological Rhythms and Sleep

Support: AAN/ABF Training Fellowship

NIH NINDS R25NS070682

NIH NINDS R21NS082854

NIH NINDS R01NS073613

NIH NINDS R01NS092652

NIH NINDS R01NS085477

NIH NINDS P01HL095491

Title: Discrete roles for SuM neuronal subpopulations in the regulation of sleep-wake and EEG activity in mice

Authors: ***N. P. PEDERSEN**[1], A. VENNER[2], L. FERRARI[4], E. ARRIGONI[5], C. B. SAPER[6], P. M. FULLER[3]

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Abstract: Basic and clinical observations for over 100 years have suggest that the caudal hypothalamus is a key node of the ascending arousal system. However, the precise region, cell group and cellular identity remains unclear. Here we show that glutamate-releasing neurons of the supramammillary region (SuM^{vglut2}) produce sustained behavioral and EEG arousal along with constant and increased theta and gamma activity when chemogenetically activated, with near abolition of these effects by selective genetic disruption of glutamate release. Acute chemogenetic inhibition of SuM^{vglut2} neurons decreased and fragmented wakefulness and suppressed theta and gamma frequency EEG activity by comparison to the baseline EEG. We also found that SuM^{vglut2} neurons could be divided into three distinct subpopulations: One containing markers of both glutamate and GABA release ($SuM^{vgat/vglut2}$), another with nitric oxide synthase (Nos1, $SuM^{vglut2/nos1}$) and a third with vglut2 alone. Chemogenetic activation of $SuM^{vgat/vglut2}$ neurons produced minimal wake, whereas optogenetic activation of $SuM^{vgat/vglut2}$ terminals in brain slices elicited simultaneous monosynaptic glutamatergic and GABAergic post-synaptic potentials in dentate granule cells. In contrast, selective chemogenetic activation of $SuM^{vglut2/nos1}$ neurons potently drove wakefulness, but chemogenetic inhibition only reduced theta activity in REM sleep. These results identify discrete roles for SuM neuronal subpopulations and reveal the SuM as a key node of the wake-sleep regulatory system.

Disclosures: N.P. Pedersen: None. **A. Venner:** None. **L. Ferrari:** None. **E. Arrigoni:** None. **C.B. Saper:** None. **P.M. Fuller:** None.

Poster

239. Sleep: Regulators

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 239.24/JJ28

Topic: F.08. Biological Rhythms and Sleep

Support: national research foundation of Korea (NRF-2016R1A2B4010897)

GIST Research Institute(GRI) grant funded by the GIST in 2017

Title: Subject-specific parameters may be of importance in improving the performance of an automatic sleep spindle detector

Authors: *J. CHOI[1], S. HAN[1], M. KWON[1], H. SEO[2], S. JANG[1], K. WON[1], S. C. JUN[1]
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Abstract: Sleep spindles are electroencephalographic activity in the sigma frequency range (11-16Hz) and spindles are known to have a central role in synaptic plasticity and memory consolidation. Identification of sleep spindle have been done by expert's visual inspection, thus it is quite subjective and time consuming. Various automatic spindle detection algorithms have been developed for generalized spindle analysis. However, these methods hardly show stable performance because performance varies over subjects or even sessions in the same subject. In this study, we explored the need of subject-specific parameter optimization for a popular automatic spindle detector. As a preliminary result, we observed notably different spindle detector performances using subject-specific parameters and typical parameters. We introduced an open source spindle detection algorithm based on constant threshold scheme. The threshold was set to root mean square (RMS) value of sigma band power which is separating specific percentile (e.g. 95^{th}) of RMS value's distribution in the NREM sleep EEG data. We set the percentage and the time window (step and length) as optimizing parameters. We applied this algorithm to public sleep database consisting of sleep EEG data with information about spindle time points determined by experts. We selected four subjects from eight who have a plenty of spindle activities for analysis. For performance evaluation, we repeatedly measured F1-scores of the detector over varying optimization parameters. One out of ten spindle points was selected randomly for the threshold measurements and remaining points were used as the golden standard. We tracked subject-specific optimal parameters. Additionally, we measured typical parameters which was set to average value of whole subject-specific parameters. We compared the performance (F1-score) of spindle detector for subject-specific parameters and typical parameters. Overall, there were statistical significant degradation in performance when using the typical parameters, compared to using the subject-specific parameters. Particularly, for one subject, F1-score far significantly changed from 0.36±0.03 to 0.32±0.02 (p-value < 1e-6). It was observed that performance degradation for sleep spindle detection algorithm with typical parameters compared to using optimal parameters for each subject. Even these results came from the limited amount of data, it may be inferred that determination of subject-specific optimization in spindle detection algorithm would be of quite importance.

Disclosures: J. Choi: None. **S. Han:** None. **M. Kwon:** None. **H. Seo:** None. **S. Jang:** None. **K. Won:** None. **S.C. Jun:** None.

Poster

239. Sleep: Regulators

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 239.25/JJ29

Topic: F.08. Biological Rhythms and Sleep

Support: Department of the Navy, Office of Naval Research Award No. N00014-11-1-0361

NASA NNX14AN49G

Clinical and Translational Research Center (CTRC) grant UL1TR000003

Defense Advanced Research Projects Agency (DARPA) and the U.S. Army Research Office (W911NF1010093)

DARPA Young Faculty Award D12AP00241

Title: MicroRNAs are cross-species markers of sleep loss in humans and rats

Authors: *N. GOEL[1], D. M. TAYLOR[2], T. ABEL[3], W. D. S. KILLGORE[4], J. PEARSON-LEARY[5], S. BHATNAGAR[6]
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Abstract: Introduction: Sleep loss has been increasingly associated with diabetes, cancer, cardiovascular disease, Alzheimer's disease and mood disorders. MicroRNAs, small non-coding RNAs that are important regulators of gene expression, typically repress the expression of their target mRNAs, and play an established role in these disorders and diseases. To determine whether miRNAs are involved in sleep regulation, we examined whether they change as a function of sleep loss and recovery in humans and rats. **Methods:** Three highly controlled laboratory studies were performed, two employing sleep restriction (SR) and one employing total sleep deprivation (TSD). In Study 1, 15 healthy adults (35.0 ± 9.9y; 6 females), participated in a SR protocol: miRNA blood samples were taken after one 10h time-in-bed (TIB) baseline night; five 4h TIB SR nights; and one 12h TIB recovery night. In Study 2, 15 adult Sprague Dawley rats (d65-70; 8 females) participated in a SR protocol: miRNA samples were taken after one baseline night, four 4h TIB SR nights, and one recovery night. In Study 3, 12 healthy adults (24.8 ± 5.4y; 6 females), participated in a TSD protocol: miRNA samples were taken after baseline, one TSD night, and recovery. MiRNAs were analyzed via Affymetrix microarrays (Studies 1 and 2) or RNA-sequencing (Study 3). Mixed linear models with Z-score log2 fold change cutoffs of ±1.645 and greater (FDR< 0.05) were used for statistical analysis. **Results:** Across all three studies, a total of 45 miRNAs, 16 with increased expression and 29 with decreased expression, showed significant log2fold changes with experimental sleep loss. The majority of these miRNAs returned to baseline expression levels after recovery sleep. Notably, 17 genes targeted by miRNAs (determined from TargetScan) showed overlap across sleep loss conditions and across species. **Conclusion:** These results provide the first experimental evidence that miRNAs can track sleep loss and recovery dynamics across species and serve as epigenetic biomarkers of sleep debt. This work establishes a definitive link between miRNA expression profiles and known diseases resulting from sleep loss.

Disclosures: N. Goel: None. **D.M. Taylor:** None. **T. Abel:** None. **W.D.S. Killgore:** None. **J. Pearson-Leary:** None. **S. Bhatnagar:** None.

Poster

239. Sleep: Regulators

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 239.26/JJ30

Topic: F.08. Biological Rhythms and Sleep

Support: NIH Grant 2P01HL095491

Title: Presynaptic cholinergic suppression of parahypoglossal glutamatergic input to hypoglossal motoneurons

Authors: *L. ZHU, L. FERRARI, D. PARK, N. CHAMBERLIN, E. ARRIGONI
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Abstract: In REM sleep, the genioglossus (GG) muscle undergoes a dramatic suppression of activity. A current hypothesis is that the loss of GG activity during REM sleep is mediated by a combination of 1) monoaminergic disfacilitation and 2) a cholinergic inhibition of hypoglossal motoneurons (HMNs). Strikingly, blockade of cholinergic receptors in the hypoglossal nucleus restores REM sleep tonic and inspiratory-modulated components of GG activity (Grace et al., 2013), suggesting that the cholinergic signal is largely responsible for the REM sleep suppression of GG activity. Respiratory rhythm generator neurons of the pre-Bötzinger complex drive the activation of HMNs through glutamatergic premotor neurons in the parahypoglossal region (PH). In the current study, we investigate how cholinergic signaling affects the PH glutamatergic input to HMNs.

We stereotaxically injected the PH region of vGluT2-*cre* mice with a cre-dependent AAV-ChR2-mCherry to express channelrhodopsin2 (ChR2) in PH glutamatergic premotor neurons. We then performed whole-cell recordings in hypoglossal neurons while photostimulating PH glutamatergic inputs expressing ChR2.

Photostimulation of the glutamatergic PH input evoked AMPA-mediated EPSCs in HMNs. These photoevoked EPSCs were maintained in TTX, indicating direct connectivity between stimulated terminals and recorded HMNs. Bath application of acetylcholine agonist carbachol strongly inhibited the PH glutamatergic excitation of HMNs via muscarinic receptors. The inhibition of carbachol on photoevoked EPSCs was maintained when 1) we blocked postsynaptic G-mediated effects by adding GDP-β-S in the recording pipette and 2) when we blocked action potential mediated transmission by adding TTX in the extracellular bath solution. These results indicate that carbachol inhibits PH excitation to HMNs through a presynaptic mechanism.

Our results provide a possible mechanism for cholinergic inhibition of the HMNs in REM sleep. We propose that the cholinergic presynaptic suppression of the excitatory drive from the PH premotor neurons can be responsible for the reduction in activity of hypoglossal motoneurons in REM sleep.

Disclosures: **L. Zhu:** None. **L. Ferrari:** None. **D. Park:** None. **N. Chamberlin:** None. **E. Arrigoni:** None.

Poster

240. Sleep: Systems

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 240.01/KK1

Topic: F.08. Biological Rhythms and Sleep

Support: NIAAA Grant R21AA021233

Title: Sleep deprivation increases alcohol-induced sensitivity and mortality in *Drosophila*

Authors: *A. K. DENOBREGA, E. J. NOAKES, A. P. MELLERS, L. C. LYONS
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Abstract: Excessive alcohol drinking and the long-term chronic abuse of alcohol has adverse consequences for individual health, society, and the economy (Sacks et al., 2015) with alcohol use disorders representing 79% of all diagnoses of substance use disorders (SAMSHA, 2015). Alcohol abuse and alcohol pathologies appear higher in populations in which sleep deprivation is common as in shift workers (Swanson et al., 2016) and aging individuals (Kendler et al., 2016). Traditionally, sleep disruption and sleep loss are viewed as consequences of alcohol abuse. However, little is known about the physiological role of sleep on alcohol toxicity. Understanding the relationship between sleep and alcohol neurobiology could help ameliorate the health and economic costs related to alcohol-induced pathologies. With conserved signaling pathways and clear parallels to mammalian physiology, *Drosophila* presents a suitable model for dissecting the molecular and neural mechanisms underlying alcohol neurobiology (Park et al, 2016) as well as an excellent model for studies of sleep (Donelson et al., 2015). In the current studies, we investigated the impact of sleep on alcohol toxicity. We found that 24 h of sleep deprivation increased the behavioral sensitivity to alcohol and alcohol-induced mortality in young and middle-aged flies. The effects of sleep deprivation appeared to be independent of stress or injury as 48 h recovery sleep in young flies was sufficient to ameliorate the exacerbation of alcohol-induced sensitivity and mortality by sleep deprivation. Sleep deprivation also inhibited the induction of long-term functional alcohol tolerance observed 24 h following the first alcohol exposure, although rapid tolerance measured 4 h following the first alcohol exposure was not affected. Pharmacological induction of sleep for 48 hrs prior to alcohol exposure using a $GABA_A$-receptor agonist, 4,5,6,7-tetrahydroisoxazolo(5,4-c)pyridin-3-ol (THIP), dose dependently decreased mortality following repeated exposures to alcohol in middle-aged flies. Increased sleep appeared to mitigate alcohol-induced mortality independently of the circadian clock as flies housed on THIP-enriched food in constant light also exhibited significantly decreased mortality following alcohol exposure. These results suggest that the amount of sleep

prior to binge-like alcohol exposure episodes directly affects alcohol toxicity and health outcomes. This research is supported by NIAAA Grant R21AA021233.

Disclosures: **A.K. Denobrega:** None. **E.J. Noakes:** None. **A.P. Mellers:** None. **L.C. Lyons:** None.

Poster

240. Sleep: Systems

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 240.02/KK2

Topic: F.08. Biological Rhythms and Sleep

Support: Human Frontiers Science Program (RGP0004/2013)

Title: State-dependent brain cFos expression in perinatal chickens

Authors: *M. POMPEIANO[1], D. MARTINEZ-GONZALEZ[2], A. CHAN[1], S. SALAHUDDIN[1], A. YIP[1], Y. LIN[1], G. WANG[1], N. C. RATTENBORG[2], E. BALABAN[1]
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Abstract: Adult mammalian wakefulness (W) is characterized by coordinated patterns of neuronal activity in a network of cell groups called the “arousal systems” (AS; Jones 2011), while sleep (S) features heightened activity in various GABAergic populations, and lack of activity in the AS. Rapid eye movement S (REMS) is supported by the activation of cholinergic pontine and melanin-concentrating hormone neurons. Widespread brain cFos expression is also seen during W, which shuts down during S. Adult birds show S and W states with similar behavioral and electroencephalographic (EEG) correlates (Lesku and Rattenborg 2014). Chickens (a precocial avian species) have S-like EEG patterns before hatching, and develop a stable W state within a few hours after hatching (Mellor and Diesch 2007; Martinez-Gonzalez et al 2012). Their AS show progressively greater cFos expression during embryonic development, but coordinated patterns and high levels of cFos activation among their constituent cell groups only become apparent in awake, newly-hatched (P1) chicks (Chan et al 2016). REMS regulatory populations show increased cFos expression at embryonic day (E) 20, the day before hatching (Chan et al 2016). The present study examined whether W behavior is accompanied by widespread cFos brain activation in P1 chicks, and S behavior by relatively low cFos expression in P1 chicks and E20 chicken embryos. Fertilized eggs were incubated at 37.5° C, 55-60% relative humidity for 20 days or until hatching. P1 chicks were left sleeping or were kept awake by gentle handling (as in Chan et al 2016). Embryos (in ovo) and hatchlings were anesthetized with isoflurane and intracardially perfused with fixative. Cryostat-cut sections were processed using standard immunohistochemical techniques. Awake P1 chicks showed patterns of cFos

expression in areas of the pallium, subpallium, diencephalon, and tectum which were strongly decreased in P1 chicks with uninterrupted S. We conclude that P1 chick brain responses share this adult-like S characteristic with mammals. At E20, cFos levels were low in pallium, thalamus, and tectum (like P1 S); they were high in amygdala, parahippocampal, striatal, septal and hypothalamic areas (like P1 W); they were also high in several hindbrain, mostly autonomic areas (unlike P1 S or W). We conclude that the low cFos expression in thalamocortical areas is compatible with the S-like EEG pattern described at E20 (Mellor and Diesch 2007; Martinez-Gonzalez et al 2012). High activation in autonomic areas is possibly related to the hatching process.

Disclosures: **M. Pompeiano:** None. **D. Martinez-Gonzalez:** None. **A. Chan:** None. **S. Salahuddin:** None. **A. Yip:** None. **Y. Lin:** None. **G. Wang:** None. **N.C. Rattenborg:** None. **E. Balaban:** None.

Poster

240. Sleep: Systems

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 240.03/KK3

Topic: F.08. Biological Rhythms and Sleep

Support: Hungarian Brain Research Program (grant no. KTIA_13_NAP-A-I/1, KTIA_NAP_13-2-2015-0010)

Title: Selective arousal patterns evoked by somatosensory and midline thalamic stimulations

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Abstract: Fast awakening from sleep is vital to animals in an unpredictable environment and sensory systems have been well adapted to fulfill this requirement. However, the existence of an internal arousal systems has long been proposed and the non-sensory midline thalamic nuclei (MT) has been considered to be a key hub in transmitting arousal signals from subcortical centers to the cortex. Taking advantage, that MT neurons selectively express calretinin (CR) within the thalamus, we injected AAV-DIO-ChR2-eYFP into the dorsal part of MT (dMT) of CR-Cre mice and by means of optical stimulation we quantitatively assessed the role of dMT in

arousal in naturally sleeping mice. Sleep-wake states was monitored by EEG/EMG signals and video tracking of the animal's movement. Intense, (10 sec, 10 Hz) optogenetic stimulation of dMT during slow wave sleep induced fast (~1 sec latency) and persistent arousal accompanied by locomotion, lasting for several minutes. Short stimulations (0.5-2 sec, 10 Hz), evoked stereotyped microarousal: an immediate desynchronization of EEG, with a characteristic drop in the power of delta (1-3 Hz) and sigma (10-15 Hz) bands, followed by a brief (2-5 sec) head-movement with relatively long (3-4 sec) latency. Microarousals could be evoked probabilistically, which was depended on stimulus duration and intensity. In cases when MT stimulations failed to evoke microarousals, the sigma but not the delta frequency band of the EEG power was selectively disrupted. In order to compare dMT induced arousal with sensory arousal, we injected syn-AAV-ChR2 into the VB of CR-Cre mice. We found that brief (1 sec) stimulation of VB during slow wave sleep, efficiently induced microarousal with similar duration, however, much faster onset (<0.5 sec), than that of dMT. Interestingly, while brief (1 sec) stimulation of dMT was also capable to induce microarousal during REM sleep, VB stimulation was not effective at all. Our findings indicate main differences between non-sensory and sensory arousal systems and indicate that MT is a good candidate to effectively induce state transitions in forebrain systems.

Disclosures: G.S. Komlosi: None. **F. Matyas:** None. **P. Bartho:** None. **A. Jasz:** None. **K. Kocsis:** None. **B. Barsy:** None. **V. Kanti:** None. **A. Magyar:** None. **L. Acsady:** None.

Poster

240. Sleep: Systems

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 240.04/KK4

Topic: F.08. Biological Rhythms and Sleep

Support: DFG SFB 654

Title: Brain structures and sleep transitions: Comparing EEG and LFP recordings

Authors: *C. N. OYANEDEL[1,3], E. DURÁN[1,3,4], N. NIETHARD[1], M. INOSTROZA[1], J. BORN[1,2]
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Abstract: Sleep is a complex phenomenon defined by several criteria, such as physical quiescence, increased threshold for arousal and latency for reactivity. Sleep in mammals, can be divided into the stages: rapid-eye movement (REM) sleep, slow wave sleep (SWS), and,

specifically in rodents, a transition state called pre-REM sleep, and the determination of these sleep stages, for the most, part relies on an assessment of surface EEG recordings. Findings from recent studies have suggested that sleep and sleep stages might not congruently catch the whole brain but can also locally occur restricted to specific networks and regions. However, how the temporal dynamics in sleep patterns differs among brain structures is not clear. Here, we compared in rats sleep stages and their transitions between neocortex and hippocampus, *i.e.*, two structures known to strongly engage in sleep-state specific processing of memory information. To this end, one EMG, two EEG and two local field potential (LFP) electrodes were chronically implanted in 5 adult male Long Evens rats. The LFP electrodes were placed in the medial prefrontal cortex (mPFC) and dorsal hippocampus (dHC), while the EEG electrodes were place in the skull above frontal and parietal lobes respectively. Determination of SWS and REM sleep, relied on the occurrence of < 4 Hz slow wave activity and 4-8 Hz theta activity respectively. Pre-REM was classified mainly based on the co-occurrence of delta activity and increased theta. Our results show that the characterization of the different sleep stages reaches 90% of congruence when EEG and LFP recordings from PFC are compared. The higher similarity was found for SWS with 97.2±0.3%. For pre-REM and REM sleep the similarity dropped down to 17.1±9.9% and 78.7±10.3% respectively. We found that this drop is the result of systematic differences in sleep stage transitions between the two brain areas, associated also with a difference in the number of episodes detected in each area. In 30% of the REM sleep episodes, REM sleep appeared first in the dHC electrode, and significantly delayed (on average by 10.8±1.0 seconds) in the neocortical LFP and skull EEG electrodes. Furthermore we found that the REM-sleep associated decrease in muscle tone (EMG) is time-locked to the increase in theta activity in the dHC electrode, but less to the signal from mPFC and surface EEG electrodes. Our data shows that it is possible to characterize different sleep stages in neocortex and hippocampus, using EEG or LFP signals. Importantly, REM sleep often starts earlier in the hippocampus than in the neocortex, indicating that the timing of sleep stage transitions depends on the brain structure we are looking at.

Disclosures: **C.N. Oyanedel:** None. **E. Durán:** None. **N. Niethard:** None. **M. Inostroza:** None. **J. Born:** None.

Poster

240. Sleep: Systems

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 240.05/KK5

Topic: F.08. Biological Rhythms and Sleep

Support: Hungarian Brain Research Program (KTIA_NAP_13-2014-0016)

NKFIH-K119650

Title: Corticothalamic effect on thalamic neurons

Authors: *V. BALOGH, S. BORBÉLY, M. CSERNAI, P. BARTHÓ
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Abstract: The thalamus receives a robust feedback projection originating from layer 6 of the neocortex (L6). This glutamatergic projection outnumbers thalamocortical projections by a magnitude and may play various roles in the thalamocortical network: altering the receptive fields of thalamocortical cells; influencing the generation of sleep rhythms; acting as classical modulatory pathway. Nevertheless, the exact firing behaviour of L6 corticothalamic neurons is unclear, also we do not know whether they exert a direct excitation on thalamic cells, or an indirect inhibition through the thalamic reticular nucleus. Here we used electrophysiological and optogenetic methods to selectively manipulate L6 corticothalamic neurons in vivo, while simultaneously recording thalamic and cortical activity. We used NTSR1-ChR transgenic mouse line in which L6 corticothalamic neurons are exclusively expressing the photosensitive channel-rhodopsin. We found that the majority (64%) of thalamocortical cells were inhibited by L6 stimulation, the rest showed excitation or a mixture of the two. In some cases the excitation/inhibition profile showed dependency on the actual network state. Thalamic reticular neurons, on the other hand, were reliably excited by L6, showing prolonged firing to stimuli as long as 500 ms. To gain an insight to the spontaneous firing pattern of L6 corticothalamic cells we performed juxtacellular recordings with optical tagging of these neurons during urethane anaesthesia induced synchronized oscillations. The activity of corticothalamic cells correlated with cortical UP-states, but surprisingly showed little association to ongoing sleep spindles.

Disclosures: V. Balogh: None. **S. Borbély:** None. **M. Csernai:** None. **P. Barthó:** None.

Poster

240. Sleep: Systems

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 240.06/KK6

Topic: F.08. Biological Rhythms and Sleep

Support: Hungarian Brain Research Program (KTIA_NAP_13-2-2014-0016)

NKFIH-K 119650

Title: Cortical layer 6 regulates network state

Authors: *S. BORBÉLY, V. BALOGH, M. CSERNAI, D. BURKA, P. BARTHÓ
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Abstract: Cortical layer 6 is the source of a massive projection to the corresponding thalamic areas, the function is which is still debated. According to the hypothesis Sherman and Guillery, L6 corticothalamic feedback functions as a modulatory system in the thalamus, as opposed to driver inputs arising from subcortical sources or cortical layer V. Here we tested this hypothesis by examining whether L6 activation can induce a state change in the thalamocortical system, similarly to other modulators. We used chronically implanted NTSR1-ChR transgenic mice, in which thalamically projecting layer 6 neurons selectively express channelrhodopsin, to measure the local field and unit responses elicited by optical stimulation of the corticothalamic feedback. Pulse-like L6 stimulation elicited spindles during light sleep, while under desynchronized and more synchronized epochs a single down-state was produced. Using longer stimuli we found that tonic activation of L6 feedback can elicit state change in the thalamocortical network in a dose- and state dependent manner. During stage II. sleep, low intensity L6 stimulation eliminated sleep spindles, but retained delta activity, transforming the network to a stage III. sleep-like state. Higher intensities, however desynchronized thalamocortical activity, with a corresponding drop in delta- and sigma-, and an increase in gamma LFP power. During deep sleep, low intensity corticothalamic activation produced little or no effect, while high intensity L6 stimulation induced desynchronization, similar to that during light sleep. The spatial extent of the state change was limited, with low intensities acting only locally, high intensities exerting effects on areas ~1mm apart. We conclude that corticothalamic feedback can indeed act as a local modulator in the thalamus.

Disclosures: S. Borbély: None. **V. Balogh:** None. **M. Csernai:** None. **D. Burka:** None. **P. Barthó:** None.

Poster

240. Sleep: Systems

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 240.07/KK7

Topic: F.08. Biological Rhythms and Sleep

Support: NIH Grant NS092383

V.A. Grant BX00155605

Title: GABAergic neurons in the preoptic hypothalamus project to midbrain structures involved in arousal state control

Authors: K.-C. HSIEH[1], S. KUMAR[2], M. H. CHASE[3], *R. S. SZYMUSIAK[4]
[1]V.A. Greater Los Angeles Healthcare Syst., Los Angeles, CA; [2]VA Greater Los Angeles Healthcare Syst., Los Angeles, CA; [3]Websciences Intl., Los Angeles, CA; [4]Res. Service, UCLA/VA Greater Los Angeles, Los Angeles, CA

Abstract: Introduction**:** GABAergic, neurons in the preoptic hypothalamus are key components of hypothalamic-brainstem circuits that regulate sleep and arousal. Many sleep-active neurons recorded in the median preoptic nucleus (MnPO) and the ventrolateral preoptic area (VLPO) exhibit elevated discharge rates during both nonREM and REM sleep compared to waking. A population of neurons in the dorsal lateral preoptic area (DLPO) exhibit REM sleep-related discharge. Preoptic nonREM/REM-active neurons may participate in control of the nonREM-REM sleep cycle. To evaluate this, we examined projections of GABAergic neurons in the preoptic area to midbrain nuclei implicated in arousal arousal state control and REM sleep, the dorsal raphe nucleus (DRN) and the ventrolateral periaqueductal gray (vlPAG). Methods: Adult Sprague-Dawley rats received unilateral injections of the retrograde anatomical tracer, cholera toxin subunit-b Alexa Fluor 594 conjugate (CTb), targeting the vlPAG or DRN. After a 14-day survival period to allow for retrograde transport of tracer, rats were euthanatized and tissue sections through the preoptic hypothalamus were processed for visualization of CTb and of glutamic acid decarboxylase (GAD), a marker of GABAergic neurons. Results: CTb injections targeting the DRN (n=3) yielded comparable retrograde labeling in the VLPO (32.7±1.5 cells/section) and the DLPO (41.0±4.4 cells/section). In VLPO, 59±8.5% of GAD+ neurons were double labeled for CTb and 21.3±6.7% of GAD+ neurons in the DLPO were also CTb+. Retrograde labeling of GABAergic neurons in MnPO from the DRN was less, with an average of 28.0±3.1 CTb+ cells/section and only 12.3±0.3% of GAD+ cells double labeled for CTb. CTb injections labeling the vlPAG (n=3) resulted in 49.7±1.5 CTb+ cells/section in the VLPO, with 40.8±3.3% of GAD+ neurons double labeled. Density of retrograde labeling was comparable In the DLPO, with an average of 47.3±1.2 CTb+ cells/section, but dual labeling occurred in only 18.3±3.8% of GAD+ neurons. In the MnPO, the average number of CTb+ cells/section was 30.3±1.3, with double labeling detected in 22±5.9% of GAD+cells. Conclusions: This study confirmed anatomical connections between GABAergic neurons in sleep-regulatory regions of the preoptic area to regions in the midbrain implicated in arousal state control and REM sleep, with the highest density of GABAergic projection neurons originating in the VLPO. These connections may integrate hypothalamic neuronal systems that regulate sleep onset and nonREM sleep with brainstem REM sleep generating circuits.

Disclosures: K. Hsieh: None. **S. Kumar:** None. **M.H. Chase:** None. **R.S. Szymusiak:** None.

Poster

240. Sleep: Systems

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 240.08/KK8

Topic: F.08. Biological Rhythms and Sleep

Support: JSPS KAKENHI 24590295

Title: Neuronal firing of mesopontine tegmental area regulating initiation and termination of paradoxical sleep

Authors: *Y. KOYAMA[1], C. SEI[1], S. MATSUDA[1], K. TAKAHASHI[2]
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Abstract: REM sleep (Paradoxical sleep: PS) is regulated by the interaction of several kinds of neurons located from midbrain to rostral pons (mesopontine tegmental area). It has been considered that the neurons most active during PS (PS-on neurons) initiate and maintain PS, while those most active during Waking (W) and least active or silent during PS (W-on or PS-off neurons) counteract the performance of PS-on neurons. However, simple interaction between PS-on neurons and PS-off neurons does not thoroughly explain the naturally occurring PS; slow and gradual shift from slow wave sleep (SWS) to PS and abrupt changes from PS to W. In addition to PS-on and PS-off neurons, there are many other types of neurons in the mesopontine tegmentum, some of which must be crucial for regulation of PS. To elucidate the neural substrates initiating and terminating PS, single neuronal activity was recorded from the mesopontine tegmental area across sleep-waking cycles focusing mainly on the transition of state from SWS to PS or from PS to W. In unanesthetized, head-restrained rats, single neuronal activity was recorded, using glass pipette electrode, from the caudal periaqueductal gray (PAG) and the midbrain reticular formation ventrolateral to the PAG, including deep mesencephalic reticular nucleus (DpMe) or nucleus pontis oralis (PnO), as well as leterodorsal and pedunclotegmental nuclei (LDT/PPT), sub laterodorsal tegmental nucleus (subLDT) and the surrounding areas. About two-third (36/54) of the recorded neurons increased activity during PS, most active during PS, active both during W and PS or during SWS and PS (PS active neurons), while 14 displayed the highest firing during W (W active neurons). Of them, 20 (56 %) PS active neurons started to increase firing prior to the transition from SWS to PS. Eight PS active neurons decreased firing prior to the transition from PS to W, while 7 PS active neurons showed phasic firing preceding the transition. Of 14 W active neurons, five continued firing during SWS, while six increased firing prior to the transition from PS to W. For the initiation on PS, increase in facilitatory influences from PS active neurons and decrease in inhibitory influences from W active neurons during SWS as well as during W, would be required. For the termination of PS, decrease in activity of PS active neurons during PS, and increase in activity of PS active or W active neurons prior to the transition from PS to W may have some roles.

Disclosures: **Y. Koyama:** None. **C. Sei:** None. **S. Matsuda:** None. **K. Takahashi:** None.

Poster

240. Sleep: Systems

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 240.09/KK9

Topic: F.08. Biological Rhythms and Sleep

Support: NIH Grant 1R01EB019804

Title: Understanding Sleep: Sleep-Wake cycle-dependent discharge patterns from simultaneous Multi-site Multi-modal recordings of NREM, REM, and Wake regulatory structures in freely behaving animals

Authors: *F. BAHARI[1,2], M. W. BILLARD[2], J. KIMBUGWE[2], K. D. ALLOWAY[2], B. J. GLUCKMAN[2]
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Abstract: The sleep-wake regulatory network (SWRN) consists of widely spread nuclei located in midbrain, pons, and sub-thalamic areas. Dorsal Raphe (DR) in midbrain and Pedunculo-Pontine Tegmentum (PPT) in pons are thought to be involved in regulation of wakefulness and rapid-eye-movement (REM) sleep, while the Ventrolateral Preoptic nucleus (VLPO) is implicated in initiating and maintaining non-REM (NREM) sleep (Datta 2007). Although mathematical models representing these cell groups in the SWRN exist (Booth 2014), they are often based on relatively brief recordings from individual cell groups across many independent experiments.

We have developed a recording system for collecting more comprehensive system-wide data from freely behaving animals. In particular, we use a novel microdrive that is capable of moving microelectrode bundles through deep targets along non-parallel trajectories. Measurements from these electrodes are complemented with local field potential recordings in hippocampus (LFP), ECoG recordings from cortical screw electrodes, and video. All physiological measurements are acquired continuously within multi-day recording sessions with a head-mounted digitizing amplifier that includes a 3-axis accelerometer. The LFP and ECoG recordings, along with head acceleration, are then used to classify state of vigilance (SOV) following the methods described in Sunderam 2007.

Here, we report the first network analysis of the SWRN derived from simultaneous measurements across multiple cell groups involved in sleep-wake regulation. We identified a variety of cells in PPT that were consistently more active during REM and/or wakefulness over periods of days to weeks. Simultaneously, we characterized cells in DR and VLPO nuclei that discharged more frequently during periods of wake and NREM, respectively. The discharging of these cell groups lead sleep-state transitions with the neuronal firing rate increasing prior to transition to a corresponding sleep-state.

In order to enhance the mathematical models of SWRN dynamics, the cell groups were further classified according to their SOV-dependent firing patterns. We derived statistical measures of mean and variance as a function of SOV cycle. This is the first study investigating network activity involved in sleep-wake regulation at the cellular level in freely behaving animals. Our approach contributes to further validation of the existing models as well as complementing the dynamics to replicate the fine temporal pattern of transitions between sleep-states.

Work Cited:

Datta S. et al. J Neurosci Biobehav Rev, 2007

Booth V. et al. Math Biosci., 2014
Sunderam S. et al. J Neurosci Meth, 2007

Disclosures: F. Bahari: None. **M.W. Billard:** None. **J. Kimbugwe:** None. **K.D. Alloway:** None. **B.J. Gluckman:** None.

Poster

240. Sleep: Systems

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 240.10/KK10

Topic: F.08. Biological Rhythms and Sleep

Support: NIH - 1R01EB019804

Title: Understanding sleep: Methodology for simultaneous multi-site multi-modal recordings from NREM, REM, and wake regulatory structures in freely-behaving animals

Authors: *M. W. BILLARD[1,2], F. BAHARI[1,2], J. KIMBUGWE[1,2], K. D. ALLOWAY[2,1], B. J. GLUCKMAN[2,1]
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Abstract: The sleep-wake regulatory network (SWRN) consists of widely spread nuclei located in the midbrain, pons, and hypothalamic areas. For example, the dorsal raphe (DR) nucleus in the midbrain and the pedunculo-pontine tegmental (PPT) nucleus in the pons are thought to be involved in regulation of wakefulness and rapid-eye-movement (REM) sleep, and the ventrolateral pre-optic (VLPO) nucleus in the hypothalamus is implicated in maintaining non-REM (NREM) sleep (Datta 2007). Although network models of the cell group interactions exist (Booth 2014), they are an aggregate of independent studies consisting of relatively brief recordings from single brain structures.
We have developed a recording system for collecting more comprehensive system-wide data from freely behaving animals. In particular, we use a novel multi-site, multi-region (MSMR) microdrive that is capable of moving microelectrode bundles into deep targets along independent and non-parallel drive trajectories. Coupled with the microdrive system are additional electrophysiological modalities that are useful for discriminating sleep-wake behavior. These modalities include field potential recordings in hippocampus and electrocorticogram recordings from screw electrodes that are acquired with a head-mounted digitizing amplifier with a 3-axis accelerometer. Animals are recorded from continuously over multiple days in a home cage freely-behaving context with supplemental video. The hippocampal and cortical activities, along with head acceleration, are used to score SOV following the methods described in Sunderam, et al, 2007.
Using this novel MSMR microdrive system, we have observed simultaneous unit activity with

sleep-wake behavior correlates from three or more distinct SWRN structures over multi-day continuous recording sessions. Furthermore, using the 35 micron spatial resolution of the microdrive, activity from many different units across multiple subregions of each structure have been characterized over the span of days to weeks. To our knowledge, this is the first demonstration of both simultaneous NREM, REM, and Wake structure recordings in freely-behaving animals and multi-site, multi-region microdrive targeting with three or more non-parallel electrode trajectories. Detailed in this work are the methodologies used to implement the MSMR microdrive recording system, techniques of our state of vigilance (SOV) scoring, and histological validation of the chronically targeted brain structures.

Work Cited:
Datta S., J. Neurosci Biobehav Rev, 2007
Booth V. et al. Math Biosci. 250:54-68, 2014
Sunderam S. et al. J Neurosci Meth, 2007

Disclosures: M.W. Billard: None. **F. Bahari:** None. **J. Kimbugwe:** None. **K.D. Alloway:** None. **B.J. Gluckman:** None.

Poster

240. Sleep: Systems

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 240.11/KK11

Topic: F.08. Biological Rhythms and Sleep

Support: NIH IRTA Program

Title: Decline of long-range temporal correlations during sustained wakefulness in the human brain

Authors: *K. BAILEY[1], P. ACHERMANN[2], D. PLENZ[3], C. MEISEL[4]
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Abstract: Sleep is crucial for daytime functioning, cognitive performance and general well-being. These aspects of daily life are known to be impaired after extended wake, yet the underlying neuronal correlates have been difficult to identify. Accumulating evidence suggests that normal functioning of the brain is characterized by long-range temporal correlations (LRTCs) in cortex, which are supportive for decision-making and working memory tasks. Here we assess LRTCs in resting state human EEG data (27-channel system) during a 40-hour sleep deprivation experiment (n = 8 subjects) by evaluating the decay in autocorrelation and the scaling exponent of the detrended fluctuation analysis from EEG amplitude fluctuations. We find with both measures that LRTCs decline as sleep deprivation progresses. This decline becomes

evident when taking changes in signal power into appropriate consideration.
Our results demonstrate the importance of sleep to maintain LRTCs in the human brain. In complex networks, LRTCs naturally emerge in the vicinity of a critical state. The observation of declining LRTCs during wake thus provides additional support for our hypothesis that sleep reorganizes cortical networks towards critical dynamics for optimal functioning.

Disclosures: K. Bailey: None. **P. Achermann:** None. **D. Plenz:** None. **C. Meisel:** None.

Poster

240. Sleep: Systems

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 240.12/KK12

Topic: F.08. Biological Rhythms and Sleep

Title: A dichotomous interplay between long- and short-range temporal correlations shapes cortex dynamics across vigilance states

Authors: *C. MEISEL[1], V. VYAZOVSKIY[2], D. PLENZ[3]
[1]NIMH, Bethesda, MD; [2]Univ. of Oxford, Department of Physiology, United Kingdom; [3]Sect Critical Brain Dynamics, Natl. Inst. of Mental Health, NIH, Bethesda, MD

Abstract: Increasing evidence suggests that cortical dynamics during wake exhibits long-range temporal correlations suitable to integrate inputs over extended periods of time to increase the signal-to-noise ratio in decision-making and working memory tasks. Accordingly, deep sleep has been suggested as a state characterised by a breakdown of long-range correlations. Detailed measurements of neuronal timescales that support this view, however, have so far been lacking. Here we study the timescales of cortex dynamics from unit activity in frontal and parietal areas during wake, extended wake, REM sleep and NREM sleep in freely-behaving rats (n=20). We observe that the long-range temporal correlations associated with the slowly decaying autocorrelation of individual neuron activity during the awake state are abrogated during non-REM (NREM) sleep. Our results indicate the existence of two distinct dynamical states in terms of timescale dynamics in cortex: one which is characterised by slow timescales and dominates during wake and REM sleep, and a second one characterised by the absence of long-range temporal correlations predominantly during NREM sleep. We observe that both timescale regimes can co-exist and, in combination, lead to an apparent gradual decline of long timescales during extended wake which is restored after sleep.
Our results provide a missing link between the observed long timescales in individual neuron fluctuations during wake and the reported absence of long-range correlations during deep sleep in EEG and fMRI studies. They furthermore suggest a network-level function of sleep, to reorganize cortical networks towards states governed by slow cortex dynamics to ensure optimal function for the time awake.

Long-range temporal correlations, such as observed during wake, naturally arise in networks poised at criticality. Their intermittent or more permanent disruption during sleep deprivation or NREM sleep may consequently indicate a transient disruption of critical dynamics and all of its beneficial qualities for brain function.

Disclosures: C. Meisel: None. **V. Vyazovskiy:** None. **D. Plenz:** None.

Poster

240. Sleep: Systems

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 240.13/KK13

Topic: F.08. Biological Rhythms and Sleep

Support: JSPS KAKENHI Grant Number JP26507001

JSPS KAKENHI Grant Number JP17K00932

Title: Sleep-wake state dependence of Ca-permeable AMPA receptor expression in the rat cortex

Authors: *A. KARASHIMA[1,2], Y. MASUDA[2], A. NAKAMURA[2], H. TSUBOKAWA[3], N. KATAYAMA[2], M. NAKAO[2]
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Abstract: Recently, many researchers are interested in the relationship between sleep and synaptic plasticity, and they hypothesize that the synaptic connection becomes stronger during wakefulness and weaker during sleep. In this study, we performed in vitro experiments in order to confirm the hypothesis at the synaptic level. Adolescent rats (4 weeks old) were placed in a plastic cage in a sound-attenuated room with a 12:12-h light-dark cycle (light, 8:00 A.M. - 8:00 P.M.). The experimental animals were divided into 8 PM Group (they were sacrificed at 8:00 P.M.) and 8AM Group (they were sacrificed at 8:00 A.M.). In addition, we prepared two groups, which were sacrificed at the same time of day (10:00 A.M.), the first group after 2 h of spontaneous sleep (10 AM Sleep-ad-lib Group) and the second group after 2 h of sleep deprivation (SD) by gentle handling (10 AM Sleep-Dep Group). Whole-cell patch-clamp recordings were made from layer II/III pyramidal neurons of somatosensory cortex in acute slices. Trafficking of Ca-permeable AMPA (CP-AMPA) receptors are known to associate with synaptic potentiation in the hippocampus and cortex. Because CP-AMPA receptors are present only transiently, presence of the CP-AMPA receptors indicates that the synapses were recently potentiated. In this study, we assessed sensitivity to CP-AMPA receptor antagonist (Philanthotoxin 74: PhTx-74) and current-voltage (I-V) relationships of the underlying AMPA receptor's EPSCs. We found that i) PhTx-74 caused a significant reduction of AMPA receptor's

EPSC in 8 AM and 10 AM Sleep-Dep Groups and the antagonist did not have any significant effect on the EPSC amplitude in 8 PM and 10 AM Sleep-ad-lib Groups, ii) analysis of the I-V curve revealed a shift toward inward rectification in 8 AM and 10 AM-Sleep-Dep Groups, but I-V curves in 8 PM and 10 AM Sleep-ad-lib Groups were linear. Because rats in 8 AM and 10 AM Sleep-Dep Groups must spend more time in wake compared with those in 8 PM and 10 AM Sleep-ad-lib Groups just before they were sacrificed, these results suggest that CP-AMPA receptors are inserted into the synapse during wakefulness. They clearly support the hypothesis that synapses become widely potentiated during wakefulness in the cortex.

Disclosures: A. Karashima: None. **Y. Masuda:** None. **A. Nakamura:** None. **H. Tsubokawa:** None. **N. Katayama:** None. **M. Nakao:** None.

Poster

240. Sleep: Systems

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 240.14/KK14

Topic: F.08. Biological Rhythms and Sleep

Support: VA CDA BX002130 (JMM)

VA Merit Awards BX001356 (RWM)

VA Merit Awards BX002774 (RES)

VA Merit Awards BX001404 (RB)

NIMH R01 MH039683 (RWM)

NIMH T32 MH016259 (DA)

Title: Development and evaluation of an automated sleep spindle detection procedure for rodent EEG recordings

Authors: J. M. MCNALLY[1], F. KATSUKI[1], D. UYGUN[1], S. THANKACHAN[1], D. D. AGUILAR[1], R. E. BROWN[1], R. BASHEER[1], *R. E. STRECKER[2], R. W. MCCARLEY[1]
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Abstract: Sleep spindles are identified in EEG records as waxing and waning rhythmic oscillatory events between 8 and 15 Hz. Generated via corticothalamic network activity, these events represent a physiological hallmark of light non-REM sleep. Recent studies in rodents and humans show that sleep spindle density is increased following learning and correlated with memory consolidation. Spindle abnormalities have been observed in many neuropsychiatric

conditions and have been implicated in deficits in executive function and memory. Accordingly, there is a growing interest in the development of techniques to detect spindles reliably and accurately. While there are numerous descriptions of attempts to develop and optimize automated techniques for analysis of human EEG, far less has been reported regarding the much more difficult task of spindle detection in rodents. Here we describe the development of an automated paradigm for reliable and consistent detection of spindles from mouse EEG.
Spindle detection procedures were developed and tested using, as exemplars, 4h frontal EEG records from C57BL6 mice (n=6). Evaluating the performance of an automated paradigm necessitated defining a consensus agreement as to what constituted a true spindle. We began these efforts by tasking human scorers with manually (visually) identifying spindles in raw EEG records. This approach proved difficult, yielding minimal agreement between scorers (<20%). Consequently, human scoring was aided by comparison of 1) raw EEG, 2) bandpass filtered EEG (10-15Hz), and 3) RMS transform of data. Using this combined approach greatly increased consensus agreement between scorers (86.5%), and was utilized to provide a gold standard for development of our automated detection procedure. Briefly, this paradigm utilized the RMS transform of bandpass filtered data, as above. Putative spindle peaks were identified via crossing of an upper threshold value, based on the mean of background spindle frequency activity for each mouse. Spindle duration was defined as the sum of time before and after the detected peak till the data drops below a lower threshold value (minimum duration of 0.5s). All threshold and duration criteria were tuned to best match consensus human scoring.
Overall, we found that 92.8%±0.5 of events consensus scored as spindles manually were also scored as spindles by the algorithm. Ongoing experiments are testing the external validity of this spindle detection algorithm using pharmacological and behavioral manipulations. While this procedure is still actively being refined, we conclude our automated paradigm is highly capable of detecting events scored as spindles by human experts.

Disclosures: **J.M. McNally:** None. **F. Katsuki:** None. **D. Uygun:** None. **S. Thankachan:** None. **D.D. Aguilar:** None. **R.E. Brown:** None. **R. Basheer:** None. **R.E. Strecker:** None. **R.W. McCarley:** None.

Poster

240. Sleep: Systems

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 240.15/KK15

Topic: F.08. Biological Rhythms and Sleep

Support: (NIH grant HL-047600)

Title: Noradrenergic termination patterns on pontomedullary hypoglossal premotor neurons

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Abstract: In obstructive sleep apnea (OSA) patients, contraction of tongue muscles innervated by the hypoglossal (XII) nerve protects the upper airway from collapse. Norepinephrine (NE) activates XII motoneurons during wakefulness but its release is reduced during sleep which contributes to OSA. In addition to their excitatory connections with motoneurons, NE projections target brain regions that contain XII premotor neurons. Our goal was to determine whether different groups of XII premotor neurons are differently innervated by NE afferents.
Seven Long-Evans rats received 5-10 nl injections of B subunit of cholera toxin (CtB; a retrograde tracer) into the XII nucleus. After seven days, they were perfused and pontomedullary sections were subjected to immunohistochemistry for dopamine-beta hydroxylase (DBH), a marker for nor- and epinephrine, and CtB. Black-labeled DBH terminals were observed adjacent to brown-labeled for CtB XII premotor neurons. We examined premotor cells located in caudal and rostral intermediate medullary reticular regions (cIRt/rIRt), ventral medullary gigantocellular region (GCv), pontine peritrigeminal region (PeriV), and parabrachial region (ParaB). Twenty CtB cells were selected from each region and DBH terminals adjacent to the cell bodies/proximal dendrites were counted.
DBH terminal numbers per premotor neuron significantly differed among the premotor groups (mean±SE): ParaB (3.8±0.015)≈GCv (3.7±0.02)>PeriV (2.9±0.01)>cIRt (2.3±0.015)≈rIRt (2.2±0.01). ParaB/Gcv differed from PeriV at p=0.004-0.009.
Thus, XII premotor groups have different densities of catecholaminergic innervation. NE may particularly strongly affect ParaB and GCv neurons. The latter may mediate signals associated with rapid eye movement sleep and/or ingestive behaviors. The PeriV region which had an intermediate level of catecholaminergic innervation controls multiple cranial motor nuclei and coordinates orofacial movements. Both ParaB and IRt groups may contribute to inspiratory modulation of tongue muscle activity which helps maintain upper airway patency. Additional information about adrenergic receptors should help further define the effects of NE on these XII premotor groups.

Disclosures: C. Boyle: None. **A. Parkar:** None. **L. Kubin:** None.

Poster

240. Sleep: Systems

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 240.16/KK16

Topic: F.08. Biological Rhythms and Sleep

Support: Human Brain Project, SGA1, Horizon 2020

ERC Advanced investigator grant

Title: Brain state dependent firing rate modulation in single neurons of naturally sleeping rats

Authors: D. I. KAPLAN[1], J. SHIN[1], J. SEIBT[2], M. E. LARKUM[1], *G. DORON[1]
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Abstract: Mammalian sleep is characterized by cyclic transitions between periods of highly synchronized and desynchronized cortical activity. These brain states are defined by their electroencephalographic (EEG) signatures, where the desynchronized rapid eye movement (REM) phase displays low power, high frequency spectral activity while the synchronized, non-REM sleep is identifiable by high power, low frequency oscillations. The canonical view states that the slow oscillations during non-REM sleep reflect synchronous activity across a broad population of neurons, while desynchronised EEG in REM sleep indicates a lack of coherent activity. However, this has not been systematically investigated during natural sleep. In order to answer this question we performed juxtacellular recordings of single neurons combined with EEG and local field potential (LFP) in the somatosensory cortex of sleeping rats. We obtained data from both superficial and deep cortical layers, from putative regular and fast spiking neurons. Preliminary results indicate that fast spiking neurons show a stronger correlation with population activity during non-REM sleep, as measured with LFP. We also observed that firing rate of regular spiking neurons was much higher in deep layers and that many superficial cells were in fact silent. We are currently quantifying the state dependent changes in neuronal firing rate and population coupling across cortical layers and between different neuronal classes. Our results suggest that contrary to current understanding, distinct neuronal subtypes are differently coupled to population activity during sleep states and that inhibitory neurons might play a significant role in sleep state dynamics.

Disclosures: D.I. Kaplan: None. **J. Shin:** None. **J. Seibt:** None. **M.E. Larkum:** None. **G. Doron:** None.

Poster

240. Sleep: Systems

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 240.17/KK17

Topic: F.08. Biological Rhythms and Sleep

Support: Doris Duke Charitable Foundation

NIH 1DP2HD087955

Title: Characterizing network dynamics differentiating fast and slow cortical spindles using electrocorticography (ECoG)

Authors: *K. GANGULY[1], E. F. CHANG[2], N. NATRAJ[3]
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Abstract: Spindles, brief 8-16Hz oscillatory electrical activity in NREM sleep, are thought to be a hallmark of motor learning and memory consolidation. Research has characterized two different types of spindles: fast spindles (12-16Hz) localized over motor areas and slower spindles (8-12Hz) localized generally over prefrontal areas (Mölle et al., 2011). Typically, these characterizations have been carried out using electroencephalography (EEG), which limit characterization of the spatial extent of fast and slow spindles. While a few studies have utilized depth EEG to characterize spindles over mesial brain regions (Andrillon et al., 2011), spindle properties at the cortex is not totally understood. In addition, the relationship between spindles and other sleep processes such as cortical slow waves and hippocampal ripples have typically been evaluated in relative spatial isolation (Staresina et al., 2015). It is unclear for instance whether global background sleep oscillations sufficiently distinguish between cortical fast and slow spindles. To address these issues, we analyzed continuous and overnight multi-site electrocorticography (ECoG) sleep data from 4 patients undergoing neurosurgical evaluation for epilepsy. We used a combination of the matching pursuit algorithm and Laplacian referencing (Carvalhaes and de Barros, 2015) to precisely characterize the spatiotemporal extent of fast and slow spindle frequency responses. Broadly, we found that fast spindles were primarily localized to the motor and premotor strip whereas slow spindles dominated the hippocampus, prefrontal, temporal and parietal areas. Interestingly, a multivariate pattern recognition framework (L2 regularized Support Vector Machine) showed significant spatiotemporal differences in background whole brain sleep oscillations when comparing slow and fast spindles (i.e. relative to the spindle peak power). Together, our findings shed new light on the large-scale network states associated with slow and fast cortical spindles.
Andrillon T et al. (2011) Sleep spindles in humans: insights from intracranial EEG and unit recordings. J. Neurosci. Carvalhaes C, de Barros JA (2015) The surface Laplacian technique in EEG. Int. J. Psychophysiology. KS SC et al. (2016) Comparison of matching pursuit algorithm with other signal processing techniques for computation of the time-frequency power spectrum of brain signals. J. Neurosci. 36:3399-3408. Mölle M et al. (2011) Fast and slow spindles during the sleep slow oscillation. Sleep Staresina BP et al. (2015) Hierarchical nesting of slow oscillations, spindles and ripples in the human hippocampus during sleep. Nat. neurosci.

Disclosures: K. Ganguly: None. **E.F. Chang:** None. **N. Natraj:** None.

Poster

240. Sleep: Systems

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 240.18/KK18

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

Support: NIH Grant HD63071

NIH Grant HD81168

Title: Self-monitoring of myoclonic twitches by the inferior olive and lateral reticular nucleus: Evidence of corollary discharge

Authors: *D. MUKHERJEE, G. SOKOLOFF, M. S. BLUMBERG
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Abstract: Developing mammals receive two kinds of proprioceptive input. One arises from stimulation in the external environment ("exafference"), such as that from a mother or littermate. The other arises from self-produced movements ("reafference"), especially those associated with the myoclonic twitches that occur abundantly during active (or REM) sleep. Neural recordings in infant rats have established that exafferent and reafferent proprioceptive inputs activate sensorimotor structures throughout the brain, but it is not known whether twitches are also accompanied by the production of corollary discharge (or efference copy) signals that inform the nervous system that the movements are self-generated. Based on recent recording studies in the red nucleus and cerebellum, we hypothesized that two precerebellar nuclei—the inferior olive (IO) and the lateral reticular nucleus (LRN)—receive twitch-related corollary discharge signals. Here, we test this hypothesis by recording the twitch-related activity of the IO and LRN during sleep and wake in infant rats. In the majority of IO units and in a subset of LRN units, neural activity was particularly pronounced at the time of twitch onset. This twitch-related activity was remarkably sharp and precise, reaching a peak in firing rate within 0-5 ms after twitch onset. This unique pattern of peri-twitch activity suggests that, unlike sensory structures that receive reafference from twitches, these two precerebellar nuclei receive corollary discharge signals from areas involved in the production of twitches. Next, we identified non-overlapping premotor areas in the midbrain mesodiencephalic junction that send projections to the IO and LRN; these areas include the red nucleus, which projects to the LRN, and the rostral nucleus of Darkschewitsch, which projects to the IO. Recordings from those areas indicate that they contribute to the production of twitches. All together, these results demonstrate for the first time that, due to the presence of corollary discharge, the infant brain has the capacity to distinguish between exafferent stimulation and twitch-related reafference. This capacity may underlie the developing infant's burgeoning ability to distinguish between other-generated and self-generated movements.

Disclosures: D. Mukherjee: None. **G. Sokoloff:** None. **M.S. Blumberg:** None.

Poster

240. Sleep: Systems

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 240.19/KK19

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

Support: NIH Grant R37-HD081168

Fulbright International Program

Title: Myoclonic twitches during active sleep drive coordinated activity in the newborn rat cortico-hippocampal network

Authors: *C. DEL RIO BERMUDEZ, J. KIM, G. SOKOLOFF, M. S. BLUMBERG
Psychological and Brain Sci., Univ. of Iowa, Iowa City, IA

Abstract: Active sleep (AS, or REM sleep), which is most abundant during the perinatal period, has long been considered an important contributor to early brain development. Using infant rats, we recently showed that AS facilitates the expression of functional connectivity in the network that comprises the hippocampus and the red nucleus, a brainstem sensorimotor structure (Del Rio-Bermudez, Current Biology, 2017). Specifically, when continuous oscillatory activity emerged by the end of the second postnatal week, coupled oscillations in the theta-frequency band (4-7Hz) in both structures were only evident during AS. Critically, before emergence of continuous oscillatory activity, brief bursts of neural activity in the hippocampus and associated networks—including the red nucleus and somatosensory cortex—were observed in close temporal association with AS-related myoclonic twitches. It was not clear from that study, however, whether twitches are necessary for the earlier expression of coordinated activity within hippocampal-dependent networks. Here we test the hypothesis that twitches drive functional connectivity between hippocampal CA1 and the barrel field of somatosensory cortex (S1BF). Using unanesthetized 8-day-old rats, we recorded from both structures to characterize twitch- and state-dependent spontaneous activity. Preliminary findings are indicating that spontaneous multiunit activity (MUA) and oscillatory events in the local field potentials (LFPs) of both S1BF and CA1 are significantly higher during periods of twitching. In addition, when whisker twitches occur, they trigger more coherent neural activity between S1BF and CA1. Therefore, our findings are supporting the hypothesis that AS-related twitching helps to synchronize activity between the somatosensory cortex and hippocampus before continuous oscillations emerge.

Disclosures: C. Del Rio Bermudez: None. **J. Kim:** None. **G. Sokoloff:** None. **M.S. Blumberg:** None.

Poster

240. Sleep: Systems

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 240.20/KK20

Topic: F.08. Biological Rhythms and Sleep

Title: Transient prefrontal delta activities and their dynamics during REM sleep in mice

Authors: *B. KIM[1], J. CHOI[2]
[1]Korea Inst. of Sci. and Technol., Seoul, Korea, Republic of; [2]Korea Inst. of Sci. and Tech. (KIST), Seoul, Korea, Republic of

Abstract: The function of sleep is consolidating learning-dependent neural activities while downscaling general connections formed during wake period. Although taking minor portion of the total sleep, REM sleep has been revealed to efficiently accomplish the downscaling function, reducing the number of synapses and slow wave activity. Also, REM sleep is known to serve important role in memory consolidation, however, circuit mechanisms realizing these functions remain to be unveiled. In case of NREM sleep, the major portion of sleep, was known to improve memory through the timely coordinated network oscillations. The transiently and orderly occurring slow and fast brain rhythms generate a short time window of synaptic potentiation for making meaningful connection. Compared to NREM, electrophysiological activity of REM sleep in rodent was less explored and regarded as one homogeneous and continuous theta oscillation (5-10 Hz) generated in hippocampus. For now, the only differentiated EEG activity during REM was period of fast theta rhythm, categorizing as phasic REM. We recently found that narrow band delta activities at 2-4 Hz were transiently (~ 5 s) observed in prefrontal cortex (PFC) during REM sleep. The 4 Hz rhythm especially attract us to investigate since the 4 Hz was known to transiently occur when mice perform working memory tasks during wake period. As recent studies suggest PFC interacts with hippocampus by 2-4 Hz oscillation, transient PFC delta activities may be involved in memory processing during REM.Here we characterize temporal dynamics of transient delta oscillations and accompanying EEG activities of them. We recorded EEG from 38 channel electrodes covering whole cortical area in mice during REM sleep. Delta oscillations were detected using power in delta band (2 - 5Hz) of power spectral density at PFC lead. During period showing delta activities, we calculated cross-frequency-coupling between the delta activities and fast oscillations in PFC and central cortex. We found that slow gamma (30 - 40Hz) was modulated by the delta activities exclusively in PFC. Then we investigated how cortico-cortical connectivity of 38 channel EEG changes after PFC delta occurred using phase synchronization index. Our data suggest distinct role of transient delta oscillation for basis of memory consolidation during REM sleep

Disclosures: B. Kim: None. **J. Choi:** None.

Poster

240. Sleep: Systems

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 240.21/KK21

Topic: F.08. Biological Rhythms and Sleep

Support: Foundation for Prader-Willi Research

Title: Oxytocin neurons promote wake in a mouse model of Prader-Willi Syndrome

Authors: *C. E. MAHONEY[1], D. M. HAWRYLUK[1], V. GRINEVICH[2], T. E. SCAMMELL[1]
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Abstract: Background. Daytime sleepiness, disrupted sleep, and cataplexy-like falling episodes are common in Prader-Willi Syndrome (PWS), but the cause of these symptoms is unknown. Patients with PWS have fewer oxytocin neurons, but the effects of oxytocin on sleep/wake behavior are not well understood. Oxytocin activates the orexin neurons, and orexins activate the oxytocin neurons. We hypothesize that this positive feedback loop normally promotes wakefulness and regulates sleep, and low oxytocin and orexin signaling in PWS may contribute to daytime sleepiness, abnormal REM sleep, and cataplexy. **Methods and Results.** Using optogenetics and EEG, EMG, and video recordings, we examined sleep/wake behavior in wild type, orexin null and MAGEL2 null mice, a validated model of PWS. We selectively expressed a light sensitive channel, channelrhodopsin 2 (ChR2), in oxytocin neurons of the PVH by co-injecting rAAV 1/2- expressing Cre recombinase under the control of the oxytocin promoter with the Cre-dependent AAV 8-EF1a-DIO-ChR2-mCherry. Optical fibers were implanted to illuminate oxytocin axons in the lateral hypothalamus. **Conclusion.** Blue-light activation of oxytocin axon terminals in the lateral hypothalamus rapidly wakes mice of each genotype from sleep and increases the amount of wake during the light period. **Summary.** These results suggest that oxytocin activates wake-promoting systems in the lateral hypothalamus, but this response does not require the orexin neuropeptides. From a clinical perspective, enhancing oxytocin signaling may help people with PWS maintain wakefulness throughout the day.

Disclosures: C.E. Mahoney: None. **D.M. Hawryluk:** None. **V. Grinevich:** None. **T.E. Scammell:** None.

Poster

240. Sleep: Systems

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 240.22/DP09/KK22 (Dynamic Poster)

Topic: F.08. Biological Rhythms and Sleep

Support: NS098541

NS052287

VA-1BX000798

Title: Visualizing MCH neurons and their projections using CLARITY

Authors: *P. J. SHIROMANI[1], S. LUO[2], C. A. BLANCO-CENTURION[3], M. LIU[4], C. F. ELIAS[5]
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Abstract: Introduction: We are familiar with the well-established protocol for immunohistochemistry (e.g. generating thin sections, such as the brain, on a cryostat or sliding microtome, exposing the tissue to antibody, and subsequently mounting these sections onto slides for visualization under a microscope). The new approach is to render the tissue transparent, scan it with a light-sheet microscope, and allow the software to compile a 3D image of the scanned images. The appeal of the new approach is that it allows visualization of the cellular network in the intact brain. This is likely to yield new information that may not be readily evident from 2D images. We now use the advanced CLARITY method (Tomer *et al.*, 2014) to visualize the distribution of MCH neurons in 3D.
Methods: A mouse brain containing MCH-EYFP neurons was cleared using the X-CLARITY Tissue Clearing System and equilibrated in refractive index matching solution to allow light to pass through with little or no scattering. The transparent tissue was scanned (896 sheets in 3 um increments; hypothalamus) with a Zeiss LightSheet microscope, and the images were stitched to yield a final image.
Results: Viewing the MCH somata and their fibers in a single block of tissue revealed for the first time a pattern of MCH somata and projections: Some MCH somata project to anterior brain regions, while other clusters project to brainstem regions. This indicates a topographical difference in the efferent projections of the MCH neurons.
Conclusion: The MCH neurons are sleep-active and sleep is induced when these neurons are optogenetically activated in both mice and rats. To understand how the MCH neurons regulate sleep it is important to clearly identify their location and projections. This is the first study to

reconstruct neurons implicated in sleep in an intact block of brain. The impact of the results is that the 3D image revealed a pattern not evident in traditional microtome based histology methods. The potential of the new tissue clearing methods is that it accelerates discovery of brain circuits underlying sleep.

Disclosures: P.J. Shiromani: None. **S. Luo:** None. **C.A. Blanco-Centurion:** None. **M. Liu:** None. **C.F. Elias:** None.

Poster

240. Sleep: Systems

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 240.23/KK23

Topic: F.08. Biological Rhythms and Sleep

Support: NIH R01 EY024067

Simons Collaboration for the Global Brain

L'Oréal USA for Women in Science Postdoctoral Fellowship

DARPA SUBNETS program under Cooperative Agreement Number W911NF-14-2-0043

Title: An instrumented volume for continuous neurobehavioral tracking system in unrestrained non-human primates

Authors: *S. QIAO[1], A. L. ORSBORN[1], A. P. DORA[2], J. KLEINBART[1], B. PESARAN[1]
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Abstract: The primate brain contains massive numbers of neurons connected across distributed networks whose activity gives rise to our mental life. The connections between neurons in the brain networks undergo activity-dependent plasticity dynamically increasing and decreasing in strength. However, the organization of neuronal dynamics in the primate brain has primarily been performed under restrained lab conditions. Neural activity during naturalistic, unrestrained behaviors over time has been limited by technical challenges and remains poorly understood. To meet this need, we have developed an instrumented volume for continuous neurobehavioral tracking in fully, unrestrained non-human primates (NHPs). The instrumented volume is a primate activity enclosure module (33" w × 80" h × 35" d), equipped with synchronized marker-based motion capture (MOCAP, Motion Analysis), 96-channel broadband wireless neural recording (Blackrock Microsystems), and video reference camera systems. Neural recordings at 30 kHz can be streamed continuously for over 12 hours. Each module in the volume has the occupancy (30" w × 50" h × 29" d) and can be assembled to form larger volumes in a lattice

structure by removing the interior panels. Occupants wear a custom-designed tracking suit and helmet to protect the brain implant and wireless transmitter. Retroreflective markers are attached to both the suit and helmet for behavior tracking by up to 16 calibrated MOCAP cameras positioned along the edges and corners of the volume. Here, we present preliminary results of how neuronal dynamics change during natural sleep in a rhesus macaque implanted over sensorimotor cortices (M1, S1, PMd, PMv) with multi-scale ECoG-field-spiking electrophysiology monitoring capability (244 ECoG channels spaced 750 µm, 32 spike/field channels spaced at 1.5 mm). We will focus on reporting the spatiotemporal dynamics of sleep spindles and their activity and correlations observed across the various spatial measurement scales. An instrumented volume for continuous neurobehavioral tracking opens the door to studying the short-, medium and long-term neuronal dynamics across large-scale brain networks during naturalistic unrestrained behaviors during waking and sleep. This research was partially funded by the Defense Advanced Research Projects Agency (DARPA) under Cooperative Agreement Number W911NF-14-2-0043, issued by the Army Research Office contracting office in support of DARPA'S SUBNETS program. The views, opinions, and/or findings expressed are those of the authors and should not be interpreted as representing the official views or policies of the Department of Defense or the U.S. Government.

Disclosures: S. Qiao: None. **A.L. Orsborn:** None. **A.P. Dora:** None. **J. Kleinbart:** None. **B. Pesaran:** None.

Poster

240. Sleep: Systems

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 240.24/DP10/KK24 (Dynamic Poster)

Topic: F.08. Biological Rhythms and Sleep

Title: Automatic sleep stage classification using only electrocardiography (ECG) data, deep learning, and a novel and robust R wave detection algorithm

Authors: *A. M. JONES[1], B. R. SHETH[2]
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Abstract: The central tenet guiding our research is that sleep is of, by, and for the brain—and the body. To that end, our objective is to develop an automated method of accurately determining sleep stages using only ECG data, with the practical motivation of creating an efficient and inexpensive alternative to polysomnography. Our prior efforts ran into several issues. To create a generalizable model, we used 1000+ subjects from the National Sleep Research Resource's databases. Since none of the ECG to RR processing tools on hand could reliably batch convert this many recordings, we made improvements to the Pan-Tompkins

algorithm to make it more robust to noise. However, given the sheer quantity and variable quality of the data, even the improved algorithm failed more often than expected. In particular, it would occasionally get confused due to unusually long periods of noise or silence, abrupt changes in R wave amplitude, and periodic noise, and then only provide an RR time series for the beginning of the night, which hampered machine learning efforts. Therefore, we developed and rigorously tested a new ECG to RR algorithm that—without any case-by-case data quality review or manual adjustments—brought the R wave detection rate over 95%, except where no R waves are visually perceivable. The new algorithm makes no *a priori* assumptions about data quality, heartbeat similarity, or even the length of gaps. Major improvements include: i) automatically detecting and removing various types of noise; ii) measuring the local (short-term) signal variance in a longer, sliding, empirically obtained window which pinpoints potential R waves, even with noise and T waves of larger amplitude; iii) using autocorrelation to find the periodic heartbeats buried in noise; iv) hierarchically processing epochs depending on signal quality, by bootstrapping information from higher quality epochs to process lower quality epochs; and v) iteratively generating a record-specific model of where beats are likely to occur. Next, we aimed to automatically label sleep stage from the RR time series just obtained. Popular machine learning algorithms, e.g. SVM, naive Bayes, and decision trees, assume time independence, which is a poor assumption for sleep stages. At short time scales, there is continuity of sleep stage, and certain between-stage transitions are more frequent; over longer time scales, there is an orderly cycle of sleep stages. Therefore, a deep learning, time-dependent recurrent neural network is desirable, as it can learn the factors necessary to determine sleep stage for a given period, while simultaneously using past and future information. Our results are presented here.

Disclosures: **A.M. Jones:** None. **B.R. Sheth:** None.

Poster

240. Sleep: Systems

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 240.25/KK25

Topic: F.08. Biological Rhythms and Sleep

Support: NINDS R37 NS21135

Title: Network topology of slow wave propagation during NREM sleep: Evidence from human intracranial EEG

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Abstract: Slow waves (SW) are a defining feature of non-rapid eye movement (NREM) sleep and associated with other states of reduced or absent consciousness; for instance, due to anesthesia, metabolic abnormalities, or structural brain damage. Classically, sleep stages have been considered global brain states; however, recent studies in intracranial electroencephalography (iEEG) have shown that most SW, as well as other sleep signals, are actually local events. Furthermore, these studies show that SW potentially originate in anterior regions and propagate along a dorso-posterior and then ventro-medial path (Nir, 2011). To further examine the spatial dispersion of SW, a trained expert performed sleep staging with polysomnography (Kales and Rechtschaffen, 1968) from seven epilepsy patients implanted with iEEG. We automatically detected SW events in scalp and intracranial EEG and applied Bayesian inference to determine the probability of observing a SW in some channel given the presence of a SW in another. This probabilistic dependence was computed for every pair of electrodes and during each sleep stage (Awake, NREM 1-4, and REM) allowing us to derive a weighted, directed network of SW connectivity for each state. Using graph theoretical tools, we find features of this SW network topology are distinctive of each sleep stage, and identify hub regions, which may be particularly critical to the generation or transmission of SWs. In summary, this novel approach provides insight into the coordinated interaction of brain regions during NREM sleep.

Disclosures: L.D. Harriger: None. **S.T. Horan:** None. **B.A. Mander:** None. **M.A. Yassa:** None. **J.S. Lowengrub:** None. **R.T. Knight:** None. **M.P. Walker:** None. **J.J. Lin:** None.

Poster

240. Sleep: Systems

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 240.26/KK26

Topic: F.08. Biological Rhythms and Sleep

Support: NIH Grant NR013693

Title: Distorted insular responses to the Valsalva maneuver in Obstructive sleep apnea

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Abstract: Introduction: The insular cortex includes five main gyri with differing roles regulating autonomic responses, with sympathetic challenges leading to greater neural activity in anterior vs. posterior and in right vs. left structures. Since autonomic regulation is impaired in obstructive sleep apnea (OSA), functional organization of the insula, structurally injured in the condition, may be affected. We examined that organization during an autonomic challenge, the Vaslsalva maneuver, using functional magnetic resonance imaging (fMRI). **Methods:** We studied 37 newly-diagnosed, untreated OSA (mean age±SD: 46.4±8.7years; mean AHI±SD:35.8±19.2; 31 male) and 56 healthy control (47.2±9.1years; 36 male) participants. Subjects performed four Valsalva maneuvers (1 min interval, duration 18s, pressure 30mmHg) during fMRI scanning. The five major gyri were parcelized from high-resolution T1-weighted scans: Three short (anterior) gyri and two long (posterior) gyri: anterior short gyrus (ASG), mid short gyrus (MSG), posterior short gyrus (PSG), anterior long gyrus (ALG), and posterior long gyrus (PLG). Timetrends from each gyri were extracted and assessed using repeated measures ANOVA. **Results:** Insular gyri functional organization differed in OSA, relative to controls. While controls showed sustained activation in right vs. left in all but the ASG, OSA subjects showed only transient right>left activation during the first 4 s of the expiratory period. Left side anterior-to-posterior organization was similar in OSA and controls, with the ASG showing the greatest responses, followed by MSG/PSG, then ALG/PLG. However, in OSA, the right ALG showed similar responses to the short gyri, in contrast with controls showing lower ALG responses than the short gyri. **Conclusions:** Reduced right-sided dominance appears in OSA during the sympathetic phase of the Valsalva maneuver. Combined with altered right-side ALG responses, the outcomes may reflect the higher resting-state sympathetic tone and weaker cardiovascular responses to the same challenges in the condition.

Disclosures: A.M. Aguila: None. **J.A. Ogren:** None. **R. Aysola:** None. **R. Kumar:** None. **R.M. Harper:** None. **P.M. Macey:** None.

Poster

240. Sleep: Systems

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 240.27/KK27

Topic: F.08. Biological Rhythms and Sleep

Support: R01 HL109706

TR001082

R01HL132150

Title: Rise time changes in delta power after sleep restriction

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Abstract: Short sleep schedules are commonly maintained to accommodate work/school and social demands resulting in chronic sleep loss for millions of people worldwide. These short sleep schedules have been shown to alter sleep architecture by reducing sleep latency, minutes of Stage 2 and REM sleep, and number and duration of awakenings while increasing sleep drive. The aim of the current analyses was to investigate the changes in rise time of delta power in the first 30 min of the sleep opportunity—a marker of homeostatic sleep drive—across 7 days of a short sleep opportunity versus an adequate sleep opportunity control. Twenty-two healthy adults (11 females) aged 24.3±4.6y (mean±SD) were randomized into the control condition (9h sleep/night) or the sleep restriction condition (5h sleep/night) for 7 days. Prior to each condition, subjects maintained at home 9h sleep/night schedules for a week and then were scheduled to 3 in-laboratory baseline nights of 9h sleep/night. Delta power was examined in 2 min bins for the first 30 min of sleep on days 1-2 and days 5-7 of sleep restriction and equivalent days for the control condition. ANOVA analysis revealed a main effect of minute bins and night for the sleep restriction condition. Delta power was significantly higher on days 1-2 and 5-7 of sleep restriction compared to baseline. This increase in power occurred for the first 18 minutes of sleep on days 1-2 and up to the 30 min examined for days 5-7 ($p<0.05$). The control condition generally showed consistent delta power across days. Overall, these findings are consistent with an increase in homeostatic sleep pressure for the sleep restriction condition compared to baseline.

Disclosures: S.J. Morton: None. **C.M. Depner:** None. **E.L. Melanson:** None. **J.R. Guzzetti:** None. **K.P. Wright:** 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, Office of Naval Research, PAC-12, Phillips Inc., CurAegis Technologies. F. Consulting Fees (e.g., advisory boards); NIH, CurAegis Technologies. Other; American College of Chest Physicians, The Obesity Society, Obesity Medicine Association.

Poster

240. Sleep: Systems

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 240.28/KK28

Topic: F.08. Biological Rhythms and Sleep

Support: Swiss National Science Foundation #168567

Title: Regional pattern of high-density electroencephalographic activity in REM sleep behavior disorder

Authors: *A. VALOMON[1], S. G. JONES[4], B. A. RIEDNER[5], R. GOODPASTER[6], G. TONONI[5], R. M. BENCA[7], D. T. PLANTE[2], M. BOLY[2,3]
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Abstract: Background: Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia in which patients are “enacting their dreams”. This disorder is often accompanied by REM sleep abnormalities, such as a loss of muscle atonia. However, the precise regional distribution of neuronal activity during NREM sleep and REM sleep in RBD patients is unknown. We here investigated topographical differences in NREM and REM sleep between RBD patients and controls using high density electroencephalography recordings (hdEEG), a technique providing high temporal and spatial resolution.
Methods: 8 RBD patients (3 women, mean age 49 y) and 8 sex- and age- matched controls underwent polysomnography that used 256-channel hdEEG (Electrical Geodesics Inc.), as well as standard monitoring with EOG, submental and tibial EMG, ECG, and respiratory sensors. Sleep staging was performed according to standard criteria by a registered sleep technologist. Epochs of steady stage N2-3 NREM and REM sleep were extracted, EEG data was filtered from 1-40 Hz and average-referenced. Clean epochs and channels were selected and independent component analysis (ICA) was applied to remove physiological noise during REM sleep. Topographical values of slow wave activity (SWA: 1-4Hz), theta (4-8Hz), alpha (8-12Hz), spindle (12-15Hz), beta (15-25Hz) and gamma (25-40Hz) powers were converted to 2D images and analyzed with statistical parametric and non-parametric mapping. Peak statistics of topographical differences were corrected for multiple comparisons using family-wise error rate (FWE).
Results: At the group level, compared to controls, patients displayed longer latency to reach REM sleep ($p<0.01$ two-sample t-test), but similar total sleep time, sleep efficiency and percentage of each sleep stage. No topographical differences in any frequency bands were found in REM sleep, to the exception of a trend for a reduction of delta power in central posterior regions, not surviving multiple comparisons. In NREM sleep, compared to controls, patients with RBD showed decreased SWA over central posterior regions (surviving FWE-corrected $p<0.05$ on the left). In RBD patients compared to controls, gamma activity in central regions and alpha activity in posterior regions were significantly reduced as well.
Discussion: Our preliminary findings suggest that decreased delta power during NREM and potentially REM sleep in scalp regions facing motor cortex might predispose RBD patients to motor behaviors during sleep. Future analyses using source localization reconstruction will be conducted to specify the cortical origins of the observed decrease in SWA in RBD subjects compared to healthy volunteers.

Disclosures: A. Valomon: None. **S.G. Jones:** None. **B.A. Riedner:** None. **R. Goodpaster:** None. **G. Tononi:** None. **R.M. Benca:** None. **D.T. Plante:** None. **M. Boly:** None.

Poster

241. Sleep: Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 241.01/KK29

Topic: F.08. Biological Rhythms and Sleep

Support: Howard Hughes Medical Institute 10147

NINDS Grant F31NS100519

Title: Conserved neuropeptides drive stress-induced sleep in *C. elegans*

Authors: *R. D. NATH, P. W. STERNBERG
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Abstract: Sleep is a genetically encoded and evolutionarily conserved behavioral state where multiple behaviors must be shut down. To determine the complete molecular architecture by which an animal shuts down multiple behaviors we used *C. elegans* as a model system because it is genetically tractable, has a fully-mapped connectome, and an experimentally accessible sleep state. In *C. elegans*, stress, such as heat shock, induces sleep by EGF-signaling. Sleep in *C. elegans* is characterized by inhibition of eating, defecation, movement, and stimulus response. To induce sleep EGF-signaling primarily requires a single neuron (ALA), which is a neurosecretory cell that loosely parallels the hypothalamus: it is peptidergic, regulates *C. elegans* behavior, and expresses many neuropeptide-encoding gene. We wanted to know how this neurosecretory cell induces sleep. We found that ALA coordinates the inhibition of multiple physiological processes with neuropeptides. Of the many ALA transcribed neuropeptide genes we found three, *flp-13*, *nlp-8*, *flp-24*, that each regulate a specific set of sleep-associated behaviors. Loss-of-function data indicate that *flp-13*, *nlp-8*, and *flp-24* work together to induce sleep. Conditional overexpression of each neuropeptide gene revealed that each gene was sufficient to shut down a specific set of sleep-associated behaviors. These data indicate that each neuropeptide gene has a specific site-of-action. Interestingly, one of these neuropeptides, *nlp-8*, is the only annotated instance of tachykinin in the *C. elegans* genome. The tachykinin neuropeptide family is found throughout bilaterians and regulates many processes and behaviors: the immune system, the gastrointestinal tract, inflammation, aggression, and pain. Overexpression analysis revealed that the tachykinin neuropeptides encoded by *nlp-8* individually inhibit behavior. The *C. elegans* genome encodes three tachykinin-related receptors (*tkr-1*, *tkr-2*, *tkr-3*), which are homologous to vertebrate tachykinin receptors. We found a partial suppression of *nlp-8* inhibition of locomotion in the *tkr-1*; *tkr-2* double null-mutant. These results support the hypothesis that *C. elegans* stress-induced sleep represents a form of sickness sleep, given tachykinins' broad role in inflammation and sickness in animals. Taken together, these results raise the possibility that tachykinin has an ancestral role in sleep-regulation.

Disclosures: **R.D. Nath:** None. **P.W. Sternberg:** None.

Poster

241. Sleep: Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 241.02/KK30

Topic: F.08. Biological Rhythms and Sleep

Support: USD SURE Program

HHMI Visiting Scientist Program

Title: Dopaminergic modulation of sleep is independent of feeding in *Drosophila*

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Abstract: Neuromodulators such as serotonin and dopamine (DA) have previously been implicated in behaviors such as sleep and feeding across vertebrates and invertebrates. The majority of the dopaminergic neurons in the fly brain project to an associative learning network called the mushroom body (MB), modulating the synaptic strength of connections within. The MB has been implicated in many motivated behaviors, including decision-making and sleep. Approximately 2,000 kenyon cells (KCs) make up the lobes of the MB and synapse onto MB output neurons (MBONs). Transgenic activation of clusters of DA neurons have been found to result in significant sleep deficits in Drosophila melanogaster. In order to ascertain whether the observed sleep deficits resulting from DA neuron activation resulted from dopaminergic regulation of a drive to forage for food, a comprehensive screen of all MB DANs and MBONs was conducted. To this end, Split-GAL4 driver lines, specifying the targeted dopamine neuron clusters previously tested for sleep phenotypes, were crossed with UAS-dTRPA1 lines. Progeny, now expressing dTRPA1 channels in these targeted dopamine neuron clusters, were collected and tested with half of male progeny on blue food at 21°C and the other half at 29°C, in which the selected neuron cluster was activated. Feeding levels resulting from activation of all MB DA neuron clusters were compared spectrophotometrically and found to be unaffected by this activation, despite their sleep phenotypes. These data indicate that sleep-modulating dopaminergic neurons may comprise a circuit modulating homeostatic control of sleep independent from circuits controlling feeding. These results may help to explain the way in which DA influences sleep suppression and behavioral arousal, but further investigation is required to understand their circuitry and mechanism.

Disclosures: **M. Driscoll:** None. **V. Coleman:** None. **D. Sitaraman:** None.

Poster

241. Sleep: Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 241.03/KK31

Topic: F.08. Biological Rhythms and Sleep

Support: UNAM-DGAPA-PAPIIT IA207316

UNAM-DGAPA-PAPIIT IN224417

Title: Sleep in crayfish: Relationships between brain electrical activity and autonomics variables

Authors: M. OSORIO-PALACIOS, J. HERNÁNDEZ-FALCÓN, *K. MENDOZA-ANGELES
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Abstract: Sleep is essential for the maintenance of life. In vertebrates sleep is accompanied by changes in heart and breathing frequencies. Crayfish sleep fulfills behavioral and electrophysiological criteria defined for vertebrates. In this animal, heart and respiratory frequencies are modified by environmental changes during wakefulness but It is not known if, and what kind of changes occur to these variables during sleep. The main goal of this work is to study the relationships between cardiorespiratory rates and sleep in crayfish *Procambarus clarkii*. We used adult male crayfish in intermolt, synchronized to light-dark cycles 12:12. In cold anesthetized animals we implanted electrodes on deutocerebrum, gill chambers and the cardiac sinus in order to obtain simultaneous recordings of these variables. We combined these recordings with behavioral videotaping during 8 continuous hours. For the analysis of behaviour we considered the animal position (walking, immobile or sleeping) and the day hour. To analize the brain electrical signal we used the wavelet transform. We also measured cardiac and respiratory rates during all recording conditions. In awake animals, brain electrical activity showed frequencies beetween 100-300 Hz, with a dominant frequency of 40 Hz. Cardiorespiratory activity oscillated randomly in different amplitudes. In the motionless animal, brain elecftrical activity showed similar frequencies but decresed amplitude, respiratory activity decreased in amplitude and frequency, and cardiac activity maintained oscillations. In the sleeping crayfish, the brain electrical activity showed slow waves in a range of 15-20 Hz, and partial inactivity in one side of the branchial chambers, and lower respiratory rate in the other. This dynamic is accompanied by cardiac oscillations of greater amplitude.

Disclosures: M. Osorio-Palacios: None. **J. Hernández-Falcón:** None. **K. Mendoza-Angeles:** None.

Poster

241. Sleep: Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 241.04/KK32

Topic: F.08. Biological Rhythms and Sleep

Support: IN224417

IA207316

Title: The best-fitted: Sensory responses in crayfish depend on its hierarchical level

Authors: *E. G. IBARRA CORONADO[1], K. MENDOZA-ANGELES[2], J. HERNANDEZ-FALCON[3]
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Abstract: Crayfish establish hierarchical orders through agonistic encounters whose outcome defines the dominant and one, or more, submissive animals; this outcome results, at least in part, from incoming sensory information, and the ability of each animal to handle it and respond in the best way. It is assumed that both, dominant and submissive animals recognize each other and also the social status for each conspecific. This recognition is established since the first few minutes of the first agonistic encounter and seems to be based on visual, chemical and mechanical cues, in a ritualistic confrontation that usually is harmless. However, we do not know what is the contribution of each of the sensory systems in this process nor how is processed the sensory information in each of the contenders. Previous results indicate that the establishment and maintenance of hierarchical dominance-submission order in crayfish depends mainly on olfactory information. However, visual and mechanical signals are also used during agonistic encounters and there are authors claiming face recognition among this crustacean. There are a number of papers dealing with visual contribution on the establishment of a hierarchy between two crayfish. But we do not know how this occurs. Is there a difference in the peripheral signal? That is, photoreceptors in dominant animals are best fitted than those from submissive ones? Is there some kind of adjustment in the processing and handling of sensory information by the brain of dominant and submissive animals? Is the best-fitted animal always the winner? In order to explore the partial contribution of vision in the establishment and maintenance of the hierarchical order we studied visual evoked potentials in otherwise intact crayfish before and after the establishment of a hierarchical order. We found that there is a difference in the way in which visual information is acquired between the dominant and submissive crayfish. The study of visual thresholds suggests that dominant individuals develop adaptation to visual stimulation that is faster and more efficient than in submissive animals. Considering that the acquisition and

processing of sensory information are fundamental for the establishment of the hierarchical order, we postulate that the individual who processes more efficiently the external information as the visual will have advantages over the other opponents.

Disclosures: E.G. Ibarra Coronado: None. **K. Mendoza-Angeles:** None. **J. Hernandez-Falcon:** None.

Poster

241. Sleep: Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 241.05/DP11/KK33 (Dynamic Poster)

Topic: F.08. Biological Rhythms and Sleep

Support: NIH

Title: Functional brain imaging in zebrafish during sleep and wake

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Abstract: All organisms sleep, yet why and how sleep happens is still largely not understood. The zebrafish larva, with its small size and optical transparency, offers the opportunity for brain-wide functional imaging across the day/night cycle, toward deciphering the basic mechanisms of sleep regulation and function. We develop a toolset to allow brain activity imaging and analysis in zebrafish larvae at single-celled resolution during sleep/wake behavior. We establish imaging conditions that minimally perturb the behaving animal, using two-photon selective plane illumination microscopy (2p-SPIM) as the modality of choice, for its high speed, low-photodamage, and invisible near-infrared illumination. Using 2p-SPIM, we capture zebrafish brain activity for periods up to 48 hours, measuring functional changes in different regions of the brain during natural sleep/wake cycle, under light and sound stimulation. Sleep state is characterized independently through concurrent body motion detection. Using this framework, we could begin to characterize the brain-wide signatures of natural/induced sleep/wake, as well as interrogate circuits that are relevant to the behavior. Insights gained by our work will contribute to the understanding of the nature and function of sleep.

Disclosures: A. Andreev: None. **S.E. Fraser:** None. **T.V. Truong:** None.

Poster

241. Sleep: Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 241.06/KK34

Topic: F.08. Biological Rhythms and Sleep

Support: ANR-1 1-IDEX-0007

CNRS PEPS EXOMOD 2015-2016

Title: Identification of two sleep states in the tegu lizard, Salvator merianae

Authors: *P.-A. LIBOUREL[1], B. BARILLOT[1], S. ARTHAUD[1], B. MASSOT[2], A.-L. MOREL[1], O. BEUF[3], A. HERREL[4], P.-H. LUPPI[1]
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Abstract: Two sleep states have been identified in terrestrial mammals and birds: Slow-Wave Sleep (SWS) and REM sleep also named paradoxical sleep (PS), defined by a wake-like activity associated with rapid eye movements. Non-avian reptiles are poikilotherms but share a common ancestor with mammals and birds. As a consequence, they are key taxa to understand the origin of sleep states and the link between sleep and thermoregulation. However, whether these animals display the two mammalian sleep states remains debatable. Indeed, the existence of SWS across non-avian reptiles is still unclear and the REM sleep state identified previously still remains to be clearly differentiated from quiet wake. To address this question we studied sleep in a lizard (*Salvator merianae).* To characterize vigilance states in this species, we implanted multiple tungsten electrodes in the medial cortex (hippocampus homologous), the dorso ventricular ridge (a possible associative structure), and the nucleus sphericus (a vomeronasal structure) in eight lizards. We wirelessly recorded local field potentials (LFPs) in all structures as well as the EMG, ECG and EOG. We quantified the behavior, sleep homeostasis, and arousal threshold. Our results reveal that slow waves are more prominent in lizards during active wake than in sleep, in contrast to mammals. We also defined two different sleep states occurring during the night. The first sleep state is characterized by the emergence of isolated high amplitude sharp waves. The second sleep state is characterized by an oscillation occurring in the low beta band (12-18 Hz), lasting 5-6 seconds, and appearing mostly at the beginning and at the end of the sleep period. The frequency of the beta oscillation slows down when the ambient temperature is decreasing. Like during mammalian REM sleep, eye movements and a decrease in heart rate variability occur during this state. There is also a tendency for a muscle tone decrease. In summary, our study shows that two sleep states exist in this lizard, but does not show a complete homology with mammalian SWS and REM sleep. Interestingly, the characteristics of these two sleep states are very different from those reported recently for the Bearded Dragon (*Pogona vitticeps*)

suggesting that sleep characteristics can be very different across lizards. This raises crucial questions on the functions and the mechanisms of sleep in these animals.

Disclosures: **P. Libourel:** None. **B. Barillot:** None. **S. Arthaud:** None. **B. Massot:** None. **A. Morel:** None. **O. Beuf:** None. **A. Herrel:** None. **P. Luppi:** None.

Poster

241. Sleep: Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 241.07/KK35

Topic: F.08. Biological Rhythms and Sleep

Support: NIH/ NIDCD 1R01DC012859

ONR/BAA 11004985

Title: A parrot species has complex sleep structure in common with mammals and songbirds

Authors: *S. CANAVAN[1,2,3], D. MARGOLIASH[1,2,4]
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Abstract: Numerous species exhibit specialized forms of sleep, namely slow wave sleep (SWS), stage 2 sleep, and rapid eye movement sleep (REM). These sleep stages are central to many hypotheses of sleep function in mammals. It remains unclear, however, how and why complex sleep architecture evolved. While SWS and REM are found in both mammals and birds, early work suggested that avian sleep differed significantly from mammalian sleep. Birds were thought to have “rudimentary” and only very sparse amounts of REM, no sleep spindles and thus no stage 2 sleep, and different time courses of SWS and REM across the night. This suggested that while avian sleep has surface resemblance to its mammalian counterpart, it may have evolved independently, be regulated differently and serve different functions. This interpretation has been challenged by recent evidence of more complex, mammalian-like sleep traits in songbirds (zebra finches and starlings), and evidence from pigeons and reptiles.
Here we examine sleep architecture in budgerigars (*Melopsittacus undulatus*), a parrot species. Parrots (Psittaciformes) are the sister group to songbirds and one of three orders of birds that possess vocal learning abilities. Our main purpose was to evaluate whether parrots exhibited the set of complex mammalian-like sleep traits previously identified in songbirds.
We collected sleep data from 5 budgerigars using a combination of EOG, multichannel EEG, and behavioral recordings. Sleep scoring was performed using both manual and automated techniques, including automated detection of slow waves, eye movements, and artifacts. Sleep was also measured in a subset of 3 budgerigars during and after exposure to constant light, to

compare with results from older studies on comparative sleep architecture which used this approach.
We found that parrots have substantial amounts of REM and SWS comparable to amounts in humans, a clear stage 2-like state of intermediate sleep, and a pattern of SWS decrease and REM increase across the night. We also showed that experimental conditions that were commonly used in older avian sleep studies can distort sleep architecture.
The similarities in sleep architecture observed in mammals, songbirds, and now budgerigars, as well as recent work in reptiles, brings into question the hypothesis that complex sleep structure emerged independently in mammals and songbirds. Instead, our findings suggest that the common ancestor of amniotes (mammals, birds, and reptiles) possessed the precursors of REM and SWS. These results also motivate continued re-examination of avian sleep architecture and the phylogenetic correlates of sleep traits across bird species.

Disclosures: S. Canavan: None. **D. Margoliash:** None.

Poster

241. Sleep: Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 241.08/KK36

Topic: F.08. Biological Rhythms and Sleep

Support: NSF and OISE (IOS-1353713)

Ribble mini grant-Biology

Title: Spiny mice (Acomys cahirinus) have distinct activity patterns and sleep with their eyes open

Authors: *C. WANG[1], L. E. GUERRIERO[1], K. JUNG[2], A. A. AJWAD[3], D. M. HUFFMAN[3], J. E. GILES[1], S. SUNDERAM[3], M. E. KLEINMAN[2], A. W. SEIFERT[1], B. F. O'HARA[1]
[1]Dept. of Biol., [2]Dept. of Ophthalmology & Visual Sci., [3]Dept. of Biomed. Engin., Univ. of Kentucky, Lexington, KY

Abstract: To understand the function and origins of sleep, sleep needs to be studied across many different species. Although it is well conserved throughout mammals, 99% of papers are restricted to just three species, *Homo sapiens*, *Mus musculus*, and *Rattus norvegicus*. We aimed to characterize sleep and wake in a Murid rodent *Acomys cahirinus.* Previous research, using a well validated, non-invasive, piezoelectric system, that picks up breathing rhythms to determine sleep or wake, have shown that *A. cahirinus* and *M. musculus* have relatively similar sleep and wake profiles, with a few interesting differences. Specifically, the activity of *A. cahirinus* sharply increases right at dark onset, which is common in nocturnal species, but surprisingly, decreases

sharply just one hour later. Using infra-red camera recordings in single and group cage conditions, we found that *A. cahirinus* is more active before the middle of the night period than after middle of the night period in single and group cages, and this decreased activity in the latter half of the night is much greater compared to *M. musculus*. In order to truly understand these differences in sleep architecture of *A. cahirinus*, electroencephalogram (EEG) recordings were performed. Our data show that *A. cahirinus* have a few key differences in sleep from *M. musculus*. *A. cahirinus* have significantly longer daily sleep periods and exhibit a higher amount of REM sleep. *A. cahirinus* are awake at dark onset, but seem to sleep more than *M. musculus* after the middle of the night. Most strikingly, *A. cahirinus* do not close their eyes virtually at all while sleeping, day or night. In order to test whether the sleep patterns of *A. cahirinus* are affected by the different light influx during day time, we set up a light flashing experiment. *A. cahirinus* spends significantly less time in REM during light flashing compared to baseline data but, *M. musculus* have no difference in REM sleep percentage. This raises further questions about *A. cahirinus* sleep architecture and why it differs from *M. musculus*. While eye closure and sleep have not been systematically studied across mammals, our observation is clearly a rare behavior that we are currently investigating with multiple approaches.

Disclosures: C. Wang: None. **L.E. Guerriero:** None. **K. Jung:** None. **A.A. Ajwad:** None. **D.M. Huffman:** None. **J.E. Giles:** None. **S. Sunderam:** None. **M.E. Kleinman:** None. **A.W. Seifert:** None. **B.F. O'Hara:** None.

Poster

241. Sleep: Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 241.09/LL1

Topic: F.08. Biological Rhythms and Sleep

Support: Veterans Affairs Medical Research Service Awards I01BX001356 (RWM)

Veterans Affairs Medical Research Service Awards I01BX001404 (RB)

Veterans Affairs Medical Research Service Awards I01BX1002774 (RES)

VA Career Development Award IK2BX002130 (JMM)

NIH Grant R21-NS079866 (RB)

NIH Grant RO1-MH039683 (RWM)

NIH Grant PO1-HL095491 (RWM)

Title: Effect of GAD67 deletion in the thalamic reticular nucleus on sleep spindle activity

Authors: *H. MIWA, R. BASHEER, H. BOUAOUDA, D. S. UYGUN, J. T. MCKENNA, J. M. MCNALLY, R. E. STRECKER, R. W. MCCARLEY, R. E. BROWN
VA Boston Healthcare Syst., Harvard medical Sch., West Roxbury, MA

Abstract: Schizophrenic (Sz) patients exhibit a reduction in waxing and waning 8-15 Hz cortical oscillations occurring during non-REM (NREM) sleep, so-called sleep spindles. Sleep spindles are thought to be generated by the GABAergic neurons of the thalamic reticular nucleus (TRN), most of which contain the calcium-binding protein, parvalbumin (PV). The expression of the GABA synthetic enzyme, glutamate decarboxylase 67 (GAD67), is decreased in cortical PV GABAergic neurons of Sz brains examined postmortem. Thus, one possible explanation for the spindle deficit in Sz is a parallel reduction of GAD67 levels in TRN neurons. Thus, here we selectively deleted GAD67 in the TRN and tested the effect on sleep spindles.
We reduced GAD67 levels in TRN neurons by injecting an adeno-associated virus (AAV) constitutively expressing a Cre recombinase-Green fluorescence protein (GFP) fusion protein (AAV-CreGFP) into TRN (AP -0.6; ML ±1.45; DV -3.25) of heterozygous and homozygous GAD67 floxed mice. The time course of reduction in GAD67 after viral injection was evaluated by immunohistochemistry. EEG activity from frontal cortex AP 1.5, ML 1.0 and nuchal muscle EMG were recorded and sleep-wake states were analyzed in 4 s epochs. A custom-designed script (Matlab) was used to detect individual spindles (10-15Hz) during NREM sleep.
Initial experiments suggested that there was minimal viral expression at 1 week post-injection. Furthermore, NREM sleep spindle density at 1 week in virally injected animals was similar to control animals (~5/min of NREM sleep). Therefore, we used 1 week values as our baseline. In heterozygous mice (N=6) with confirmed bilateral viral transduction in ~50% of the anterior TRN area; NREM spindle density during the light period was decreased by ~11% after 2 and 4 weeks of AAV injection when compared to the values in the same animals recorded 1 week after injection (2 week, 88.8 ± 2.5%; 4 week, 88.5 ± 4.7%; of the one week values). In homozygous mice (N=2) spindle density was further reduced by ~ 35% at 4 weeks.
Our results suggest GAD67 floxed mice are a useful tool to test whether reduced levels of GAD67 levels in TRN results in decreased spindle density, similar to the findings observed in schizophrenia patients. Furthermore, such a model may be useful in the future for dissecting out the potential role of sleep spindles in sleep-dependent memory consolidation.

Disclosures: H. Miwa: None. **R. Basheer:** None. **H. Bouaouda:** None. **D.S. Uygun:** None. **J.T. McKenna:** 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.; Merck MISP. **J.M. McNally:** None. **R.E. Strecker:** None. **R.W. McCarley:** None. **R.E. Brown:** None.

Poster

241. Sleep: Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 241.10/LL2

Topic: F.08. Biological Rhythms and Sleep

Support: VA Merit I01 BX002661

Title: Basal forebrain cholinergic neurons are vital for cortical desynchronization and behavioral arousal observed after nicotine consumption

Authors: *A. SHARMA, R. SHARMA, C. MACKEY, P. SAHOTA, M. THAKKAR
Univ. of Missouri/Va Med. Ctr., Columbia, MO

Abstract: Purpose: Nicotine is an addictive constituent of tobacco which severely affects behavior. Sleep disruptions including reducing total sleep time, increasing sleep fragmentation and reducing sleep efficiency are very common in nicotine users. However, the underlying neuronal mechanism of how nicotine promotes desynchronization and disrupts sleep is unknown. We have shown that the basal forebrain (BF) is a key brain region, mediating nicotine's effects on sleep-wakefulness (SFN 2015; Poster#166). The BF contains multiple neuronal phenotypes including cholinergic, GABAergic and glutamatergic subtypes. Thus, this study was designed to examine the neuronal subtype responsible for nicotine effects on sleep-wakefulness. As a first step, we focused on BF cholinergic neurons because BF cholinergic neurons are wake-promoting, express nicotinic receptors and supply acetylcholine to the prefrontal cortex, hippocampus and amygdala. We hypothesized that lesions of BF cholinergic neurons will attenuate nicotine induced cortical arousal/desynchronization. **Methods:** To test our hypothesis, adult male Sprague-Dawley rats were implanted with sleep recording electrodes and were divided into two groups: ***Lesion***: Selective lesion of the BF cholinergic neurons was performed by bilateral administration of immunotoxin, 192-IgG-Saporin (SAP; 0.28 µg/0.5µL/side) in the BF; ***Sham (controls):*** Rats were bilaterally infused with saline (0.5µL/side). After injections, animals were left undisturbed for 3 weeks. Day 1: saline was administered subcutaneously at light/sleep onset. Day 2: Nicotine (0.3 mg/Kg) was administered at the same time. Sleep-wakefulness was examined for next 6 hours. On completion, animals were euthanized and the brains were processed for choline acetyltransferase (ChAT) immunohistochemistry to verify BF cholinergic lesions. **Results:** Our preliminary results: As compared to controls, lesioned rats, with a 64% reduction in cholinergic neurons, displayed attenuated nicotine induced cortical desynchronization and behavioral arousal. **Conclusions:** Our results suggest that the BF cholinergic neurons mediate nicotine induced cortical arousal/desynchronization that may be the cause of sleep disruptions in nicotine users.

Disclosures: **A. Sharma:** None. **R. Sharma:** None. **C. Mackey:** None. **P. Sahota:** None. **M. Thakkar:** None.

Poster

241. Sleep: Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 241.11/LL3

Topic: F.08. Biological Rhythms and Sleep

Support: VA Merit I01 BX002661

Title: Gender differences in sleep homeostasis: Chemogenetic approach to examine the role of melanin concentrating hormone

Authors: *R. SHARMA[1], A. SHARMA[2], C. MACKEY[2], P. SAHOTA[2], M. THAKKAR[2]
[1]Univ. of Missouri/Va Med. Ctr., Columbia, MO; [2]Neurol., Univ. of Missouri/VA Med. Ctr., Columbia, MO

Abstract: Purpose: While male and female have minimal differences in spontaneous sleep, gender differences have been observed in homeostatic response to sleep deprivation. Recent studies suggest that neurons containing melanin concentrating hormone (MCH) play a crucial role in sleep regulation. More importantly, the expression of MCH and its receptors is modulated by female sex hormone, estrogen. Is MCH responsible for differential homeostatic response in males and females mice? **Methods:** To address this question, we performed chemogenetic silencing of MCH neurons in male (N=4) and female (N=4) MCH-cre transgenic mice. Under standard surgical conditions, mice were implanted with electrodes to record brain (EEG) and muscle (EMG) activities. Inhibitory DREADD (AAV/hSyn-DIO-hM4Di-mCherry; 300nl/site) was bilaterally infused into the MCH-rich lateral hypothalamus region. On completion, mice were left undisturbed for three weeks. On experiment day (proestrous day in females), sleep deprivation (gentle handling; last six hours of light period)-recovery sleep (six hours) paradigm was used to examine homeostatic response. Chemogenetic silencing was achieved by systemic administration of clozapine-N-oxide (CNO; 5 mg/Kg in 0.3 mL saline). Three days (coinciding with proestrous day in females) later a second sleep deprivation-recovery sleep along with control (0.9% Saline; 0.3 mL) treatment was performed in the same mice. On completion, mice were euthanized, brain removed and processed for MCH immunofluorescence to determine the percentage of MCH neurons with DREADD expression. **Results:** Preliminary studies suggests that DREADD was expressed in >50% of MCH neurons. MCH silencing had differential effects on recovery sleep in males and females (proestrus stage). Two-way repeated measure ANOVA suggested significant main effects of gender ($p<0.05$) and treatment ($p<0.05$). **Conclusions:** Our preliminary results suggest that MCH neurons may have a causal role in differential homeostatic response observed in male and female mice.

Disclosures: **R. Sharma:** None. **A. Sharma:** None. **C. Mackey:** None. **P. Sahota:** None. **M. Thakkar:** None.

Poster

241. Sleep: Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 241.12/LL4

Topic: F.08. Biological Rhythms and Sleep

Title: Chronic REM sleep restriction alters body weight and food intake in male rats

Authors: A. K. LEON-OLGUIN, N. MENDOZA-ELIZALDE, J. VELAZQUEZ-MOCTEZUMA, *A. JIMENEZ-ANGUIANO
Univ. Autonoma Metropolitana-Iztapalapa, Mexico City, Mexico

Abstract: Sleep-wake cycle has an important role in the regulation of several physiological processes, such as the energy balance. During the sleep occurred the release of several neurohormones and neurotransmitters involved in the metabolic modulation. It has been shown in different animal species, a relation between quantity of sleep and corporal weight. However, the effect of chronic REM sleep restriction (CSR) in metabolic parameters (MP) has not been completely studied. The purpose of the present study was to analyze the influence of CSR in food and water intake, corporal weigth and several MP. We used 12 male adult Wistar rats (250-300 g), which were grouped under the following conditions: 1) Control with water and food ad libitum (n=6), 2) With CSR for 21 days (n=6), and 3) With two weeks of recuperation after the CSR. CSR was realized with the modified multiple platform method for 20 h and 4 h in the home cage. All animals were weighed, MP, food and water intake was measured twice a day, during the first 2 h of darkness period and in the last third of the light period. Finally we quantified the levels of cholesterol, triglycerides and glucose. Results showed that CSR produced in the first weeks a decrease in the food intake and corporal weight. Both parameters were partially recupered after the CSR period. In the MP, the CSR decreased glucose levels and increased the levels of triglycerides. From the obtained results we suggest that CSR has a crucial effect on metabolic regulation.

Disclosures: **A.K. Leon-Olguin:** None. **N. Mendoza-Elizalde:** None. **J. Velazquez-Moctezuma:** None. **A. Jimenez-Anguiano:** None.

Poster

241. Sleep: Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 241.13/LL5

Topic: F.08. Biological Rhythms and Sleep

Title: The essential role of microglia in regulating sleep structure in mice

Authors: *H. LIU, X. LIANG, Q. XIONG
Dept. of Neurobio. & Behavior, SUNY At Stony Brook, Stony Brook, NY

Abstract: Microglia is the resident immune cell in the brain, executing immunoactivity to maintain stability of the central nervous system. Accumulating studies indicated that microglia is also involved in regulating fundamental physiological functions of the brain, including circadian and sleep. Sleep is impaired in diseases that affect microglia activation, such as Alzheimer disease and parasite infection. Here, we set up several experiments to examine the contribution of microglia in regulating sleep structure in mice. By comparing microglia morphology during daytime and nighttime, we found that in sleep-promoting brain regions, microglial activity was high during daytime which is the mostly sleep period for mice, indicating microglial activity exhibited circadian rhythm that is synchronized with cortical neural activity. Using transgenic mice that express both tamoxifen-inducible Cre recombinase under the control of the CX3CR1 promoter and Cre-dependent diphtheria toxin (DT) receptor, we globally depleted microglia in the whole brain. Sleep structure was monitored via EEG recordings when microglia was repopulated from the depletion. Mice that had microglia depletion showed decreased wake proportion and increased NREM sleep proportion only during nighttime. 10 days following depletion, microglia repopulated to the normal cell density and the sleep structure was recovered to baseline. However, the power spectrum of EEG was still impaired even one month after microglia depletion, which might be caused by abnormal high activity of repopulated microglia. In conclusion, we found microglial activity in sleep-promoting brain regions displayed circadian rhythm, and microglia population and activity is critical for regulating the sleep structure.

Disclosures: H. Liu: None. **X. Liang:** None. **Q. Xiong:** None.

Poster

241. Sleep: Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 241.14/LL6

Topic: F.08. Biological Rhythms and Sleep

Support: Craig H. Neilsen Foundation

NIH/NIGMS Institutional Research and Academic Career Development Award, 5K12-GM000680-17

Title: Characterizing sleep state respiration changes after spinal cord injury using non-contact electric field sensors

Authors: *H. KLOEFKORN, C. MACDOWELL, M. SAWCHUK, B. GOOLSBY, M. HALDER, S. HOCHMAN
Physiol., Emory Univ., Atlanta, GA

Abstract: Background: After spinal cord injury (SCI), respiratory function and sleep quality are altered. Studying sleep in rodents is challenging and invasive (Sandhu, *Respir. Physiol. Neurobiol*. 2009), but changes in respiration can differentiate REM from non-REM sleep states as measured by whole body plethysmography (Bastianini, *Sci. Rep.* 2017). Respiration can be captured in an animal's home-cage using non-contact electric potential integrated circuit (EPIC) sensors (Noble, *J. Neurosci. Methods* 2016). Here, we use these sensors to characterize REM and non-REM (NREM) sleep state changes in mouse after SCI.
Methods: Three male C57/bl6 mice (3 months) were pair-housed in standard vivarium conditions in home-cages designed to divide into two electrically shielded compartments during testing with 60mm petri dish nests. A PS25251 EPIC sensor (1x1x0.25cm, 1kHz, Plessey Semiconductors), placed outside the cage beneath each nest, was able to transform the summation of respiration and other body movements into a voltage output. Animals were acclimated to the instrumented home-cages for 3 days then recorded for 3 days 12 hours/day (midnight to noon) prior to receiving an upper thoracic spinal cord transection. Cages were recorded daily for 7 days after SCI. Resting respiration events were identified, divided into 4-second epochs, and manually assigned a state: "NREM," or "REM." Animal averages of respiration rate, intra-epoch range of respiration rate, intra-epoch variability of respiration rate, half-amplitude width, and intra-epoch variability of half amplitude width were calculated.
Results: After SCI, resting respiration rate was decreased at early timepoints relative to baseline ($p<0.036$). NREM and REM sleeps states were successfully identified from respiration recorded remotely via EPIC sensors. REM intra-epoch frequency variability was larger than NREM at all timepoints ($p<0.003$), but tended to increase in both REM and NREM states after SCI. After SCI, variability of intra-epoch half-amplitude width of a respiratory cycle increased for both NREM and REM states relative to their baseline values ($p<0.027$). At all timepoints, REM state respiration encompassed a wider frequency range than NREM ($p<0.013$), though NREM ranges increased at day 1 after SCI relative to baseline ($p=0.016$).
Discussion: After SCI, respiratory rate variability increased and both NREM and REM sleep states changed. Interestingly, frequency-based changes were most severe immediately after SCI, while half-amplitude width features became progressively more severe at later timepoints. Overall, EPIC sensors were able to detect NREM and REM sleep state changes in home-cages after SCI.

Disclosures: **H. Kloefkorn:** None. **C. MacDowell:** None. **M. Sawchuk:** None. **B. Goolsby:** None. **M. Halder:** None. **S. Hochman:** None.

Poster

241. Sleep: Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 241.15/LL7

Topic: F.08. Biological Rhythms and Sleep

Title: The role of M1 intrinsically photosensitive retinal ganglion cells in the light induction of sleep in mice

Authors: *M. REN, J. LI, F. TUREK, T. M. SCHMIDT
Neurobio., Northwestern Univ., Evanston, IL

Abstract: Melanopsin-expressing, intrinsically photosensitive retinal ganglion cells (ipRGCs) are involved in a wide range of behaviors including non-image forming visual behaviors, such as circadian photoentrainment, the light induction of sleep, and contrast sensitivity for pattern vision. M1 ipRGCs, which is the ipRGC subtype that drives non-image forming visual behaviors, can be subdivided based on whether or not they express the transcription factor Brn3b. Brn3b positive M1 cells are necessary for normal pupillary light reflex, while Brn3b negative M1 cells are sufficient for photoentrainment. Nocturnal light exposure in mice results in rapid sleep induction and M1 ipRGCs are necessary for this light induction of sleep. However, which M1 ipRGC subtype is involved in this behavior has not been examined. To define the role of Brn3b positive and Brn3b negative M1 cells in this behavior, we used a mouse line in which Brn3b positive ipRGCs are ablated. We analyzed states of wake, NREM sleep, and REM sleep using EEG and EMG recordings during experiments with manipulations in light and dark signals to assess the sleep-promoting effect of light and the arousal-promoting effect of darkness. We found that mice lacking Brn3b positive ipRGCs showed no induction of sleep after nocturnal light exposure, despite extensive innervation of the SCN by the remaining Brn3b negative M1 cells. This indicates that while the SCN regulates sleep and circadian rhythms, it does not promote sleep following nocturnal light exposure. We also find that M1 innervation of the ventrolateral preoptic area (VLPO) is absent in mice lacking Brn3b positive ipRGCs, consistent with a role for this nucleus in light induction of sleep. Collectively, these data indicate that Brn3b positive ipRGCs are necessary for the light induction of sleep.

Disclosures: **M. Ren:** None. **J. Li:** None. **F. Turek:** None. **T.M. Schmidt:** None.

Poster

241. Sleep: Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 241.16/LL8

Topic: F.08. Biological Rhythms and Sleep

Support: NSF GRFP

NEI R00EY021503

Title: Cortical firing dynamics during consolidation of sleep-dependent visual plasticity

Authors: *B. C. CLAWSON[1], J. DURKIN[2], A. K. SURESH[4], C. BROUSSARD[1], E. J. PICKUP[1], S. J. ATON[3]
[2]Neurosci. Grad. Program, [3]Molecular, Cellular, and Developmental Biol., [1]Univ. of Michigan, Ann Arbor, MI; [4]Univ. of Chicago, Chicago, IL

Abstract: Recent studies suggest that sleep differentially alters the activity of neurons based on firing rates during preceding wake - increasing the rates of slow firing neurons and decreasing those of faster firing neurons. Because sparsely firing neurons may play a critical role in sensory information processing, it is tempting to speculate that sleep may facilitate consolidation of experience-dependent plasticity via selective actions on sparsely firing neurons. To test this hypothesis, we performed a meta-analysis of longitudinal electrophysiological recordings from visual cortical neurons during consolidation of orientation specific response potentiation (OSRP). OSRP is induced by exposing the mouse to a single oriented-grating prior to sleep. After subsequent sleep, OSRP is expressed as an increase in neuronal responsiveness to the stimulus orientation.
Similar to prior studies, cortical neurons were grouped into sextiles based on their baseline spontaneous firing rates. We saw that sleep preferentially increased firing rates of the most sparsely firing neurons and decreased those of faster firing neurons. Interestingly, the most sparsely firing neurons showed the largest increases in orientation preference (i.e. OSRP) while higher firing neurons did not show OSRP. This relationship indicates that sleep may be selectively increasing the activity of the slow, plastic population of neurons, while reducing the noise in the network by decreasing the activity of less orientation-selective, faster firing neurons.

Disclosures: **B.C. Clawson:** None. **J. Durkin:** None. **A.K. Suresh:** None. **C. Broussard:** None. **E.J. Pickup:** None. **S.J. Aton:** None.

Poster

241. Sleep: Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 241.17/LL9

Topic: F.08. Biological Rhythms and Sleep

Support: NSERC Discovery RGPIN/346135-2012

Title: The effects of circadian disruption by inappropriately-timed melatonin influences sleep quality, cognitive control and changes in diffusion tensor imaging (DTI)

Authors: *J. F. DESOUZA[1], C. G. H. STEEL[2], S. E. LEUNG[2]
[1]Psychology & Biol., York Ctr. For Vision Res., Toronto, ON, Canada; [2]Biol., York Univ., Toronto, ON, Canada

Abstract: It has long been known that the circadian system regulates daily rhythms in numerous physiological parameters, including oscillations in cognitive function. However, the relationship between the circadian system and cognitive performance, such as selective attention, remains illusive. 10 healthy adults (age = 26.8 ± 6.25 years) underwent a baseline period followed by an 8-day experimental period whereby 1.5-mg of melatonin was administered sublingually at inappropriate times to develop a human model of circadian de-synchronization. Subjects were told they could be receiving a placebo or melatonin but in actual fact all received the treatment. Participants were asked to perform a test of cognitive control efficiency as measured by the emotional Stroop task 4x during each period, followed by two DTI scans at the end of baseline and experimental period. All participants also kept daily logs for the duration sleep/wake, meal times, sleep quality ratings and activities. The results showed that experimental sleep and wake times were significantly shifted compared to baseline ($p<0.05$), consistent with literature reported by those participating in shift work and undergoing jetlag. Self-reported sleep quality ratings was significantly decreased while on the treatment ($p<0.05$), demonstrating that improper use of melatonin may actually result in worse sleep. When examining the cognitive control effects, processing of emotional words but not emotional faces was negatively affected by the treatment, as demonstrated by a trade-off between RTs and errors in the incongruent word condition of the Stroop task. Our two DTI time points showed significant decreases in FA values ($p<0.01$) and significant increases in MD values ($p<0.05$) in the IFG when comparing the baseline and experimental scans. Our results demonstrate the evidence of the effects of inappropriately timed melatonin on cognitive performance and the resulting architectural structural brain changes. Our findings from the current work are suggestive of the fact that the melatonin treatment elicited short-term de-synchronization in the participants and demonstrates that though observable deficits in performance on cognitive tasks may not always be apparent, an important node in the attentional brain network underlying executive functions show disruption

after only 8 days of inappropriately timed melatonin. Long term internal de-synchronization as a result of shift work or frequent jet lag may therefore lead to white matter microstructure changes that could correlate with impaired cognitive performance.

Disclosures: J.F. DeSouza: None. **C.G.H. Steel:** None. **S.E. Leung:** None.

Poster

241. Sleep: Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 241.18/LL10

Topic: F.08. Biological Rhythms and Sleep

Support: Autism Speaks

Title: Cognitive and sleep/wake architecture abnormalities in Cntnap2 and Fmr1 knockout rat models of autism spectrum disorders

Authors: *C. K. JONES[1], L. S. SCHMIDT[2], C. S. BERTSCH[2], M. BUBSER[3], B. GUNTER[3], R. W. GOULD[3]
[2]Vanderbilt Col. of Arts and Sci., [3]Pharmacol. & VCNDD, [1]Vanderbilt Univ. Med. Ctr., Nashville, TN

Abstract: Autism spectrum disorder (ASD) constitutes neurodevelopmental disorders characterized by impaired social communication, repetitive behaviors and co-morbid symptoms of seizures, cognitive deficits and altered sleep/wake architecture. Currently available medications do not adequately treat the core symptoms of ASD or associated co-morbidities. Thus, there remains a critical unmet need to develop better treatment approaches for patients with ASD. Validating genetic rodent models relevant to the symptoms associated with ASD constitutes an important strategy for future therapeutic development. Here we evaluated age-related changes in sleep/wake architecture and behavioral domains relevant to the diagnostic criteria of ASD in two genetic ASD models, the Contactin Associated Protein-Like 2 (Cntnap2) and fragile X mental retardation protein 1 (Fmr1) knockout (KO) rat strains (Sage Labs Inc) in comparison with wildtype rats (N=12-16/cohort). Following completion of behavioral testing, rats were implanted with electroencephalography (EEG) telemetry transmitters to evaluate sleep/wake architecture, quantitative EEG, and changes in spontaneous seizure activity. The Cntnap2 KO rats showed increased social interaction and social play behaviors, in the 3-chamber social approach and juvenile reciprocal social interaction tests versus the wildtype rats Cntnap2 KO rats also displayed disruptions in cognitive performance relative to the wildtype rats in novel object recognition, fear conditioning, and Morris water maze. In comparison, the Fmr1 KO rats only exhibited impairments in contextual fear conditioning, a preclinical model of hippocampal learning and memory. In addition, the Cntnap2 KO rats displayed abnormalities in qEEG,

including decreases in alpha power frequency and increases in high gamma power frequency that appear to correlate with increased seizure activity. Fmr1 KO rats also exhibited significant abnormalities in sleep-wake architecture and qEEG, including decreased NREM sleep, which is known to be critical for memory consolidation. Collectively, the Cntnap2 and Fmr1 KO rat strains represent important preclinical models of the social, cognitive and/or sleep/wake architecture deficits observed in ASD.

Disclosures: C.K. Jones: A. Employment/Salary (full or part-time):; The authors declare the following competing financial interest(s): Over the past year, M.B. and C.K.J. received research/salary support from AstraZeneca and/or Bristol Myers Squibb. The remaining auth. **L.S. Schmidt:** None. **C.S. Bertsch:** None. **M. Bubser:** A. Employment/Salary (full or part-time):; The authors declare the following competing financial interest(s): Over the past year, M.B. and C.K.J. received research/salary support from AstraZeneca and/or Bristol Myers Squibb. The remaining auth. **B. Gunter:** None. **R.W. Gould:** None.

Poster

241. Sleep: Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 241.19/LL11

Topic: F.08. Biological Rhythms and Sleep

Support: Office of Naval Research Grant # N00014-15-1-2809

Title: Mycobacterium vaccae enhances sleep and counteracts effects of stress and sleep disruption in mice

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Abstract: Warfighters, emergency technicians, and medical staff are regularly exposed to acute stressors and long work hours that disrupt regular sleep. There is growing evidence that sleep disruption can potentiate the negative effects of acute stress, including impairments in cognition. There is a need, therefore, to investigate countermeasures that combat this "double-hit" of acute stress and sleep disruption. Immunization with heat-killed Mycobacterium vaccae, an environmental bacterium and known immunomodulator, has been shown to promote stress resilience in mice. However, its effects in the context of sleep disruption have not been studied. In this experiment, we investigated M.vaccae as a countermeasure to the double-hit. Mice (C57BL/6N) were surgically implanted with EEG/EMG recording devices then given three weekly injections of heat-killed M.vaccae preparations, followed by five days of 20-hour sleep

disruption with a four-hour sleep opportunity. Immediately following sleep disruption, animals were exposed to a one-hour episode of social defeat, allowed 24 hours of recovery sleep, then tested in a hippocampal memory task. Mice that received social defeat alone or social defeat plus sleep disruption showed impaired learning and reduced habituation to the testing chamber. M.vaccae treated animals, however, did not display these memory deficits. Furthermore, M.vaccae treated animals that received social defeat alone or social defeat plus sleep disruption showed increased total sleep, particularly increased REM. These results indicate that immunization with M.vaccae curtails the synergistic effects of the double hit to cognition. Our findings suggest that host-microbial immunity merits investigation as therapeutic targets for stress-related pathologies.

Disclosures: S. Lambert: None. **S.J. Bowers:** None. **C.J. Olker:** None. **E. Song:** None. **K.P. Wright:** None. **M. Fleshner:** None. **C.A. Lowry:** None. **M. Vitaterna:** None. **F.W. Turek:** None.

Poster

241. Sleep: Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 241.20/LL12

Topic: F.08. Biological Rhythms and Sleep

Title: Sleep deprivation and voluntary alcohol consumption in adult rats

Authors: *C. M. COWAN[1], N. MACK[1], S. SEQUEIRA[1], K. PONDER[2], D. HOLT[1], J. DYCHE[3]
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Abstract: Alcohol is one of the most common psychoactive drugs, and has been used by humans for thousands of years. Historically, research has focused on the effects of alcohol on sleep, however recent trends in the literature have taken a more bidirectional approach to the relationship between alcohol and sleep. This research is concerned with the relationship between sleep deprivation, voluntary alcohol consumption, and the ever-present confound of sleep research: stress. Previous research in our laboratory revealed that rats voluntarily consumed more alcohol while being sleep deprived via forced exercise wheels. However, this prior research also found that rats consumed more alcohol inside the forced exercise wheels when they were not moving, and thus not sleep depriving the subjects. In this study, twelve Sprague Dawley rats were given free access to water, a 7% alcohol solution, and food for the duration of the study beginning approximately two weeks prior to initial exposure to forced exercise sleep-deprivation chambers. All rats were then given a seven day acclimation period inside of the three forced-exercise wheels over the course of one month. After the acclimation period, all rats were exposed

to an 18-hour and 6-hour sleep deprivation conditions in the wheels, counterbalanced for order. All subjects then spent an additional seven days inside non-moving forced exercise wheels. Results indicate a significant effect of sleep condition on voluntary alcohol consumption F (2, 23) = 5.90, p = .008. Rats consumed more alcohol during sleep deprivation conditions than in their home cage environment ($p < .05$).

Disclosures: C.M. Cowan: None. **N. Mack:** None. **S. Sequeira:** None. **K. Ponder:** None. **D. Holt:** None. **J. Dyche:** None.

Poster

241. Sleep: Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 241.21/LL13

Topic: F.08. Biological Rhythms and Sleep

Support: Swiss National Science Research Fund

Title: Hypocretin (Orexin) signaling is critical in sustaining theta/gamma-rich waking behaviors

Authors: *A. VASSALLI, P. FRANKEN, S. LI, M. TAFTI
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Abstract: Hypocretin (Hcrt) has potent neuromodulatory effects in a variety of motivated and survival behaviors. Hcrt was shown to be critical for behavioral state stability, although the mechanisms underlying these effects and resulting impairments in its absence in narcolepsy are not yet solved. We show that while *Hcrt-KO* mice respond to 6-h sleep-deprivation (SD) with a slow-wave-sleep (SWS) EEG δ power rebound as *WT* controls, spontaneous waking fails to induce a δ power reflecting prior waking duration. This correlates with impaired θ and fast-γ (55-80 Hz) activity in prior waking. We algorithmically identify a theta-dominated-waking (TDW) substate underlying motivated behaviors and typically preceding cataplexy in *Hcrt-KO* mice. *KO* mice fully implement TDW when waking is enforced, but baseline TDW bout duration is greatly reduced. A reformulation of the classic sleep homeostasis model, where homeostatic pressure rises solely in TDW rather than in all wake, predicts δ power dynamics both in *KO* and *WT* mice, baseline and recovery SWS. The low homeostatic weight of *KO* mice' spontaneous waking correlates with decreased cortical expression of neuronal activity-related genes (*Bdnf, Egr1*/*Zif268* and *Per2*). Thus baseline TDW stability relies on Hcrt to sustain θ/fast-γ network activity and associated plasticity, while other arousal circuits sustain TDW in SD. We propose that TDW identifies a discrete brain activity mode which is regulated by context-dependent neuromodulators and acts as major driver of sleep homeostasis. Hcrt loss causes impaired TDW maintenance in baseline wake and blunted δ power in SWS, reproducing respectively, narcolepsy excessive daytime sleepiness and poor sleep quality. To tackle the circuits mediating these

effects we generated conditional KO (cKO) alleles of *Hcrtr1* and *2* receptor genes and inactivated the receptors in Noradrenergic (NA) and Dopaminergic cells selectively. These mice show specific impairments in adapting electrocortical activity to behavioral contexts. The EEG of NA cell-specific *Hcrtr1* cko (*Hcrtr1*$^{Dbh\text{-}cko}$) mice was examined in distinct paradigms. While baseline wake was almost normal, exposure to challenging contexts led to more profound spectral changes. Our data evidence the role of an intact Hcrt-to-NA signaling pathway to build an appropriate θ/fast-γ response in stress-associated environments, a slowing of the EEG in its absence, but also evidences behaviors in which the Hcrt-to-NA signaling pathway may serve to curb hyperarousal. Moreover we show that altered waking causes specific changes in ensuing SWS quality, with a selective slow-δ oscillatory component deficit following impaired waking θ/fast-γ activity.

Disclosures: **A. Vassalli:** None. **P. Franken:** None. **S. Li:** None. **M. Tafti:** None.

Poster

241. Sleep: Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 241.22/LL14

Topic: F.08. Biological Rhythms and Sleep

Support: P50 HL117929 (Taylor) pilot to K.N.P.

8G12MD007602 to J.C.E.

5T32HL7609-29 to to C.L.G.

Title: A causal role for sleep in resilience to chronic social defeat stress

Authors: *C. L. GRAY[1], B. BUSH[1], J. SANCHEZ[1], K. N. PAUL[2], J. C. EHLEN[1]
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Abstract: Neuropsychiatric disorders such as PTSD and depression have sleep dysfunction as a core feature. Sleep dysfunction is often viewed as merely a symptom of these disorders. More recently, sleep has been proposed as a key factor in the severity of neuropsychiatric disorder progression. Furthermore, treatment of sleep dysfunction can ameliorate the severity of these conditions. In these studies we utilized the mouse model of social-defeat stress to understand the mechanism by which sleep is involved in stress-induced neuropsychiatric disorders. Previously, we found measures of sleep homeostasis during baseline sleep could predict susceptibility to stress-induced behavioral changes, namely social avoidance. Based on these findings, we hypothesized that sleep changes are a necessary factor in the stress-induced behavioral changes observed after social-defeat stress. In testing this hypothesis, we performed sleep deprivation in the first five days of social defeat during the first 6 hours of the animals' inactive period. We

predicted that this sleep deprivation would increase susceptibility to social avoidance in defeated mice. We also examined fecal corticosterone levels in order to assess the stress-response associated with sleep deprivation. These measurements were taken during control treatment (novel cage exposure) prior to and during social defeat. Preliminary findings indicate that sleep deprivation during the first five days of social defeat increased resilience to social avoidance. The results also indicate that sleep deprivation during social defeat did not increase the stress response over social defeat alone. Taken together, these data indicate that sleep deprivation increased resilience to social-defeat stress in mice and that the effects of sleep deprivation are not likely to be the result of an increased corticosterone stress response.

Disclosures: C.L. Gray: None. **B. Bush:** None. **J. Sanchez:** None. **K.N. Paul:** None. **J.C. Ehlen:** None.

Poster

241. Sleep: Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 241.23/LL15

Topic: F.08. Biological Rhythms and Sleep

Support: Funding from Université de Montréal

Canada Research Chair in Sleep Molecular Physiology

CIHR Foundation Grant

Title: Implication of 4E-BP1 and 4E-BP2 in sleep architecture and electroencephalographic activity

Authors: *C. C. AREAL[1,2], R. CAO[3], N. SONENBERG[4], V. MONGRAIN[5,2]
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Abstract: Introduction: Several studies support an implication of synaptic proteins in sleep regulation. Nevertheless, little is known about the role of the protein synthesis machinery in sleep. The translational repressors 4E-BP1 and 4E-BP2 normally inhibit protein synthesis, but their phosphorylation by the mTORC1 complex releases their inhibition (1). 4E-BP1 is highly expressed in the suprachiasmatic nucleus and has notably been implicated in circadian rhythms (2). 4E-BP2 that is widely expressed in the brain is critical for memory and plasticity. In addition, 4E-BP2 knockout (KO) mice exhibit autistic behaviours (3). However, there is no data

on their implication in sleep regulation. Hence, the aim of this study is to verify the contribution of 4E-BP1 and 4E-BP2 in sleep regulation.
Methods: Wild-type (WT), 4E-BP1 and 4E-BP2 KO mice were implanted with electroencephalography (EEG) and electromyography (EMG) electrodes and recorded continuously for 48 h including a 24-h baseline followed by a 6-h sleep deprivation (SD) starting at the beginning of the second day. Behavioural states were assessed based on EEG/EMG traces. Changes in mRNA and protein expression after SD in the cerebral cortex were measured by qPCR and Western Blot, respectively. Immunohistochemistry analysis was done on brain slices to localize the expression of 4E-BP1 and 4E-BP2 after SD.
Results: 4E-BP1 KO mice are less awake during the night without changes in sleep fragmentation. Changes in EEG activity were observed for wakefulness and NREM sleep, including less overall delta activity during baseline. However, after SD, the sleep of 4E-BP1 KO mice is similar to WT mice. Analyses for 4E-BP2 KO mice and of the molecular response to SD are underway. Because 4E-BP2 is more expressed in the brain, a stronger phenotype is expected.
Conclusion: Our findings indicate that the protein synthesis machinery has a role in the regulation of sleep and wakefulness. More precisely, our results show that the translational repressor 4E-BP1 regulates vigilance state duration and EEG activity.
(1) Laplante M, Sabatini DM: *J Cell Sci* 2009, **122**:3589-3594.
(2) Cao R et al.: Neuron 2013, 79:712-724.
(3) Aguilar-Valles A et al.: J Neurosci 2015, 35:11125-11132.

Disclosures: C.C. Areal: None. **R. Cao:** None. **N. Sonenberg:** None. **V. Mongrain:** None.

Poster

241. Sleep: Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 241.24/LL16

Topic: F.08. Biological Rhythms and Sleep

Title: Sleep quantity influences stress perception, daytime sleepiness, and depresive symptoms

Authors: *R. WILLIAMSMORRIS[1], T. RAMBANA[2], R. ROBERTS[2]
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Abstract: Poor sleep quality and consequent adverse outcomes have been well documented in the research literature as they specifically relate to the nursing profession. Empirical evidence supports the claim that problems with sleep have impacts on nurses' health, the quality of their work performance, and the risk of medical errors. Being a profession implicated understood to be stressful, previous research has discovered that stress, both acute and chronic, is related to both subjective and objective measures of stress in study participants who are nurses. Other studies

show that there is a continuous decline in sleep quality in nurses from their days as students into the first years of their professional lives.
The purpose of this study was to examine the relationships among the following variables: quantity of nightly sleep, daytime sleepiness, and depressive symptoms, subjective and objective measures of stress in a sample of nursing students at a university in the southeastern United States. 27 participants (19 female) were administered the Epworth Sleepiness Scale, Center for Epidemiological Studies- Depression (CES-D), a self-rating scale on how stressed they felt at the moment, and measurements of their blood pressure (diastolic/systolic). Participants were randomly assigned to either a control or experimental condition. The control condition consisted of participants watching a relaxing nature video for fifteen minutes which in the experimental conditions, participants were administered a very difficult math test with the advanced instructions that the test could be indicative of future success in the nursing field.
Results show that the average age of participants was 22 .88 years who slept on average 6.98 hours of sleep per night, had an average amount of daytime sleepiness (8.96), exhibited less than the norm in depressive symptoms, had normal blood pressure readings, and about average subjective self-reported measures of stress. Correlational analysis showed a positive relationship between quantity of nightly sleep and daytime sleepiness, accounting for 22% of the variation explained.

Disclosures: R. Williamsmorris: None. **T. Rambana:** None. **R. Roberts:** None.

Poster

241. Sleep: Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 241.25/LL17

Topic: F.08. Biological Rhythms and Sleep

Support: NIH P01 NS083514-03

Title: A nap but not quiet rest prevents local EEG changes induced by intensive training with a motor adaptation task

Authors: *A. B. NELSON[1], R. MEHRARAM[1], S. RICCI[1], E. TATTI[1], P. PANDAY[1], M. BOSSINI-BAROGGI[1,2], B. ARULEBA[1], G. TONONI[3], C. CIRELLI[3], M. F. GHILARDI[1]
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Abstract: We previously found that extended practice on a task of visual sequence learning leads to increase in errors on a test that required similar neural and cognitive resources. Such behavioral effects were reversed by a nap but not by quiet rest. Here we determined whether

intense training in a motor adaptation task to rotated visual displays (ROT) leads to progressive, regionally-specific EEG changes during the execution a brief motor test (MOT), a simple motor reaching test partly sharing the neural substrates of ROT, and whether a nap or quiet rest reverses such EEG changes. We hypothesize that the EEG changes should involve the low frequency spectrum (<8Hz) and may represent neuronal tiredness likely induced by increased synaptic weight.

Twenty young subjects performed a reaching task with visuomotor learning (ROT) in one-hour blocks, three in morning (AM) and three in the afternoon (PM). Before and after each block, we assessed performance in MOT that shares some neural substrates and characteristics of ROT but not the learning component. After the AM session, ten subjects slept for 90 minutes (NAP) and ten subjects rested quietly with eyes closed (REST). High-density EEG (256 electrodes) was recorded throughout the entire experiment.

Performance in MOT was similar in the two groups in AM, but worsened in the PM in the REST group and not in the NAP group. EEG analyses of MOT revealed an activation pattern similar to ROT with a prominent beta modulation over the left sensorimotor and a frontal area and with alpha activity in a right posterior parietal area. Compared to the first MOT, the three AM MOT recordings showed a progressive significant power increase in electrodes over the left sensorimotor area that involved, first, alpha (19 to 27%) and then the low frequencies (5 to 25%). Similar progressive increases were found in the other two areas. In the PM, the REST group showed a further progressive increase of power in the low frequency range in the left sensorimotor area from 3 to 50% compared to the last AM recording. The first MOT recorded after the NAP was instead similar to the first AM MOT with a decrease of 28% compared to the last AM MOT with a modest increase (10%) in the subsequent MOTs.

These results demonstrate that intense training leads to EEG progressive local changes involving the low frequency spectrum. Most importantly, we found that sleep but not quiet rest restores performance and activation EEG patterns in the areas previously involved in learning. In agreement with previous studies in humans and animals, such changes are likely to represent neuronal tiredness induced by increased number of synapses and thus, by greater need of cellular supplies and energy consumption.

Disclosures: **A.B. Nelson:** None. **R. Mehraram:** None. **S. Ricci:** None. **E. Tatti:** None. **P. Panday:** None. **M. Bossini-Baroggi:** None. **B. Aruleba:** None. **G. Tononi:** None. **C. Cirelli:** None. **M.F. Ghilardi:** None.

Poster

241. Sleep: Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 241.26/LL18

Topic: F.08. Biological Rhythms and Sleep

Support: NIH P01 NS083514-03

Title: Intensive training with a visual learning task induces local increases of EEG low frequencies during a test with similar characteristics

Authors: *E. TATTI[1], S. RICCI[1], A. B. NELSON[1], J. LIN[1], P. PANDAY[1], M. GADALLA[1], J. BORKOWSKI[1], G. TONONI[2], C. CIRELLI[2], M. F. GHILARDI[1]
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Abstract: We have previously found that extended practice on a task of visual sequence learning (VSEQ) leads to a trace in the spontaneous EEG recorded at rest in the areas that are active during the task. This trace is evident as an increase in low frequencies (< 8Hz) power. Here we determine whether intensive training in VSEQ leaves progressive, regional-specific EEG changes in the EEG recorded during MEM, a test that requires similar cognitive resources and shares neural bases with VSEQ. We hypothesize that such changes will involve the low frequency spectrum and thus might reflect neuronal tiredness likely induced by local increases in synaptic weight.
Twenty-eight subjects performed VSEQ, a task involving visual sequences learning and, thus, significant attentional and memory load in one-hour blocks, for a total of three blocks. During VSEQ subjects learned 12-element sequences presented on a screen. Before and after each block, we assessed performance in a brief visual working memory test (MEM), for a total of four MEMs. In MEM, sequences of 6 targets were presented at a 1/s interval (TARGET): subjects were requested to learn the sequence, to hold it in memory for 10 second (HOLD) and to verbalize it. Similar to VSEQ, MEM engages attention and working memory mechanisms, but unlike VSEQ, mem does not require subjects to form long-term sequence memory. High-density EEG (256 electrodes) was recorded throughout the experiment.
On average subjects learned nine sequences per each VSEQ block. During VSEQ we found a significant activation pattern that included increase of power in the electrodes over frontal, right temporal and left parieto-occipital areas in the theta and alpha range. EEG analyses of MEM during TARGET presentation revealed, compared to the first MEM, a progressive and significant increase in power in electrodes over the left frontal area that involved theta (MEM4: 150%) and delta range (MEM4: 58%). Significant increases were found for the right temporal area: in MEM4 theta increased to 65% and delta 43%. During HOLD, instead we found significant power increases in a centro-frontal area, a right temporal and a left parieto-occipital areas that involved alpha (40%) theta (50%) and delta (20%) ranges.
These results demonstrate that intense training leads to local, task-related increases in EEG low frequency ranges that reflect the protracted use of such areas and thus might represent neuronal tiredness.

Disclosures: E. Tatti: None. **S. Ricci:** None. **A.B. Nelson:** None. **J. Lin:** None. **P. Panday:** None. **M. Gadalla:** None. **J. Borkowski:** None. **G. Tononi:** None. **C. Cirelli:** None. **M.F. Ghilardi:** None.

Poster

241. Sleep: Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 241.27/LL19

Topic: F.08. Biological Rhythms and Sleep

Support: NIH P01 NS083514-03

Title: Intensive practice induces progressive task-specific changes in the spontaneous EEG during rest

Authors: *S. RICCI[1,2], A. B. NELSON[1], J. LIN[1], P. PANDAY[1], R. MEHRARAM[1], B. O. THOMSON[1], H. CHEN[1], C. CIRELLI[3], G. TONONI[3], M. F. GHILARDI[1]
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Abstract: We have found that intense training in a task leads to progressive performance worsening in a test that shares its characteristics and neural substrates even without sleep deprivation. This is accompanied by a progressive, specific power increase in low frequencies in the test over the areas that are active in both task and test (Nelson et al. NS abstract 2017). Here we will determine whether such specific, practice-related EEG changes are also present in the spontaneous EEG (sEEG) recorded during rest after the execution of two tasks that require different neural substrates and different cognitive demands.
Twenty-seven subjects (age 19-26) were tested on two separate days with high-density EEG (256 electrodes) recorded throughout the sessions. One day they performed a task involving visual sequences learning (VSEQ); the other, a task of motor adaptation to rotated displays (ROT). In both days, tasks were performed in the morning in one-hour blocks for a total of three blocks. Each block was preceded and followed by a 2-minute recording of sEEG with eyes open.
In VSEQ, subjects learned an average of 9 sequences of 12 targets each, without difference between blocks. In ROT, all subjects adapted to the rotated displays with an average error < 5° at the end of the each block. EEG analyses revealed during VSEQ a significant activation of the electrodes on left frontal and left temporo-parietal areas as well as right temporal area in the theta and alpha range, while during ROT we found significant modulation of beta power over the left sensorimotor and frontal area and of alpha power in a right posterior parietal area, as described in previous studies. sEEG recorded after the first block of VSEQ showed prominent significant increase (25%) of alpha power over the right temporal area. In the subsequent sEEGs, we found further increase in the same area in alpha (50 %) but also in theta (20-47%) and delta ranges (10 & 26%). Significant increases with a similar progression but of lesser magnitude were found also over the left frontal and temporo-parietal areas. sEEG recorded after ROT showed increase in

electrodes over the left sensory motor area in alpha power (30 and 50%) that spread to the theta (14 and 30%) and delta (5 and 12%) ranges in the sEEGs recorded after the second and third ROT blocks. Similar increases were also seen for the other clusters of electrodes over the left frontal and right posterior parietal area.
We conclude that intense training leads to task-specific traces in the sEEG localized in the areas active during the task, progressively promoting power increase in the low frequency range. This might reflect neuronal tiredness induced by practice-related increase of synaptic weight.

Disclosures: S. Ricci: None. **A.B. Nelson:** None. **J. Lin:** None. **P. Panday:** None. **R. Mehraram:** None. **B.O. Thomson:** None. **H. Chen:** None. **C. Cirelli:** None. **G. Tononi:** None. **M.F. Ghilardi:** None.

Poster

241. Sleep: Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 241.28/LL20

Topic: F.08. Biological Rhythms and Sleep

Support: Ribble Mini Grant - Biology

Title: The effect of previous night sleep on the psychomotor vigilance boost following meditation

Authors: *L. E. GUERRIERO, S. S. JOSHI, W. NOWAK, B. F. O'HARA
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Abstract: In a previous study by our lab, meditation was shown to improve psychomotor vigilance even in novices. Performance is measured using the psychomotor vigilance test (PVT) which measures reaction time and performance errors over a sustained period of time (e.g. 10 min). During complete sleep deprivation, performance was impacted but was still improved with meditation. The current study aims to further investigate this relationship by gathering more data on sleep and how it effects meditation. Sleep data were gathered using actigraphy, a sensor worn on the wrist to gather movement and light exposure. In the field of meditation research, there have been many studies done suggesting improvements, but controls for these “treatment” effects are often lacking or difficult to obtain. A majority of studies have utilized between-subject comparisons of meditators and non-meditators, which lack some of the power of within-subject comparisons. This study used a within-subjects’ design to reduce problems of inter-subject variability and also attempts to control for both meditation effect and for closed eyes associated physiological changes. The meditation done in this project was a simple, focused-breathing, concentrative meditation done with closed eyes. Two controls conditions were used: an eyes-closed sedentary activity and an eyes-open sedentary activity. To investigate how long a

person must meditate to receive the previously described performance boost, 5 and 20-minute testing protocols are used. Data analysis has shown that subjects with short sleep (< 6 hours of sleep) perform more poorly on the PVT, with normal (6-8 hours) and long sleepers (> 8 hours) performing better before meditation. All sleep groups showed better performance after 20 minutes of meditation, with 5 minute bouts still in-conclusive Meditation and sleep are likely to interact bi-directionally, via increases in cortical neuron synchronization or other physiological changes that may be similar during these otherwise distinct arousal states.

Disclosures: L.E. Guerriero: None. **S.S. Joshi:** None. **W. Nowak:** None. **B.F. O'Hara:** None.

Poster

241. Sleep: Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 241.29/LL21

Topic: F.08. Biological Rhythms and Sleep

Support: Y1AA-3009

Title: What is in your sleep? Test-retest reliability, age and gender differences in sleep stages and their potential consequences for brain health

Authors: *S. B. DEMIRAL[1], *K. KE[1], *T. SRIVASTAVA[1], *A. ZEHRA[1], *V. RAMIREZ[1], *C. FREEMAN[1], *C. WEIRS[1], *G.-J. B. WANG[1], N. D. VOLKOW[2]
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Abstract: Sleep is an important component of our life. Lack of sleep can lead to fatigue, and dementia, acting as a precursor for Alzheimer disease (Lim et al., 2013). Assessing long-term sleep habits is mainly done via questionnaires or actigraphy (Buysse et al., 2008), while polysomnography (PSG) is generally used as a short-term clinical diagnostic tool. The number of studies exploring the relationship between sleep stages (i.e., sleep duration, slow-wave sleep, rapid-eye movement (REM) sleep) to questionnaire and actigraphy data is limited (Grandner, Kripke, Yoon, & Youngstedt, 2006). Understanding long- and short-term changes, and gender differences in sleep patterns can provide an important link to determine the potential effects of sleep stages on brain health. Increased availability of mobile sleep recording devices represents a perfect opportunity to evaluate test/re-test reliability and validity of sleep preferences. Here, we use Sleep Profiler device (Levendowski, Popovic, Berka, & Westbrook, 2012), to detect sleep tet/re-test reliability of the durations of sleep stages measured in two nights while patients stayed in the Inpatient Unit (N=23, 11 females (age=39.1±11.3); 12 males, age=39.2±12.1). We also calculated mean duration of sleep stages, and examined age and gender differences. We found that the highest sleep reliability was in N3 (slow-wave/deep sleep; Chronbach α: .96), followed by shallow sleep stages N2(α=.67), and N1(α=.58), where REM sleep reliabilty was very low

(.32). In addition, there was a significant positive correlation between age and N1 sleep duration (r^2=.32), while aging reduced REM and N3 sleep durations (ns) (and also did not show a significant effect on overall sleep duration.) There was a trending effect between males and females (females > males in N3 and REM sleep; males > females in N1 and N2). Our results indicate that aging increases shallow sleep (N1) duration replacing N3 and REM, while gender and individual differences can modulate the proportion of this effect.

Disclosures: S.B. Demiral: None. **K. Ke:** None. **T. Srivastava:** None. **A. Zehra:** None. **V. Ramirez:** None. **C. Freeman:** None. **C. Weirs:** None. **G.B. Wang:** None. **N.D. Volkow:** None.

Poster

241. Sleep: Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 241.30/LL22

Topic: F.08. Biological Rhythms and Sleep

Support: CSIC_I+D_2016, UdelaR, Uruguay

Title: Consequences of the extreme nocturnality of the Uruguayan youth

Authors: *A. SILVA[1], I. ESTEVAN[2], D. SIMÓN[3], B. PANNUNZIO[1], B. TASSINO[4]
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Abstract: Two main topics derived from modern urban life are in current debate in Chronobiology: the consequences of increasing daily light exposure, and of the internal clock chronic desynchronization imposed by social schedules. Both topics are exacerbated in persons with late chronotypes. In this study, we took advantage of the extreme nocturnality recently reported in Uruguay (South America) to address both issues. The impact of light on sleep habits and changes in the dim light onset of salivary melatonin pulse of a group of university students (24.5 ± 3.1 y/o, n=20) were compared between the semester start in the fall equinox 2016 (Montevideo, Uruguay, 34° 54’ S; 56° 11’ W, LD 12:12) and the 2016 Uruguayan Summer Antarctic School (King Georges Island, 62° 11’ S; 58° 52’ W, LD 20:4). The Munich Chronotype Questionnaire confirmed the lateness of the population: midsleep point of free days corrected for sleep debt on work days (MSFsc=5.8 ±0.9 h, proxy of individuals’ chronotype), and social jetlag (SJL=1.8±0.7 h, misalignment between individual biological clock and social time). Actimetry showed that students were significantly more exposed to natural daylight in Antarctica versus Montevideo. Sleep logs showed that midsleep point, waking time, and sleep duration were significantly lower in Antarctica versus Montevideo, while sleep onset time

remained unchanged. Social pressures upon the circadian clock may likely explain these changes as only the subpopulation of students in which waking time was < 8 am in both sites, significantly delayed their sleep onset time in Antarctica versus Montevideo, probably due to the long-lasting light exposure of the Antarctic summer. The impact of circadian desynchronization on academic performance was evaluated in high school students (16.5 ± 1.1 y/o) between the morning (starting at 7:30 am, n=109) and afternoon (starting at 11:30 am, n=94) shifts of the Public High School N°10, Montevideo, Uruguay. Afternoon students were extremely late (MSFsc=7.1±1.6 h), but reported an adequate sleep duration during weekdays (SDw=8.1±1.4 h). In contrast, morning students reported an important sleep deprivation (SDw= 6.4±1.3 h) but the expected average chronotype for their age (MSFsc=5.5±1.6 h). Interestingly, only the morning-shift-students' academic performance (actual 2016 average mid-term grades provided by the institution) correlated with circadian preferences, indicating that the desynchronization of the biological clock impacts more than lateness in academic achievement. Taken together, these evidences stress the advantages of Uruguayan youth to evaluate the effects of environmental and social pressures on the circadian clock.

Disclosures: A. Silva: None. **I. Estevan:** None. **D. Simón:** None. **B. Pannunzio:** None. **B. Tassino:** None.

Poster

242. Appetitive and Incentive Learning and Memory I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 242.01/LL23

Topic: G.01. Appetitive and Aversive Learning

Support: Natural Science and Engineering Research Council 387224-2010

Title: Temporally-defined optogenetic activation of the infralimbic cortex attenuates the renewal of Pavlovian sucrose-seeking

Authors: *F. R. VILLARUEL, N. CHAUDHRI
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Abstract: Background: The infralimbic cortex (IL) is thought to promote extinction: however, the temporal relation between IL activity and response suppression after extinction is poorly understood. Using an appetitive Pavlovian conditioning procedure, we tested the hypothesis that IL activity during epochs in which subjects expect but do not receive reinforcement mediates response suppression following extinction.
Methods: We used *in vivo* optogenetics to examine the impact of selectively activating the IL either during non-reinforced conditioned stimulus (CS) trials or inter-trial intervals (ITI) on context-induced renewal. Male, Long-Evans rats received IL microinfusions of a virus

containing channelrhodopsin with enhanced yellow fluorescence protein (ChR2-eYFP) or eYFP alone (0.5 µL, unilateral) and implanted with an optical fiber targeting the IL (AP +2.9; ML +/- 0.6; DV -5.1). After recovering, rats received Pavlovian conditioning in a distinct context (Context A) in which a conditioned stimulus (10 s white noise) was paired with the delivery of 10% sucrose into a fluid port (0.2 mL per CS trial, 14 trials per session). Entries into the port before, during and after the CS were recorded. In a different context (Context B), rats then underwent extinction, in which the CS was presented but sucrose was withheld. In subsequent renewal tests, rats were returned to Context A and presented with the CS in the absence of sucrose. At test, optogenetic activation (473 nm, 20 Hz, 5 ms pulse) of the IL either coincided with CS trials or occurred outside of the CS, during the ITI.
Results: We found that optical activation of IL neurons during the CS, but not during the ITI, significantly attenuated the renewal of sucrose-seeking. Further, CS-paired optical activation of the IL reduced the duration of port entries and increased the latency to initiate a port entry during the occurrence of the CS. These data suggest that the role of the IL in maintaining response suppression after extinction may be temporally bound to the occurrence of the CS. Ongoing studies are investigating the role of neural projections from the IL to the nucleus accumbens shell and the basolateral amygdala in the renewal of context-induced sucrose-seeking.

Disclosures: F.R. Villaruel: None. **N. Chaudhri:** None.

Poster

242. Appetitive and Incentive Learning and Memory I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 242.02/LL24

Topic: G.01. Appetitive and Aversive Learning

Support: NIH Grant R01DA027688

NIH Grant F31MH107138

First-Year Summer Research Award from Dartmouth College

Title: Increased sign-tracking behavior and incentive salience in adolescent rats

Authors: *N. E. DEANGELI[1], S. B. MILLER[1], H. C. MEYER[2], D. J. BUCCI[1]
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Abstract: Compared to adults, adolescents exhibit hyper-sensitivity to primary rewards as well as increased sensitivity to the rewarding qualities of drugs and alcohol. Importantly, adolescents also display increased responsiveness to otherwise neutral cues that come to predict reward. In other words, in adolescents, conditioned stimuli (CSs) are more apt to elicit behaviors directed

towards obtaining the reward. This is particularly significant in the context of drug use since an increased sensitivity to drug-related cues has been associated with addiction and substance abuse. One explanation for this increased sensitivity is that stimuli paired rewards become imbued themselves with excessive incentive salience, or motivational value. Here we used an autoshaping procedure to test the notion that CSs gain greater incentive salience during adolescence than adulthood. Rats were single-housed and placed on food restriction during 10 daily training sessions in which a lever (CS^+) was presented then followed immediately by a food unconditioned stimulus (US). A second lever (CS^-) was presented on intermixed trials and was not reinforced. Despite the fact that food delivery was not contingent on the rats' behavior, all rats exhibited behaviors directed towards the lever (i.e., sign-tracking). In the adolescent group, the rate of lever pressing and the percentage of trials with a lever press were higher than in adults. Group differences were not observed when rats were retrained when the adolescents had reached adulthood. These findings support the hypothesis that cues that come to predict reward become imbued with excessive motivational value in adolescents, perhaps contributing to the hyper-responsiveness to reward-related stimuli typically observed during this period of development.

Disclosures: **N.E. DeAngeli:** None. **S.B. Miller:** None. **H.C. Meyer:** None. **D.J. Bucci:** None.

Poster

242. Appetitive and Incentive Learning and Memory I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 242.03/LL25

Topic: G.01. Appetitive and Aversive Learning

Support: NSERC

Title: Theophylline blocks the acquisition of inverse incentive learning in rodents

Authors: *J. F. ROCCA, R. J. BENINGER
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Abstract: Contextual stimuli paired with dopamine D2-like receptor antagonists like haloperidol lose the ability to elicit approach and other responses, a phenomenon referred to as inverse incentive learning. This form of learning is revealed by sensitization of descent latencies in the bar test, and conditioned increases in descent latency following a saline-only injection. Adenosine A2A receptors are co-localized on D2 receptor-expressing medium spiny neurons in the striatum, and A2A receptor antagonism has been shown to modulate effects of dopamine antagonists (Beeler et al., 2012). In this study we assessed the potential role of A2A receptors in inverse incentive learning by administering 0, 0.1, 5, or 10 mg/kg of the adenosine receptor antagonist, theophylline, with 0.25 mg/kg haloperidol prior to daily conditioning sessions with

the bar test. Animals in the 0 and 0.1 mg/kg theophylline group showed a gradual increase in descent latency in the bar test across 10 conditioning days with haloperidol. Animals given 5 or 10 mg/kg showed significantly less sensitization to haloperidol. All animals except those that received 0 mg/kg theophylline failed to show a conditioned increase in descent latencies when tested drug free. In a second experiment, the same doses of theophylline were given but after 10 days of conditioning with haloperidol only. Co-administration of theophylline with haloperidol for the next ten days produced a decrease in descent latencies, but statistical tests failed to reach significance. Together, these data suggest a role for the adenosine A2A receptor in the acquisition, more so than the expression, of inverse incentive learning. These data may help further our understanding of the interaction between adenosine and dopamine in the control of behaviour, and may have implications for the pathophysiology and treatment of disorders of dopamine regulation.

Disclosures: J.F. Rocca: None. **R.J. Beninger:** None.

Poster

242. Appetitive and Incentive Learning and Memory I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 242.04/LL26

Topic: G.01. Appetitive and Aversive Learning

Support: NIH Grant R56DA03558

NIH/NIDA Grant R01DA019473

NIH/NIDA Grant R01DA038412

NARSAD Young Investigator Award

The Klarman Family Foundation. Two-year award

Title: Blocking NMDA receptors in the nucleus accumbens interferes with appetitive conditioning: What are the specific effects on learning and learning-related neuronal activity?

Authors: *M. VEGA VILLAR[1,2], J. C. HORVITZ[3], S. M. NICOLA[2]
[1]The Grad. Center, CUNY, New York, NY; [2]Dept. Psychiatry, Albert Einstein Coll Med., Bronx, NY; [3]Dept Psychology, City Col., New York, NY

Abstract: Various studies suggest that NMDA receptor activation in the nucleus accumbens (NAc) is necessary for reward-related learning to occur. This conclusion is drawn from the finding that blockade of NMDA receptors in the NAc during training impairs acquisition of different kinds of reward-directed behaviors. However, NMDA receptor antagonists might

interfere with performance as well, which makes their specific effects on acquisition hard to interpret. The goal of this study was to specifically examine the role of accumbens NMDA receptors on learning by using an experimental design that addresses the abovementioned confound. In this study, animals in two groups received either infusions of an NMDA receptor antagonist (*AP5 group*) or saline infusions (*yoked vehicle group*) in the NAc core throughout training in a cued approach task. The behavioral paradigm was designed to ensure that both groups received the cue alone, or the cued paired with reward, the same number of times. As a result, any observed differences in learning between these two groups cannot be attributed to a performance deficit. By eliminating this confound, we observed that blockade of NMDA receptors in the NAc interferes with acquisition of cued reward approach behaviors independent of effects on performance.
Consistent with the behavioral observations, electrophysiological unit recordings in behaving animals demonstrated that cue-evoked excitations emerge in NAc neurons during task acquisition. These excitations are necessary for the cued approach response (Du Hoffmann and Nicola, J Neurosci 2014). We are using a novel technique that enables colocalized simultaneous unit recordings and local infusions to determine whether NMDA receptor blockade within the NAc prevents the appearance of these excitations in NAc neurons during learning, thus describing a mechanism by which NMDA receptor-dependent plasticity in the NAc facilitates the acquisition of cued approach.

Disclosures: **M. Vega Villar:** None. **J.C. Horvitz:** None. **S.M. Nicola:** None.

Poster

242. Appetitive and Incentive Learning and Memory I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 242.05/LL27

Topic: G.01. Appetitive and Aversive Learning

Support: Israel Science Foundation (Grant No. 757/16)

DFG

Gatsby Charitable Foundation

Title: Striatal action-value neurons reconsidered

Authors: *L. ELBER-DOROZKO, Y. LOEWENSTEIN
Hebrew Univ., Jerusalem, Israel

Abstract: It is generally believed that striatal neurons represent the values associated with different actions. This hypothesis is based on a large number of electrophysiological studies, in which the activity of striatal neurons was measured while the subject was learning to prefer the

more rewarding action in a repeated, two-alternative operant learning experiment (e.g., Semajima et al. 2005, Science; Lau and Glimcher, 2008, Neuron; Kim et al. 2009, J. Neurosci.; Wang et al. 2013, Nat. Neurosci.; Ito and Doya, 2015, J. Neurosci.). Typically, the spike count of recorded neurons is regressed on the values of the actions and the neurons whose regression coefficient on exactly one of the action-values is significant are considered action-value neurons. Here, we point out that when applying this method, and other methods considered in this literature, researchers have ignored a known caveat in regression analysis - it can result in erroneous identification of neurons as representing action-values if the firing rates are temporally correlated. This occurs because both the predictors (action-values) and the independent variable (spike counts) are temporally correlated. Therefore, trials are not independent, violating the independence assumption of the statistical analysis.
To demonstrate this, we used Q-learning to simulate learning in a two-alternative operant task. We applied the regression analysis on the spike counts of simulated Poisson neurons, whose firing rate follows a random-walk process, using action-values estimated from our simulations as predictors. Remarkably, this analysis erroneously identified a substantial fraction of the random-walk neurons (~40%) as representing action-values. This fraction of identified “action-value” neurons is comparable with those previously reported in the striatum. Similar results were obtained when considering the spike counts of motor cortex, auditory cortex and basal ganglia neurons, recorded in unrelated experiments.
Furthermore, we show that even alternative analyses used to find action-value, which were aimed specifically to address the issue of temporal correlations, still erroneously detect action-value representations in unrelated recordings. We propose a new method for identifying action-value neurons that is not subject to this caveat. Employing this method on neuronal recordings from the ventral striatum, in which action-value representations had been previously detected, we fail to detect action-value representations. Following a systematic literature search we conclude that there is no conclusive evidence for the generally-accepted belief that striatal neurons encode action-values.

Disclosures: L. Elber-Dorozko: None. **Y. Loewenstein:** None.

Poster

242. Appetitive and Incentive Learning and Memory I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 242.06/LL28

Topic: G.01. Appetitive and Aversive Learning

Title: Resolving ambiguity to facilitate extinction learning in sign-trackers and goal-trackers

Authors: *C. CARR[1], T. E. ROBINSON[2]
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Abstract: Reward-associated cues (conditioned stimuli, CS) are attributed with incentive salience to a greater degree in some animals (sign-trackers, STs) than others (goal-trackers, GTs). While initially highly adaptive, incentive stimuli can also contribute to maladaptive behaviors such as overeating and drug seeking, and therefore, extinction training has been used to try and reduce such undesired behaviors. This has not proven very effective, however, in part because extinction leaves the initial memory intact, as indicated by several post-extinction phenomena, such as spontaneous recovery and reinstatement; the latter referring to the return of conditioned responding after re-exposure to the unconditioned stimulus (US). Dunsmoor et al. (2015) developed a novelty facilitated extinction (NFE) procedure that appeared to successfully reduce the ambiguity of the CS following fear conditioning by signaling a change in the environment to promote new learning, and providing a more substantive alternative association. Here we sought to apply this procedure to an appetitive Pavlovian conditioned approach procedure that produces STs and GTs, as STs are relatively resistant to Pavlovian extinction (Ahrens et al., 2016). Following Pavlovian conditioned approach training using a lever-CS, Sprague-Dawley rats were classified as STs or GTs and assigned to one of two extinction conditions. Both procedures began with five CS only trials, but the remaining 25 CS only trials were accompanied by a novel compound light and tone stimulus during the last 6 s of the lever presentation in the NFE version. Both spontaneous recovery and reinstatement were assessed a week after extinction training. The NFE procedure did not result in significant differences on any measures of conditioned responding for STs or GTs. However, following extinction, in a test for reinstatement, GTs significantly reinstated magazine-directed conditioned responding, preferentially during presentation of the CS. In contrast, STs did not reinstate lever-directed conditioned responding when exposed to the US, but instead increased non-specific magazine directed behavior. Previous research suggests that GTs are influenced to a greater degree by changes in context, and given that reinstatement has been suggested to be due to a change in context, broadly defined, this may explain these results. These findings further suggest that other approaches may be required to facilitate appetitive Pavlovian extinction, in the attempt to reduce potentially maladaptive behavior.

Disclosures: C. Carr: None. **T.E. Robinson:** None.

Poster

242. Appetitive and Incentive Learning and Memory I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 242.07/LL29

Topic: G.01. Appetitive and Aversive Learning

Title: Chemogenetic activation/inhibiton of dorsal vagal complex (DVC) regulates feeding and energy homeostasis in ChAT-cre mice

Authors: *C. NAMKOONG[1,2], H.-I. SONG[1], M.-S. KIM[1,3], Y.-H. LEE[1,3], J. LEE[1], D. CHEON[1,3], H. SONG[1,3], J.-W. SOHN[4], S.-Y. SEONG[5], H.-J. CHOI[1,3,2,5]
[1]Seoul Natl. Univ. Colleage of Med., SEOUL, Korea, Republic of; [2]Neurosci. Res. Inst., Seoul, Korea, Republic of; [3]BK21Plus Biomed. Sci. Project Team, Seoul, Korea, Republic of; [4]Dept. of Biol. Sci., KAIST, Daejeon, Korea, Republic of; [5]Wide River Inst. of Immunol., Hong Chun, Korea, Republic of

Abstract: Neural circuits are known to regulate food intake and energy expenditure, in the brainstem (NTS;DMV) and hypothalamic (LH,PVH,ARC) nuclei. The dorsal vagal complex (DVC) encompasses the nucleus tractus solitarii (NTS), the dorsal motor nucleus of the vagus nerve (DMX) modulate autonomic nervous system. Which regulates fuel availability, feeding behavior, energy storage and glucose metabolism in liver, adipose tissue, pancreas and other organs. However, the direct role of DVC on appetite and energy metabolism has been poorly understood. In the present study, we investigated the role of DVC in regulation of feeding behavior and energy metabolism by chemogenetic methods using DREADDs (designer receptors exclusively activated by designer drugs). The stimulatory hM3Dq and inhibitory hM4Di DREADD receptors were selectively expressed on a population of neurons in dorsal motor nucleus of the vagus (DMV) and NTS by stereotaxic surgery infusion of cre-recombinase-dependent adeno-associated virus vectors into the DVC of Phox2b-Cre and ChAT-IRES-Cre mice. Acute activation of DVC by intraperitoneal i.p injection of the M3-muscarnic receptor ligand clozapine-N-oxide (CNO) (1mg/kg), significantly suppressed food intake. During intraperitoneal glucose tolerance test, DVC activation via hM3Dq significantly decreased blood glucose, whereas DVC inhibition via hM4Di significantly increased blood glucose. Stimulation of DVC complex via i.p injection of CNO(1mg/kg) increased oxygen consumption and energy expenditure by Comprehensive Laboratory Animal Monitoring System (CLAMS). These results suggest that direct activation of DVC decreases food intake and improve glucose tolerance. These findings indicate that dysfunction of the DVC could predispose type 2 diabetes mellitus, and modulating DVC could be a therapeutic target for obesity and type 2 diabetes mellitus.

Disclosures: C. Namkoong: None. **H. Song:** None. **M. Kim:** None. **Y. Lee:** None. **J. Lee:** None. **D. Cheon:** None. **H. Song:** None. **J. Sohn:** None. **S. Seong:** None. **H. Choi:** None.

Poster

242. Appetitive and Incentive Learning and Memory I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 242.08/LL30

Topic: G.01. Appetitive and Aversive Learning

Support: BBSRC (grant number BB/M009017/1)

The University of Sussex Strategic Development Funds

Sussex Neuroscience 4-year PhD programme

Sussex School of Psychology Impact Funds

Title: Changes in appetitive associative strength modulates nucleus accumbens, but not orbitofrontal cortex neuronal ensemble excitability

Authors: *E. KOYA, S. HESSLER, M. C. SIEBURG, G. MARGETTS-SMITH, H. S. CROMBAG, J. J. ZIMINSKI
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Abstract: Cues that predict the availability of food rewards influence motivational states and elicit food-seeking behaviors. If a cue no longer predicts food availability, animals may adapt accordingly by inhibiting food seeking responses. Sparsely activated sets of neurons, coined neuronal ensembles, have been shown to encode the strength of reward-cue associations. While alterations in intrinsic excitability have been shown to underlie many learning and memory processes, little is known about these properties specifically on cue-activated neuronal ensembles. We examined the activation patterns of cue-activated orbitofrontal cortex (OFC) and nucleus accumbens (NAc) shell ensembles using wild-type and Fos-GFP mice following appetitive conditioning with sucrose and extinction learning. We also investigated the neuronal excitability of recently activated, GFP+ neurons in these brain areas using whole-cell electrophysiology in brain slices. Exposure to a sucrose cue elicited activation of neurons in both the NAc shell and OFC. In the NAc shell, but not the OFC, these activated GFP+ neurons were more excitable than surrounding GFP— neurons. Following extinction, the number of neurons activated in both areas was reduced and activated ensembles in neither area exhibited altered excitability. These data suggest that learning-induced alterations in the intrinsic excitability of neuronal ensembles is regulated dynamically across different brain areas. Furthermore, we show that changes in associative strength modulate the excitability profile of activated ensembles in the NAc shell.

Disclosures: E. Koya: None. **S. Hessler:** None. **M.C. Sieburg:** None. **G. Margetts-Smith:** None. **H.S. Crombag:** None. **J.J. Ziminski:** None.

Poster

242. Appetitive and Incentive Learning and Memory I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 242.09/LL31

Topic: G.01. Appetitive and Aversive Learning

Support: KBF Research grant (EP)

FWO Research grant 1519516N (EP)

IAP grant P7/10 (JMR)

Title: The glycine alpha 2 receptor is required for adequate reward-motivated behavior

Authors: *E. PICCART[1], J. DEVOGHT[1], R. J. HARVEY[2], J.-M. RIGO[1], B. BRONE[1]
[1]Uhasselt, Hasselt, Belgium; [2]UCL Sch. of Pharm., London, United Kingdom

Abstract: The cortico-mesolimbic circuit comprises cortical glutamatergic and midbrain dopaminergic projections to the striatum, and integration of these inputs underlies adequate reward-motivated behavior. We have earlier demonstrated that the homomeric glycine alpha 2 receptor plays a crucial role in the development of the cortico-mesolimbic circuit: glycine alpha 2 receptor knockout mice exhibit impaired proliferation and migration of cortical layer 5 projection neurons as well as striatal medium spiny neurons, a shift in the excitation/inhibition balance of cortical projection neuron activity, and altered cortical input to the striatum at adult age. The role for the glycine alpha 2 receptor on midbrain dopamine neuron activity and cortico-mesolimbically orchestrated reward-related behavior has however not yet been investigated. Here, we hypothesized that burst firing of dopamine neurons in response to cortical input would be impaired in glycine receptor 2 knockout animals, as a result of the earlier described changes in cortical activity. Moreover, we hypothesized that developmental deficits in the cortico-mesolimbic circuit results in altered reward-motivated behavior. We report an enhanced horizontal locomotor response to amphetamine, yet unaltered baseline locomotor behavior recorded over 24 hours. Moreover, an increase in appetitively conditioned nose poke behavior is present in glycine receptor alpha 2 knockout animals at highly demanding reward schedules. We performed a t-maze task in order to distinguish between altered associational learning, hedonic response and motivational deficits, and report both increased learning and motivation. These data, together with earlier data from our lab, clearly show that the glycine alpha 2 receptor is crucial to cortico-mesolimbic circuitry development and function at the cellular, network and behavioral level.

Disclosures: E. Piccart: None. **J. Devoght:** None. **R.J. Harvey:** None. **J. Rigo:** None. **B. Brone:** None.

Poster

242. Appetitive and Incentive Learning and Memory I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 242.10/LL32

Topic: G.01. Appetitive and Aversive Learning

Support: Grant-in-Aid for JSPS Fellows 16J01187

The Uehara Memorial Foundation Post-doctoral Fellowship

Title: Stop the clock: Optogenetic activation of the GABAergic nigrotectal pathway resets interval timing

Authors: *K. TODA[1,3,4], N. A. LUSK[1], G. D. WATSON[1], D. LU[2], W. H. MECK[1], H. H. YIN[1]
[1]Psychology & Neurosci., [2]Neurobio., Duke Univ., Durham, NC; [3]Natl. Inst. of Advanced Industrial Sci. and Technol., Tsukuba, Japan; [4]Japan Society for the Promotion of Sci., Tokyo, Japan

Abstract: Interval timing in the seconds to minutes range is observed across many species. Animals create the sense of interval timing based on the integration of sensorimotor information of self and perceivable objective events in the external world. Previous work has implicated the basal ganglia network in interval timing, yet the underlying mechanisms remain unknown. Here, we designed a novel experimental setup that combined behavioral, computational, and neurobiological approaches to reveal the mechanism of interval timing. Using a fixed-time interval task with head-fixed mice, we examined the role of basal ganglia output in interval timing. Robust and reliable interval timing behavior was trained rapidly in head-fixed mice. We demonstrate that the variance in timing of the licking behavior is proportional to the interval between rewards (scalar property, a hallmark of timing behavior). Furthermore, bouts of licking behavior can be described with discrete stepping dynamics with variable onset times. On sporadic peak probe trials with reward omission, the duration of the lick bout or step onset was determined by motivational state, but centered around the expected time of reward delivery. We expressed channelrhodopsin selectively in GABAergic output neurons of the substantia nigra pars reticulata (SNr), and optogenetically manipulated the basal ganglia projections from SNr to the intermediate/deep layers of the superior colliculus (SC). Photo-stimulation of axon terminals in SC not only stopped ongoing licking movement, but also reset the initiation of anticipatory licking for the next interval. These results suggest that this nigrotectal circuit integrates top down command information about the current behavioral execution and determines the future timing of licking behavior.

Disclosures: K. Toda: None. **N.A. Lusk:** None. **G.D. Watson:** None. **D. Lu:** None. **W.H. Meck:** None. **H.H. Yin:** None.

Poster

242. Appetitive and Incentive Learning and Memory I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 242.11/LL33

Topic: G.01. Appetitive and Aversive Learning

Support: Korea Research Foundation Grant (NRF-2014R1A1A2058480)

Title: Role of lateral habenula in the process that reward prediction error in Pavlovian appetitive conditioning

Authors: *D.-H. KIM, B.-R. CHOI, J.-S. HAN
Konkuk Univ., Seoul, Korea, Republic of

Abstract: Midbrain dopaminergic (DA) system is activated by reward delivery, whereas lateral habenula (LHb), as a major inhibitory center of DA system, is working in an opposite manner. Previous studies have shown that DA system and LHb is involved in reward prediction error. Specifically, LHb is activated and midbrain DA neuron is inhibited when negative prediction error is occurred. However, a specific role of LHb has been not studied so far. Therefore, the present study examined role of LHb in two different training protocols of Pavlovian appetitive conditioning (alterations of probability of reward presentation and changes of reward magnitude). 1) In the training with alterations of probability of reward presentation, all animals received the training with pseudo-random control (PRC) protocol-presented 4 paired light-food and 8 unpaired stimuli (4 unpaired lights and 4 unpaired foods)- during 8 days. On day 9, these rats were divided into three groups and then animals in each group received one of three different training protocols (from PRC to Paired: positive prediction error, PRC to PRC: no change, and PRC to Unpaired: negative prediction error). 2) In the training with alterations of changes of reward magnitude, all animals received the PRC training during 8 days. On day 9, these rats were divided into three groups and then animals in each group received one of three different protocols (increase of reward, no change, decrease of reward). We measured food-cup behavior during Pavlovian conditioning and reward prediction error test. Food-cup behavior was decreased in negative prediction error. In addition, we examined alteration of c-fos expression levels using immunohistochemistry. These results suggest that the LHb would be recruited more in negative reward prediction error than positive reward prediction error. Supported by the Korea Research Foundation Grant funded by the Korean Government (NRF-2014R1A1A2058480) to Jung-Soo Han

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

Poster

242. Appetitive and Incentive Learning and Memory I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 242.12/MM1

Topic: G.01. Appetitive and Aversive Learning

Support: Pire Program:Neural Mechanisms of Reward & Decision NSF Partnerships in International Research and Education

Biology Department, University of Puerto Rico

Title: Role of dopamine (DA) on honey bee foraging decisions

Authors: *F. NOEL, SR, T. GIRAY, A. PADILLA, J. AGOSTO R., C. SEIDE, S. FELICIANO, J. ALEMÁN RÍOS, W. NORZE, M. PEREZ TORRES
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Abstract: Honey bees may decide to forager on a particular flower over others. These foraging decisions may show plasticity. Foraging decision may balance reward quality and quantity, risk and energy expenditure. Previous Work have been shown that neuromodulators modify reward sensitivity, and response to aversive stimuli. We examined whether Dopamine (DA) influences foraging strategies in honey bees. We performed the experiments using an artificial flower patch, and presented to Puerto Rican honey bees (Apis mellifera) different foraging situations to choose: 2 flower colors (Blue versus White) and 2 flower morphologies with different rewards were combined. As a result either color was associated with short stamen, easy access flowers with low reward (0.5M of sucrose) versus long stamen difficult access flowers with high reward (2M of sucrose). We determined foraging strategies of each individual as preferring higher reward (Energy Maximizers) or preferring easy access (Work Minimizers) or individuals that could not solve the choice problem (Generalists). We fed bees DA then we compared foraging decision before and after administrating the DA. Application of DA did not alter total number of foraging strategies but influenced foraging decision, and increased the membership of group of generalist bees. We discuss these results in relation to effects of DA on responses to aversive and appetitive stimuli and its role in motivation pathways.

Disclosures: F. Noel: None. **T. Giray:** None. **A. Padilla:** None. **J. Agosto R.:** None. **C. Seide:** None. **S. Feliciano:** None. **J. Alemán Ríos:** None. **W. Norze:** None. **M. Perez Torres:** None.

Poster

242. Appetitive and Incentive Learning and Memory I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 242.13/MM2

Topic: G.01. Appetitive and Aversive Learning

Support: Sussex Neuroscience 4-year PhD Programme

Title: Characterising the effects of devaluation on cue-evoked neuronal ensemble activity and its underlying excitability properties in the nucleus accumbens

Authors: *M. C. SIEBURG, G. MARGETTS-SMITH, L. S. BREBNER, J. J. ZIMINSKI, H. S. CROMBAG, E. KOYA
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Abstract: Learned associations between food and the environmental cues that predict its availability guide appetitive behaviours. In laboratory animals, exposure to food-associated cues elicits conditioned approach behaviours towards the food delivery site. We recently demonstrated that this exposure activates a minority of sparsely distributed sets of neurons called 'neuronal ensembles', in the nucleus accumbens, that were more excitable than their surrounding neurons. To date, little is known about how changes in internal states modulate neuronal ensemble activity, and its intrinsic excitability properties following exposure to food-associated cues. Therefore, the aim of this study was to examine in mice, changes in cue-evoked approach responses and the underlying changes in accumbens neuronal ensemble activity and its intrinsic properties following food reward devaluation.
To that end, mice were trained to associate an auditory cue with sucrose delivery. Three days following the last conditioning session, sucrose was devalued in one group of mice by providing them access to four days of *ad libitum* sucrose, whereas the control group did not receive sucrose. On test day, seven days following the last acquisition session, both groups were tested for cue-evoked approach responses under extinction conditions, and the underlying accumbens neuronal activity was measured using Fos immunohistochemistry. Devaluation decreased the ability of the cue to elicit conditioned approach responses and accumbens Fos, indicating that this brain area encodes the incentive value of the reward. Investigations are underway into characterising the excitability properties of the activated accumbens neurons using *Fos-GFP* mice that express GFP in behaviourally activated neurons.

Disclosures: M.C. Sieburg: None. **G. Margetts-Smith:** None. **L.S. Brebner:** None. **J.J. Ziminski:** None. **H.S. Crombag:** None. **E. Koya:** None.

Poster

242. Appetitive and Incentive Learning and Memory I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 242.14/MM3

Topic: G.01. Appetitive and Aversive Learning

Title: Role of dissociable basolateral amygdala pathways in sign- And goal-tracking behaviors

Authors: *H. M. NASSER, E. N. LESSER, D. S. LAFFERTY, S. Z. BACHARACH, D. J. CALU
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Abstract: The Pavloivan lever autoshaping procedure reliably distinguishes sign- tracking (ST) and goal-tracking (GT) behaviors in rats. In this procedure a lever is inserted and retracted, after which a food reward is delivered into a food cup. Rats are not required to press the lever or approach the food cup, but ST rats approach the lever, while GT rats approach a food cup. Prior studies indicate that ST rats display greater appetitive cue-driven motivation and reduced

behavioral flexibility compared to GT rats, suggesting that these behaviors may be mediated by dissociable brain pathways. We hypothesize that sign- and goal-trackers activate distinct basolateral amygdala (BLA) projections that mediate behavioral differences during appetitive conditioning. Prior studies demonstrate that disconnecting basolateral amygdala (BLA) and nucleus accumbens (NAc) impairs lever directed, but not foodcup directed behavior, while BLA projections to the insular and orbitofrontal cortex (IC/OFC) are involved in behavioral flexibility. We predict that cue-value encoding in dissociable BLA pathways underlies divergent motivational processes observed ST and GT phenotypes. Here, we characterize the real-time neural activity of BLA to NAcC and BLA to IC/OFC projection neurons in ST and GT rats. We use an antidromic optical phototagging approach, in which we express channelrhodopsin (ChR2) in BLA and optically stimulate BLA terminals in NAcC or IC/OFC after recording BLA single unit activity during CS+/CS- discrimination and/or reversal procedures. Offline waveform, frequency, and collision testing of antidromic and spontaneously evoked spikes verifies identification of BLA to NAcC and BLA to IC/OFC neurons in awake, behaving rats. We currently apply this methodology to optically probe and record from both BLA pathways during CS+/CS- discrimination and/or reversal procedures. Together these studies will test our hypothesis that individual differences of ST and GT rats are mediated by activation of dissociable BLA projections to the NAcC and to IC/OFC.

Disclosures: H.M. Nasser: None. **E.N. Lesser:** None. **D.S. Lafferty:** None. **S.Z. Bacharach:** None. **D.J. Calu:** None.

Poster

242. Appetitive and Incentive Learning and Memory I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 242.15/MM4

Topic: G.01. Appetitive and Aversive Learning

Title: CB1 receptor activation is required for sign- and goal-tracking behaviors early in Pavlovian lever autoshaping

Authors: *S. Z. BACHARACH, H. M. NASSER, H. M. DANTRASSY, N. E. ZLEBNIK, J. F. CHEER, D. J. CALU
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Abstract: Sign-tracking (ST) and goal-tracking (GT) rats are characterized by their cue or reward directed behaviors in a Pavlovian lever autoshaping (PLA) task. Sign-tracking rats approach and interact with an inserted lever cue that predicts reward, while goal-trackers approach and interact with the foodcup where food is delivered. Prior studies suggest that dopamine (DA) in the Nucleus Accumbens (NAc) plays a time limited role in driving appetitive motivated behavior of sign-, but not goal-trackers. Endocannabinoids (EC) are critical

gatekeepers of dopaminergic signaling and manipulations of the EC system alter DA dynamics in the NAc to influence cue-motivated behavior in instrumental procedures that resemble PLA. Here, we investigate the role of the EC system in early and late phases of PLA. We theorized that antagonizing the EC system via CB1 receptor blockade during PLA would mimic the behavioral effects observed when antagonizing the NAc dopamine system during this task. More specifically, we tested the hypothesis that systemic injections of CB1 receptor inverse agonist, rimonabant, would block sign- but not goal-tracking behaviors. To test this, we trained male (n =20) and female rats (n=20) rats in four PLA sessions to determine their sign-, goal,- or intermediate-tracking phenotype. We then administered systemic injections of rimonabant (0, 1, 3 mg/kg), during early (sessions 5-7) and late (sessions 15-17) reinforced PLA sessions using a counterbalanced, within-subject design. In early PLA sessions, rimonabant dose-dependently decreased both lever and food cup contacts, latency and probability. When analyzing preferred behavior (lever or foodcup) there were no drug interactions with either sex or tracking phenotype factors. Similarly, rimonabant had no effect on either behavior in late PLA sessions. Our results suggest that ECs are required for early expression of learned approach responses in Pavlovian lever autoshaping regardless of sex or tracking phenotype.

Disclosures: S.Z. Bacharach: None. **H.M. Nasser:** None. **H.M. Dantrassy:** None. **N.E. Zlebnik:** None. **J.F. Cheer:** None. **D.J. Calu:** None.

Poster

242. Appetitive and Incentive Learning and Memory I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 242.16/MM5

Topic: G.01. Appetitive and Aversive Learning

Support: CRC 1080

SFB 815

Title: Alternative splicing of KCNIP4 in dopamine VTA neurons controls the dynamics of learning from reward omission

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Abstract: Fast-inactivating A-type currents in substantia nigra (SN) dopamine (DA) midbrain neurons are mediated by Kv4.3/KChIP3-containing potassium (K) channels and control pacemaker frequency. A-type K-channels of neighboring DA neurons in the ventral tegmental area (VTA) show slower inactivation kinetics and can amplify inhibitory pauses (Tarfa *et al*,

2017). We recently showed that K channel interacting protein 4 (KChIP4) regulates A-type current properties and consequently firing pauses in VTA DA neurons *in vitro* and *in vivo* (Costa *et al*, 2016 SFN). In order to investigate the behavioral role of KChIP4 splice variants in VTA DA neurons, we generated a conditional mouse model where the alternative Exon 3 of KCNIP4, which codes for the K channel inactivation suppressor (KIS) domain of KChIP4 that slows A-type current inactivation and reduces Kv4 channel surface expression, is deleted selectively in DA neurons (Ex3d). Using an appetitive reinforcement learning task, we show that Ex3d selectively accelerated extinction learning compared to littermate controls (≈55% decrease in time spent in the reward-dispensing port in the first extinction session), while acquisition of the appetitive response was indistinguishable from controls. This phenotype was not due to shorter durations of port checks, but rather a decrease in the number of checks per trial (≈55% difference in the first extinction session). Indicative of a selective learning phenotype, performance in the first extinction trial was similar between the groups, with divergence between Ex3d and control mice occurring only after the second trial. In a subsequent behavioral phenotyping battery, we found no difference in spontaneous behaviors between Ex3d and control mice, including open field locomotion and working memory. Computational fitting with a modified Rescorla-Wagner model revealed that the extinction-related Ex3d phenotype can be attributed to a selective increase in learning rates from negative prediction errors. This is congruent with prevalent theories of reinforcement learning, which propose that pauses in DA neuron firing code negative prediction errors. Semi-quantitative immunohistochemistry indicated that Ex3d mice have a VTA-selective increase (≈50% increase in fluorescence signals) in Kv4.3 subunits. These results suggest that the selective enhancement of extinction learning by Ex3d may be mediated by an increased number of functional Kv4.3 channels in VTA DA neurons. However, we are currently characterizing the biophysical phenotype of Kv4.3 channels in DA neurons of Ex3D mice in order to define the possible contribution of altered gating kinetics on the observed phenotypes.

Disclosures: K.M. Costa: None. **J. Roeper:** None.

Poster

242. Appetitive and Incentive Learning and Memory I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 242.17/MM6

Topic: G.01. Appetitive and Aversive Learning

Support: MEXT/JSPS KAKENHI 15F15107

MEXT/JSPS KAKENHI 15H04275

MEXT/JSPS KAKENHI 16K14579

MEXT/JSPS KAKENHI 16H06568

Title: Nucleus Accumbens D1 receptor expressing neurons control autoshaping behavior

Authors: *T. MACPHERSON[1,2], T. HIKIDA[1,2]
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Abstract: The striatum of the basal ganglia is known to control learning about the properties of environments, as well as the appropriate behavioral response that will maximize reward or minimize harm in these environments. Indeed, dysfunction of the striatum is known to contribute to a number of decision-making-associated neuropathologies, including drug addiction and schizophrenia. However, it is still unclear how attribution of motivational value (incentive salience) towards primary rewards, or environmental stimuli predictive of rewards, may be controlled by the activity of different striatal subregions and neuron types. Neurons in the striatum can be broadly divided into dopamine D1 or D2 receptor-expressing populations. Thus, here we explore the role of D1-expressing and D2-expressing neurons originating from three striatal subregions, the nucleus accumbens (NAc), the dorsomedial striatum (DMS), and the dorsolateral striatum (DLS), in mediating Pavlovian approach behavior in an autoshaping task. Using a reversible neurotransmission blocking (RNB) technique (as described in Hikida et al, 2010) to separately inhibit activity in each neuron group, we revealed a specific role of NAc D1-expressing neurons in controlling Pavlovian approach behavior to an environmental cue associated with a natural food reward. Blockade of NAc D1-expressing neuron activity impaired sign-tracking responses to the CS, while leaving goal-tracking responses intact. These findings provide insight into the neural circuits underlying Pavlovian conditioning, and may be important in the identification of therapeutic targets for the treatment of disorders associated with a loss of impulse control, including drug addiction and schizophrenia.

Disclosures: T. Macpherson: None. **T. Hikida:** None.

Poster

242. Appetitive and Incentive Learning and Memory I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 242.18/MM7

Topic: G.01. Appetitive and Aversive Learning

Support: NIH NIDDK DK085721 to GDP

Title: Basolateral amygdala-medial prefrontal cortex circuitry regulates behavioral flexibility during Pavlovian appetitive reversal learning, but not during discriminative conditioning or conditioned taste aversion

Authors: *S. E. KEEFER, G. D. PETROVICH
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Abstract: Environmental cues can become predictors of food through Pavlovian appetitive conditioning. Two forebrain regions important in this associative learning are the basolateral amygdala (BLA) and medial prefrontal cortex (mPFC). Recently, we showed the BLA-mPFC pathway is activated when a single cue reliably signals food, suggesting the BLA informs the mPFC of the cue's value. The current experiment tested this hypothesis after discriminative conditioning by altering the value of two cues during reversal learning and devaluation by conditioned taste aversion (CTA). Male, Long-Evans rats received contralateral, ipsilateral, or sham excitotoxic lesions of the BLA-mPFC (n=8-9/group). After recovery and subsequent 85% bodyweight food deprivation, rats received ten sessions of discriminative conditioning. Two auditory stimuli (tone; white noise) were each presented six times within each session, with one stimulus co-terminating with the delivery of two palatable food pellets (CS+), and the other stimulus unrewarded (CS-; counterbalanced). Learning was measured through assessment of conditioned responding: the percentage of time rats spent at the food cup during the presentations of the CSs. All groups successfully discriminated between the two auditory stimuli, demonstrating this learning does not require BLA-mPFC communication. Next, the outcomes of the stimuli were reversed: the CS+ was now unrewarded (reversal CS-; rCS-), and the CS- was now rewarded (reversal CS+; rCS+). During 15 sessions of reversal learning, the rats that received the contralateral disconnection of the BLA-mPFC showed rapid, increased responding to the rCS+ compared to the other groups, suggesting less inhibition to the previous CS-. Next, half of the rats in each lesion group underwent CTA and were then tested for devaluation through assessment of CS responding to both stimuli without reward. Rats either received 10 min access to 5g of test food in their home cage followed by immediate injection of LiCl (i.p.; 0.3M LiCl in 0.9% sterile saline; 5 ml/kg) to induce sickness (devalued group), or received food pellets and LiCl injections on different days, resulting in no CTA to the pellets (non-devalued). All groups successfully learned CTA, and there was no immediate evidence of cue devaluation or differences across groups. Interestingly, by test 8, the non-devalued contralateral group was still responding more to the rCS- compared to the devalued contralateral group with no differences within the sham or ipsilateral groups. These results suggest BLA-mPFC communication is necessary for appropriate responding during periods of behavioral flexibility.

Disclosures: S.E. Keefer: None. **G.D. Petrovich:** None.

Poster

242. Appetitive and Incentive Learning and Memory I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 242.19/MM8

Topic: G.01. Appetitive and Aversive Learning

Support: AA023141

AA024499

AA010761

Title: Glutamatergic projections to the nucleus accumbens shell regulate response strategy selection

Authors: *J. M. BARKER[1], K. G. BRYANT[2], A. MONTIEL-RAMOS[3], L. CHANDLER[4]
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Abstract: The ability to toggle between flexible actions and efficient habits in order to adapt behavior is critical for ideal behavioral performance in changing environments. Many neuropsychiatric illnesses including addiction and alcohol use disorders are characterized by impairments in behavioral flexibility and an overreliance on habitual response strategies. Goal-directed actions are performed in relation to their outcomes, while this sensitivity to change in action-outcome relationship is lost in habitual responding. We can thus assess the ability to flexibly regulate behaviors through the use of contingency degradation paradigms that degrade the relationship between the action and outcome. Response strategy selection is in large part mediated by substrates within limbic corticostriatal circuits. A number of structures that have been directly implicated in response strategy selection, including the infralimbic PFC (IL) and the basolateral amygdala (BLA) project to the nucleus accumbens shell (NAcS), in addition to structures that have general roles in behavioral flexibility such as the ventral hippocampus (VH), but which may not have been specifically implicated in habits. The present study used pharmacological and chemogenetic tools to assess the role of NAcS glutamate signaling as well as specific glutamatergic projections to the NAcS in response strategy selection. Specifically, we observe that pharmacological regulation of glutamate signaling via local administration of an mGluR2/3 agonist (LY379268) in the NAcS is sufficient to restore goal-directed actions. In addition, we found that global silencing of IL glutamatergic projections via agonism of a Gi-coupled inhibitory DREADD, as well as selective silencing of IL-NAcS projections similarly both restores goal-directed behavior (i.e., sensitivity to change in action-outcome contingency). In addition, globally silencing glutamatergic neurons in the VH also restores sensitivity to changes in contingency. Our preliminary findings suggest that this is also mediated by projections from the VH to the NAcS. These data suggest that regulation of glutamate signaling in the NAcS mediates response strategy selection, and that glutamatergic projections from the IL and potentially VH may underlie this effect.

Disclosures: J.M. Barker: None. **K.G. Bryant:** None. **A. Montiel-Ramos:** None. **L. Chandler:** None.

Poster

242. Appetitive and Incentive Learning and Memory I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 242.20/MM9

Topic: G.01. Appetitive and Aversive Learning

Support: CRC Tier 2 Behavioural Neuroscience

FRQNT 2017-NC-198182

CFI John R. Evans Leaders Fund

BBRF/NARSAD Young Investigator

Title: Infralimbic cortex regulation of reduced outcome expectancy

Authors: A. USYPCHUK, H4B 1R6[1], M. NICOLOSSI[3], B. P. LAY[3], *M. D. IORDANOVA[2]
[1]Psychology/CSBN, [2]Psychology, Concordia Univ., Montreal, QC, Canada; [3]Psychology/CSBN, Concordia Univerisity, Montreal, QC, Canada

Abstract: The ability to reduce outcome expectancies in the face of changing environmental contingencies is critical for survival so that effortful action is engaged in search of unavailable rewards. Extinction and overexpectation are two paradigms that provide conditions under outcome expectancies are reduced. In both paradigms following the establishment of an expectation of an outcome, this expectation is violated by delivering no outcome (extinction) or by generating an expectation of double the outcome and delivering a single outcome (overexpectation). Both paradigms generate a negative prediction error, which drives a reduction in outcome expectancy. The infralimbic cortex (IL) has been implicated in regulating behaviour in line with extinction training in fear and reward albeit somewhat inconsistently. One view aimed at explaining these results along with the IL role in habitual responding is to suppose that the IL plays an important role in regulating stimulus-response, in contrast to stimulus-outcome, associations. Indeed, in extinction both of these associations serve to regulate behaviour with some emphasis having been placed on the former (Rescorla). We used overexpectation in order to examine the role of the IL cortex in learning to reduce outcome expectancies in the *presence* of the outcome, thus reducing the possible influence of stimulus-(no)response associations. Our results show that IL inactivation during overexpectation learning has no effect on reducing outcome expectations and in turn reduced responding on test. Inactivation of the IL in the same rats resulted in faster reduction in responding during a subsequent extinction learning phase but higher response compared to controls on a subsequent test of extinction retention. These results provide evidence that the IL regulates stimulus control over responding and not stimulus control

over outcome expectations, in turn suggesting that IL function is in line with model-free as opposed to model-based representations of the world.

Disclosures: A. Usypchuk: None. **M. Nicolossi:** None. **B.P. Lay:** None. **M.D. Iordanova:** None.

Poster

242. Appetitive and Incentive Learning and Memory I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 242.21/MM10

Topic: G.01. Appetitive and Aversive Learning

Support: MRC Discovery award

Sussex Neuroscience 4-year PhD programme

Title: Characterising medial prefrontal cortex neuronal ensemble recruitment patterns during appetitive conditioning

Authors: *L. S. BREBNER[1], T. G. HEINTZ[2], L. LAGNADO[2], J. HIRRLINGER[3], C. N. HALL[1], E. KOYA[1]
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Abstract: Learned associations about food and the cues that predict their availability are encoded by a sparsely distributed set of neurons coined 'neuronal ensembles' in brain areas such as the medial prefrontal cortex (mPFC). This area contains excitatory pyramidal cells that control various appetitive behaviours, and their activity is modulated by local inhibitory interneurons. In laboratory animals, exposure to food-associated cues trigger conditioned appetitive responses (e.g. food-seeking) and activate both of these neuronal populations in this area, suggesting that associative representations are stored in these cue-activated neurons. To date, very little is known about how mPFC pyramidal cell and interneuron ensembles are recruited during the formation of appetitive (food-cue) associations.
Hence, the aim of this study was to examine pyramidal cell and interneuron recruitment patterns during the formation of food-cue associations in the dorsal mPFC, using a Pavlovian conditioning procedure with sucrose. To that end, we generated *Fos-GFP x GAD-tdTomato* transgenic mice that express GFP in strongly activated neurons, and the red fluorescent protein 'tdTomato' in interneurons. Thus, the activated pyramidal cells (GFP+/tdTomato-) and interneurons (GFP+/tdTomato+) are readily identified.
We imaged the dorsal mPFC using a microprism-based *in vivo* 2 photon (2P) imaging procedure that is better-suited for imaging deeper cortical structures located in brain fissures than

conventional cranial windows 2P imaging methods. Investigations are underway into characterising the pyramidal cell and interneuron activation patterns during sucrose conditioning.

Disclosures: L.S. Brebner: None. **T.G. Heintz:** None. **L. Lagnado:** None. **J. Hirrlinger:** None. **C.N. Hall:** None. **E. Koya:** None.

Poster

242. Appetitive and Incentive Learning and Memory I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 242.22/MM11

Topic: G.01. Appetitive and Aversive Learning

Support: NSERC-RGPIN 341673

Title: Preadolescent treatment with MK-801 and effect on adolescent operant acquisition and extinction

Authors: *M. R. HOLAHAN[1], K. GOHEEN[2], K. HUDAK[2]
[1]Dept Neurosci., [2]Carleton Univ., Ottawa, ON, Canada

Abstract: Parsing out the contribution of dopamine and glutamate in the neural networks that subserve reward learning is of critical importance. When given to adult rats, the noncompetitive NMDA receptor antagonist, MK-801, has been shown to increase the probability of operant responding during extinction and reduce infralimbic prefrontal (IL) cortical activation. Pretreatment with a dopamine antagonist, Flupenthixol, produced a dose-dependent decrease in MK-801-induced bar pressing behavior and locomotor activity and a dose-dependent increase in IL pERK1/2 labeling. A parallel set of questions that we have addressed concerns the way in which memories are processed and consolidated during preadolescence. The hippocampus shows widespread connectivity-based changes from 18 - 24 days old that are correlated with the emergence of spatial performance. Examination of axonal and dendritic processes (structural changes) and c-Fos labeling (functional changes) in the CA3 region revealed enhanced connectivity patterns and developmentally-dependent increases in c-Fos positive cells that preceded the emergence of spatial behavior. These results lead to the hypothesis that this developmental time period (p18 - p24; preadolescence) represents a sensitive period for hippocampal development and the emergence of spatial information processing. It is possible that this developmental period is not selective for spatial information processing but equally critical for later reward processing. As such, male Long Evans rats received either saline, repeated injections of MK-801 at 0.05 mg/kg from p18 - 24, or an acute injection of 0.1 mg/kg MK-801 during adolescence, 15 mins prior to extinction testing. During food-rewarded acquisition, compared to saline, early MK-801 treatment delayed the acquisition of the operant (bar pressing) but had no effect on port entries or locomotion. During the extinction session,

early MK-801 treatment was associated with fewer lever presses and less locomotion then acute MK-801 treatment but port entries were similar. These data suggest that MK-801 treatment from p18 - 24 may impede an instrumental learning process but leave reward representations intact. We will compare these responses to those produced by dopamine receptor antagonism (flupenthixol) and AMPA receptor antagonism (NBQX) during preadolescence and before adolescent acquisition, as well as c-Fos labeling in the nucleus accumbens and infralimbic cortex, to determine how the brain develops and permits cognitive function based on environmental rewards to progress later in life.

Disclosures: **M.R. Holahan:** None. **K. Goheen:** None. **K. Hudak:** None.

Poster

242. Appetitive and Incentive Learning and Memory I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 242.23/MM12

Topic: G.01. Appetitive and Aversive Learning

Support: NIH F32 DK107077-

HHMI

Title: Molecular profiling of an insular - amygdala circuit in feeding behavior

Authors: ***S. A. STERN**[1], E. P. AZEVEDO[1], K. DOERIG[1], J. M. FRIEDMAN[1,2]
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Abstract: Feeding is a complex motivated behavior that is controlled not just by metabolic and homeostatic factors, but also by environmental factors such as emotion and the hedonic nature of the food itself. Yet, little is known about how brain regions involved in cognition and emotion might contribute to overeating, and therefore, obesity. The Insular Cortex (IC), otherwise known as Gustatory Cortex is a region critical for taste perception that has recently been shown to be involved in cue-food associations (Kusumoto-Yoshida I 2015). Using modern viral tracing methods, we have confirmed that the IC has reciprocal connections with the amygdala – specifically, the IC receives projections from the basolateral amygdala (BLA) and sends axons to the central amygdala (CeA), a region involved in emotion regulation that can positively and negatively impact feeding. Although the projection is likely to be important for the regulation of feeding behavior, the identity of the neurons that project from IC to CeA remains unknown. Therefore, to probe the molecular connectivity of these two regions, we have used the recently developed method, retro-TRAP (Retrograde - Translating Ribosome Affinity Purification), to profile projections from the IC to the CeA (Ekstrand 2014). We injected the retrograde canine

adenovirus, CAV-GFP, into the CeA of SYN-NBL10 mice which contain anti-GFP–tagged ribosomal subunit proteins. Two weeks later, we dissected out the insular cortex and immunoprecipitated GFP, therefore pulling down polysome-bound, translating mRNAs of neurons that project to CeA. High throughput RNA-sequencing has enabled us to identify markers for projections from IC to CeA and therefore to investigate the role of these projections in the non-homeostatic regulation of feeding behavior.

Disclosures: S.A. Stern: None. **E.P. Azevedo:** None. **K. Doerig:** None. **J.M. Friedman:** None.

Poster

242. Appetitive and Incentive Learning and Memory I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 242.24/MM13

Topic: G.01. Appetitive and Aversive Learning

Support: NIDA IRP

NIDA/INSERM fellowship

Title: Neural correlates in basolateral and central amygdala during responding for reward in the face of punishment

Authors: *Y. PELLOUX[1], B. F. SADACCA[2], A. M. MINIER-TORIBIO[1], Y. SHAHAM[1], G. SCHOENBAUM[2]
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Abstract: Background: The ability to withhold responding in face of adverse consequences fails in compulsive disorders. This depends on the amygdala. Here we investigated whether this dependence reflects changes in activity of amygdala neurons at the time of the decision or at the time of the consequences.
Methods: Rats began each trial by pressing the initiation lever. This triggered an auditory cue (white noise, pure tone or clicker, counterbalanced), which signaled the availability of three possible outcomes (1- 100% reward, 2- 20% reward, or 3- 80% reward + 20% footshock). Five second later, a second (completion) lever was presented. Pressing the completion lever terminated the auditory cue and resulted in the onset of a 1s visual cue (steady light, house light, or flashing light) followed by the associated outcome (food, reward omission, shock). After initial training, we implanted 8 tetrodes in the amygdala (basolateral, 7 rats or central, 5 rats) and recorded single-unit activity during stable performance on the task.
Results: We recorded ~100 neurons in each region. They were sensitive to the different auditory and visual cues and to the presentation of the levers. Activity to the visual cues and their associated outcomes (i.e activity during feedback) did not predict the latency to initiate the next

trial. In contrast, activity during presentation of the levers predicted the latency to press on this lever.
Conclusions: These data suggest that the role of the amygdala in the withholding of responding in the face of punishment occurs at the time of the decision to lever press and not at the time of punishment.

Disclosures: Y. Pelloux: None. **B.F. Sadacca:** None. **A.M. Minier-Toribio:** None. **Y. Shaham:** None. **G. Schoenbaum:** None.

Poster

243. Fear and Aversive Learning and Memory: Acquisition

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 243.01/MM14

Topic: G.01. Appetitive and Aversive Learning

Title: Chemogenetic interrogation of cell type specific translation in fear memories

Authors: *P. SHRESTHA[1], P. AYATA[3], P. M. HERRERO-VIDAL[4], F. LONGO[4], A. GASTONE[2], N. HEINTZ[5], E. KLANN[2]
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Abstract: Decades of studies have established that *de novo* protein synthesis is a requirement for the conversion of short to long term memories. However the extensive use of broad antibiotics, such as anisomycin, for blocking protein synthesis in classical studies is problematic due to the lack of specificity of these drugs and their undesirable side effects, for instance superinduction of immediate early genes and activation of the cellular stress pathways. To circumvent these issues and to confer spatiotemporal precision, we have developed a novel chemogenetic strategy - conditional inducible protein synthesis inhibitor (ciPSI)- to inducibly block cell type specific translation at a key regulatory step during initiation. The active component of ciPSI is a drug activatable kinase for eukaryotic translation factor eIF2α that has been made inducible by tailoring an NS3/4 protease site within the kinase. In addition, the effector kinase is expressed under the control of Cre/LoxP recombination to target specific cell types. Phosphorylation of eIF2α at Serine 51 residue blocks translation initiation by limiting the abundance of eIF2 ternary complex, one of the rate limiting steps in translation. Dephosphorylation of eIF2α, on the other hand, has been shown to be a crucial molecular event for the switch from short to long term plasticity and memory in Pavlovian fear conditioning paradigms. Thus, the ciPSI strategy targets a physiologically relevant molecular event during long term memory consolidation. Pavlovian fear conditioning, in which long term associative memory is formed between a neutral tone and a mild footshock such that the tone alone can elicit defensive responses at a later time, is a powerful paradigm to study long term memories because the associative memory forms quickly

and is stable for long time. We have used pan-neuronal Nestin.ciPSI mouse line to validate our system and to investigate the role of neuronal translation in consolidation of conditioned fear memory. Our data indicate that the ciPSI system expressed pan-neuronally rapidly and reversibly blocks*de novo* translation, and impairs consolidation of long term fear memory. Further, we find that the molecular target of ciPSI, eIF2α phosphorylation, has a temporally defined role in long lasting plasticity in the amygdala with the sensitive period for eIF2α phosphorylation spanning only up to an hour following fear conditioning. The spatiotemporal precision of the ciPSI system enables us to study the contribution of specific cell types in amygdala nuclei toward the stabilization of long term memory trace.

Disclosures: P. Shrestha: None. **P. Ayata:** None. **P.M. Herrero-Vidal:** None. **F. Longo:** None. **A. Gastone:** None. **N. Heintz:** None. **E. Klann:** None.

Poster

243. Fear and Aversive Learning and Memory: Acquisition

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 243.02/MM15

Topic: G.01. Appetitive and Aversive Learning

Support: Department of Veterans Affairs (Merit Award)

NIMH (5R01MH085724)

NHLBI (R01HL113863)

NARSAD Independent Investigator Award

The Carver Foundation

Fondation Leduq

NIMH (T32MH019113)

Title: ASIC1A in neurons is critical for fear-related behaviors

Authors: *R. J. TAUGHER[1,4], Y. LU[1,4], R. FAN[1,4], A. GHOBBEH[1,4], C. J. KREPLE[2,5], F. M. FARACI[3,6], J. A. WEMMIE[1,4,7,5,8]
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Abstract: Acid-sensing ion channels (ASICs) have been implicated in fear-, addiction-, and depression-related behaviors in mice. While these effects have been attributed to ASIC1A in

neurons, it has been reported that ASICs may also function in non-neuronal cells. To determine if ASIC1A in neurons is indeed required, we generated neuron-specific knockout mice with floxed *Asic1a* alleles disrupted by Cre recombinase driven by the neuron-specific synapsin I promoter (*SynAsic1a KO mice).* We confirmed that Cre expression occurred in neurons, but not all neurons, and not in non-neuronal cells including astrocytes. Consequent loss of ASIC1A in some but not all neurons was verified by western blotting, immunohistochemistry, and electrophysiology. We found ASIC1A was disrupted in fear circuit neurons, and *SynAsic1a KO* mice exhibited prominent deficits in multiple fear-related behaviors including Pavlovian fear conditioning to cue and context, predator odor-evoked freezing, and freezing responses to carbon dioxide inhalation. In contrast, in the nucleus accumbens ASIC1A expression was relatively normal in *SynAsic1a KO* mice, and consistent with this observation, cocaine conditioned place preference (CPP) was normal. Interestingly, depression-related behavior in the forced swim test, which has been previously linked to ASIC1A in the amygdala, was also normal. Together, these data suggest neurons are an important site of ASIC1A action in fear-related behaviors, whereas other behaviors likely depend on ASIC1A in other neurons or cell types not targeted in *SynAsic1a KO* mice. These findings highlight the need for further work to discern the roles of ASICs in specific cell types and brain sites.

Disclosures: R.J. Taugher: None. **Y. Lu:** None. **R. Fan:** None. **A. Ghobbeh:** None. **C.J. Kreple:** None. **F.M. Faraci:** None. **J.A. Wemmie:** None.

Poster

243. Fear and Aversive Learning and Memory: Acquisition

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 243.03/MM16

Topic: G.01. Appetitive and Aversive Learning

Support: NIH Grant ZIAMH002798

Title: Neural responses to aversive conditioned stimuli at ultra-high field

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Abstract: Research in animal models has consistently demonstrated that the lateral and central nuclei of the amygdala are critical in forming associations between aversive outcomes and previously neutral stimuli during Pavlovian learning paradigms. However, despite the abundance of research reporting increased BOLD responses within the human amygdala to aversive conditioned stimuli, recent meta-analyses suggest that the amygdala is not consistently activated during the acquisition of aversive Pavlovian associations. The use of ultra-high field (7-tesla)

fMRI provides increased spatial resolution and signal to noise ratio, and may shed light on the role of the amygdala during aversive Pavlovian learning in humans. Seventeen participants underwent an aversive Pavlovian learning paradigm wherein one stimulus (CS+) was paired with a mild electrical shock (75 % reinforcement) and another stimulus (CS-) was never paired with an aversive outcome. Increased BOLD responses to the CS+, compared to the CS-, were observed in the dorsal anterior cingulate, anterior insula, and thalamus. However, no differential responses to the CS+ were detected in any region of the amygdala at corrected statistical thresholds. Follow up analyses will focus on specific amygdala sub-nuclei to determine the time course of amygdala activity to the CS+, compared to the CS-, over the course of Pavlovian learning. Collectively, our results may serve as a bridge between human neuroscience and the finer grained methods used in animal models of aversive Pavlovian learning.

Disclosures: A.X. Gorka: None. **S. Torrisi:** None. **M. Ernst:** None. **C. Grillon:** None.

Poster

243. Fear and Aversive Learning and Memory: Acquisition

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 243.04/MM17

Topic: G.01. Appetitive and Aversive Learning

Support: NHMRC Program Grant #1073041

Title: Attachment primes reduce the acquisition of fear-potentiated startle

Authors: *M. KOKKINOS, B. J. LIDDELL, R. A. BRYANT
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Abstract: Recent research has begun to examine the link between the human social attachment system and fear networks. There is evidence to suggest that attachment activation down-regulates arousal and the stress response. The literature so far has not extended these findings to fear learning, which is often used to model the development of fear underlying certain psychological disorders. This study aimed to assess whether attachment primes could have an effect on fear-potentiated startle during acquisition of conditioned fear. Participants (N=50) were randomly allocated to 2 groups and were primed with a vivid imagery task of either an attachment or positive control prime. Both groups then underwent a differential fear conditioning and fear extinction paradigm and returned two days later for an extinction recall task. Fear conditioning involved learning that a conditioned stimulus (CS+) predicted the delivery of the unconditioned stimulus (US - a mild electric shock to the forearm) while a CS- was never associated with the US. The eye-blink startle response was measured using electromyography (EMG) of the left orbicularis oculi muscle in response to a 40ms burst of white noise (108dB). Fear-potentiated startle was defined as the differential startle response to the CS+ relative to the

CS- across blocks of trials. The attachment prime significantly reduced the acquisition of fear-potentiated startle (p=0.024). This is the first study to have demonstrated that attachment primes can modulate the acquisition of conditioned fear. These findings provide preliminary evidence for the protective nature of attachment relationships at times that are characterized by fear learning, for example during a traumatic experience.

Disclosures: M. Kokkinos: None. **B.J. Liddell:** None. **R.A. Bryant:** None.

Poster

243. Fear and Aversive Learning and Memory: Acquisition

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 243.05/MM18

Topic: G.01. Appetitive and Aversive Learning

Support: NIGMS NIH RISE 4R25GM060566-16

Title: Unconditioned fear and contextual conditioning of syrian hamsters exposed to natural predator odors

Authors: *C. M. MARKHAM[1], M. EDWARD[1], M. SMITH[1], J. BEST[3], J. BYRD[2], T. LACEY[3]
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Abstract: Predator odors have come to be recognized as providing an important tool in the elicitation of unconditioned defensive behaviors related to fear and anxiety in laboratory animals. In addition, animals previously exposed to predator odors will exhibit cue and context conditioning by avoiding the source, as well as the area previously associated with the odor. In contrast, animals exposed to purely aversive, non-biological odors also show unconditioned defensive behaviors, but importantly, they do not exhibit cue and context conditioning. While there are numerous studies examining the effect of predator odors on defensive responding in rats and mice, there is currently no studies examining predator odor-induced defensiveness in hamsters. The present study was conducted to compare the relative effectiveness of natural, biologically-based predator odors (coyote urine) with a non-biological odor (formadehyde) in the elicitation of defensive behaviors and to determine whether these defensive responses are conditioned to stimuli associated with these odors. The apparatus consisted of a 60-cm long alley constructed of Plexiglas. The odors (or saline) were applied to cotton pads and put into a petri dish and placed on the end opposite to where the subject was placed. Animals were first habituated to the test environment for two days, and then tested with the appropriate odor for 10 minutes (Exposure Day). On the next day (Conditioning Test Day), the animals were placed back into the apparatus, but without the odor present for an additional 10 minutes. Results show that the coyote odor elicited avoidance to, and an increased latency to contact the odor stimulus on

Exposure Day, indicating that it was detected as an aversive odor. In contrast, formaldehyde did not elicit avoidance or latency to contact compared to the saline control group. Neither group exhibited avoidance behavior on the Conditioning Test Day. While the avoidance behavior in the coyote odor group was consistent with previous findings with rats, the lack of avoidance in the formaldehyde exposure group was unexpected. In addition, the lack of aversive conditioning in both groups was also inconsistent with previous studies. These findings raise the question of whether there are specific aspects of defensiveness to the presence of an odor (or, potentially other aversive stimuli) that predict its ability to serve as a UCS in an aversive paradigm.

Disclosures: C.M. Markham: None. **M. Edward:** None. **M. Smith:** None. **J. Best:** None. **J. Byrd:** None. **T. Lacey:** None.

Poster

243. Fear and Aversive Learning and Memory: Acquisition

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 243.06/MM19

Topic: G.01. Appetitive and Aversive Learning

Title: Microinfusion of serotonin 5-HT2C receptor antagonist at the RMTg blocks cocaine conditioned avoidance

Authors: *Y. S. CHAO, M. EID, D. PULLMANN, H. LI, T. JHOU
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Abstract: Serotonin neuron innervation of the brain is widespread, and produces varied actions that depend on multiple neural substrates and a diverse family of receptors. While the anti-depressive and anxiolytic properties of serotonin have been widely appreciated and exploited for therapeutic purposes, serotonin's aversive effects and associated mechanisms are less well understood. However, recent studies show that serotonin engages an extended amygdala circuit that promotes anxiety and fear, while conversely acute tryptophan depletion in humans impairs punishment-induced inhibition. Adding to this emerging literature, we recently identified strong expression of serotonin 5-HT2C receptors in the rostral tegmental area (RMTg), a critical processor of aversive stimuli, and a region that receives robust habenular input and sends intense GABAergic projections to midbrain dopamine neurons. Given our previous findings that the lateral habenula and RMTg mediate cocaine conditioned avoidance and there exist reciprocal projections between the RMTg and dorsal raphe, we tested the role of serotonin in cocaine's aversive effects. Toward this aim, we used a runway operant task developed by Ettenberg and colleagues, in which rats traverse a 5-foot long corridor to obtain a single cocaine infusion. We found that intra-RMTg injection of SB-242084 (a specific 5-HT2C receptor antagonist) blocked the development of aversion, showing that serotonin may play key roles in aversive processing via its influence on the RMTg. For future studies, we plan to test serotonin's role in RMTg

processing and learning of other aversive stimuli, examine this pathway's alterations upon chronic drug use, and explore these changes' implications for drug related psychiatric and affective disorders.

Disclosures: Y.S. Chao: None. **M. eid:** None. **D. pullmann:** None. **H. li:** None. **T. Jhou:** None.

Poster

243. Fear and Aversive Learning and Memory: Acquisition

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 243.07/MM20

Topic: G.01. Appetitive and Aversive Learning

Support: UC Riverside IC funds

Title: Encoding of discriminative fear memory by input-specific LTP in the amygdala

Authors: J.-H. CHO, W. KIM
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Abstract: In auditory fear conditioning, experimental subjects learn to associate an auditory conditioned stimulus (CS) with an aversive unconditioned stimulus. With sufficient training, animals fear-conditioned to an auditory CS show fear response to the CS but not to irrelevant auditory stimuli. Although long-term potentiation (LTP) in the lateral amygdala (LA) plays an essential role in auditory fear conditioning, it is unknown whether LTP is induced selectively in the neural pathways conveying specific CS information to the LA in discriminative fear learning. To determine this, we used a novel combined approach of neural activity-dependent behavioral labeling and electrophysiological recordings and found that postsynaptically expressed LTP was induced selectively in the CS-specific auditory pathways to the LA in a mouse model of auditory discriminative fear conditioning. Moreover, optogenetically induced depotentiation of the CS-specific auditory pathways to the LA suppressed conditioned fear responses to the CS. Our results suggest that input-specific LTP in the LA contributes to fear memory specificity, enabling adaptive fear responses only to the relevant sensory cue.

Disclosures: J. Cho: None. **W. Kim:** None.

Poster

243. Fear and Aversive Learning and Memory: Acquisition

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 243.08/MM21

Topic: G.01. Appetitive and Aversive Learning

Support: K-State start-up funds

Title: Infralimbic cortex is involved in encoding operant overtraining in the fear incubation task

Authors: *A. PAJSER, B. GAEDDERT, H. FISHER, C. LONG, P. KALLENBERGER, A. LIMOGES, C. L. PICKENS
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Abstract: Previous research has shown that extended fear conditioning leads to initially low fear that grows over time, often termed fear incubation. This is contrary to the pattern seen after limited fear conditioning, which results in high fear initially that is sustained over time. The neurobiological basis of these differences is unknown. The current study was designed to investigate these neurobiological causes by examining neuronal activity in infralimbic cortex (IL), a brain area implicated in extinction-related fear decreases, in the decreased fear seen after fear over-training. Male Long-Evans rats acquired lever-pressing and then underwent training for 1 or 10 days. During these training sessions, half of the animals experienced 10 30-sec tones pseudo-randomly throughout the 90-min session and half of the animals experienced the same tones co-terminating with a 0.5-sec foot-shock. As a result, there were 4 groups of experimental subjects: animals that received 1 day of training with tone-shock pairings, animals that received 1 day of training with tones only, animals that received 10 days of training with tone-shock pairings, and animals that received 10 days of training with tones only. The day after fear conditioning was completed, animals underwent a contextual fear test, and the following day they underwent a cued fear test. Fear was measured using with conditioned suppression of lever-pressing and brain tissue was extracted 120 minutes after the beginning of the cued fear test and processed for c-Fos expression. We found that rats with 10 days of fear conditioning showed lower fear than rats with 1 day of fear conditioning. Additionally, the presence of shock during training had no effect on c-Fos expression in IL, but both extended training groups had higher levels of c-Fos expression in IL than the limited training groups. This suggests that IL encodes operant over-training, but not fear memories, in our task. One possibility is that extended lever-press training leads to habit formation. We plan to examine whether rats with extended operant training show insensitivity to devaluation of the reinforcer, and whether sensitivity to devaluation is altered by fear conditioning.

Disclosures: **A. Pajser:** None. **B. Gaeddert:** None. **H. Fisher:** None. **C. Long:** None. **P. Kallenberger:** None. **A. Limoges:** None. **C.L. Pickens:** None.

Poster

243. Fear and Aversive Learning and Memory: Acquisition

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 243.09/MM22

Topic: G.01. Appetitive and Aversive Learning

Support: MH097320

Title: Conditioned fear modulates sensory responsiveness: Neural mechanisms revealed by simultaneous EEG-fMRI

Authors: *S. YIN[1], Y. LIU[2], M. DING[1], A. KEIL[3]
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Abstract: In classical fear conditioning, a neutral stimulus, through repeated pairing with an adverse stimulus, begins to elicit the psychological and autonomic expressions of fear in the absence of the adverse stimulus. In addition, the conditioned threat also triggers sensory cortical facilitation, and the increased sensory responsiveness enables the threatening stimulus to compete more effectively for attentional resources. The neural mechanisms underlying sensory facilitation and increased sensory responsiveness in classical fear conditioning, however, remain unclear. We addressed this problem by recording simultaneous EEG-fMRI from 18 subjects during a classical differential fear conditioning paradigm. Two Gabor patches (45° and 135°) were used as conditioned stimuli. One Gabor patch, the CS+, was occasionally paired with an aversive human scream (US; 25% reinforcement rate), whereas the other Gabor patch, the CS-, was never paired with the US. We report two results. First, time-frequency analysis of EEG data demonstrated that the magnitude of visual alpha oscillations, a well-established index of visual cortical facilitation and responsiveness, was significantly lower following CS+ than CS-. Second, EEG-informed fMRI analysis revealed that the trial-by-trial fluctuations of alpha were significantly correlated with areas of the ventral attention network, including right temporoparietal junction (rTPJ) and right inferior frontal gyrus (rIFG), but not with amygdala. These results suggest that visual cortical responsiveness is facilitated by the conditioned threat and such increase of sensory responsiveness is likely affected by the attentional orienting system as opposed to the emotional salience system.

Disclosures: **S. Yin:** None. **Y. Liu:** None. **M. Ding:** None. **A. Keil:** None.

Poster

243. Fear and Aversive Learning and Memory: Acquisition

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 243.10/NN1

Topic: G.01. Appetitive and Aversive Learning

Support: CAPES

CNPq/Universal 456691/2014-6

Title: MicroRNA expression in the dorsal striatum after tone fear conditioning task

Authors: *J. C. SOARES[1], J. FERNANDES[2], T. L. FERREIRA[3], M. G. M. OLIVEIRA[1,3]
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Abstract: Many studies have suggested that microRNAs (small non-coding RNAs) may be involved in regulating the molecular mechanisms underlying neural plasticity and memory. Regarding this transcriptional regulation, the miR-132/212 family was identified as a target of the cAMP-response element binding (CREB) protein transcription factor. Indeed, CREB-miR-132 pathway in hippocampus has been implicated in synaptic plasticity and long-term memory. In dorsal striatum, the miR-212 expression was found to modulate cocaine-induced plasticity and others drug addiction behaviors by indirectly promoting CREB signaling. Given these observations, our hypothesis is that this pathway could also mediate memory that has been related to dorsal striatum, such as tone fear conditioning task (TFC). To begin to explore this question male Wistar rats were submitted to TFC and 1hour after the expression of CREB by Western Blotting, and of the microRNAs miR-132 and mir-212 by quantitative RT-PCR, was measured in the dorsal striatum. The analysis did not reveal significant differences in expression of CREB or microRNAs. Although additional studies will be required, these results indicate that the microRNA expression patterns in dorsal striatum was distinct from that of hippocampus, suggesting that role of microRNAs mir-132 and mir-212 in TFC memory in dorsal striatum is probably different from hippocampus.

Disclosures: **J.C. Soares:** None. **J. Fernandes:** None. **T.L. Ferreira:** None. **M.G.M. Oliveira:** None.

Poster

243. Fear and Aversive Learning and Memory: Acquisition

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 243.11/NN2

Topic: G.01. Appetitive and Aversive Learning

Support: National BioResource Project from Japan Agency for Medical Research and Development (AMED)

JSPS KAKENHI JP15H02370

JSPS KAKENHI JP16H01651

Title: The study of the amygdalar and hippocampal functions in zebrafish

Authors: *K. KAWAKAMI[1,2], H. TANABE[1], P. LAL[1,3]
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Abstract: The amygdala and hippocampus are two major components of the mammalian brains and perform crucial roles in the processing of emotional memory and episodic and spatial memory, respectively. In teleost, the medial and lateral zones of the dorsal telencephalon (Dm and Dl) have been postulated to be homologs of the mammalian amygdala and hippocampus based on neuroanatomical studies and ablation experiments. However, Dm and Dl are broad areas in the telencephalon and the neural circuitry mediating the amygdalar and hippocampal functions has yet to be explored. Here we identify the neuronal circuitry that is essential for emotional learning and episodic and spatial learning by a genetic approach in zebrafish. We performed large-scale gene trap and enhancer trap screens and generated transgenic fish that expressed Gal4FF, a synthetic Gal4 transcription activator, in specific regions and neuronal circuits in the brain. Then we crossed these brain-specific Gal4FF transgenic fish lines with UAS-neurotoxin lines to inhibit the activity of the Gal4FF-expressing neurons, and analyzed behaviors of the double transgenic fish. We found that, when the activity of a subpopulation of neurons in the Dm or Dl was inhibited, the fish showed deficits in emotional learning (fear conditioning) or episodic (trace fear conditioning) and spatial learning paradigms. Thus, we think that these neuronal populations are functional equivalents of the mammalian amygdala and hippocampus, respectively. This finding provides a basis for understanding essential neuronal circuits mediating evolutionarily conserved behaviors in vertebrates and opens up possibilities to study molecular and cellular bases of learning and memory using genetic approaches in zebrafish.

Disclosures: **K. Kawakami:** None. **H. Tanabe:** None. **P. Lal:** None.

Poster

243. Fear and Aversive Learning and Memory: Acquisition

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 243.12/NN3

Topic: G.01. Appetitive and Aversive Learning

Support: MOST 105-2410-H-006-017

MOST 105-2420-H-006-004-MY2

Title: Spatial information acquired during training is critical to the inhibitory avoidance learning under dexmedetomidine-induced anesthesia in rats

Authors: *H.-Y. HSIAO, D.-Y. CHEN
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Abstract: Anesthesia may interfere with normal function of brain, but animals and human still preserve certain kinds of learning and memory under general anesthesia. For example, we have demonstrated that rats can learn a two-stage inhibitory avoidance task when they were anesthetized by dexmedetomidine (DEX). The association between dark chamber and foot-shock can be acquired under anesthesia. In addition, rats without exposure to the light chamber during training could not show avoidance responses to the dark chamber paired with shock under anesthesia. It seems that the spatial knowledge about the entire apparatus including both light and dark chambers plays a critical role. In the present study, we examined the importance of exposure to the light chamber under awake or anesthetized state in such learning paradigm. On Day 1, rats were allowed to shortly explore the entire apparatus. On Day 2-4, they were subjected to different training conditions. In the first stage of training, the light-exposure group (LE) was placed into the light chamber while they were awake, and the non-exposure group (NE) was staying in their home cage. The irrelevant context group (IC) was placed into an irrelevant environment. Rats underwent the second stage about one hour later. They were anesthetized by DEX (60 μg/kg, s.c.), then were placed directly into the dark chamber and received 10 foot-shocks (1.2 mA, 2 s, ITI: 30 s). Animals were injected with atipamezole (0.84 mg/kg, s.c.) to recover from anesthesia immediately after the last foot-shock. Another group received very similar treatment as the LE group but without shocks during training (non-shock group, NS). On Day 5, they were placed into the light chamber for a memory retention test. The LE group showed that their latencies of stepping into the dark chamber were significantly higher than all other groups. These results indicated that fear conditioning could be acquired under anesthesia when rats were exposed to the light chamber during training. Additional two groups were used to examine whether the memory can be formed if the first stage was under anesthesia. Similar to

the LE group, the anesthetized group (LE-An) received DEX before exposure to the light chamber. The interval between two stages was six hours to prevent possible interference of drugs. The awake group (LE-Aw) received similar treatments as LE-An group but without anesthesia. The LE-An group also showed significant higher stepping through latency, similar to LE and LE-Aw groups. The results of the present study suggested that spatial information acquired during exposure to light chamber, no matter under anesthesia or awake, is critical to the fear conditioning under anesthesia.

Disclosures: H. Hsiao: None. **D. Chen:** None.

Poster

243. Fear and Aversive Learning and Memory: Acquisition

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 243.13/NN4

Topic: G.01. Appetitive and Aversive Learning

Support: Conacyt 252379

PAPIIT 204615.

Gabriela Vera technical support

Alejandro Rangel technical support

Title: Differential effects of NMDA receptors activation in the insular cortex during inhibitory avoidance and its latent inhibition

Authors: *M. J. OLVERA-CALTZONTZIN[1,2], M. MIRANDA[2]
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Abstract: During inhibitory avoidance (IA) rodents inhibit their natural tendency to cross to and explore a dark compartment (DC) to avoid an electric foot shock. On the other hand, during latent inhibition of IA (LI-IA) there is a decrement in the association between the DC and the electric shock due to the pre-exposure to the DC, generally one day before IA training, registered as a lower entry latency to DC in comparison to non-DC pre-exposed subjects. Previous findings suggest that the insular cortex (IC) have a function during learning and memory retrieval on aversive task, including IA. Also, several neurotransmitter systems have been involved during memory formation of IA, including glutamate. For example, previous evidence indicates that NMDA and AMPA receptor activation in the hippocampus is needed during IA; therefore, IC glutamatergic activity mediated by NMDA receptors could be a key component for enhancing

aversive learning. However, the effects of NMDA receptor activation in the IC during IA or its IL are not yet known. Thus, the aim of this research was to evaluate the effect of the NMDA receptor activation during IA acquisition and during LI-IA process. For this purpose, male rats 200-250 gr. were bilaterally injected in the IC with NMDA (6.8μM) 8 min before IA acquisition in cohorts that were pre-exposed or not to the DC one day before. IA was conducted applying a 0.5 mA foot shock after rats stepped inside the DC, and stayed additionally 300 s in the DC after the foot shock. 24 hr later, memory retention was tested. The results show that the NMDA injections impair IA but they also improve the LI-IA when rats were pre-exposed to the DC, indicating that NMDA receptors activation in the IC has a different role during incidental and aversive context memory.

Disclosures: M.J. Olvera-Caltzontzin: None. **M. Miranda:** None.

Poster

244. Motivation: Neural Circuits I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 244.01/NN5

Topic: G.02. Motivation

Support: NIH Grant R01DA006214

NIH Grant F31DA042588

Title: Role of lateral septum input to lateral hypothalamus orexin neurons in cocaine demand

Authors: *C. PANTAZIS[1], B. S. BENTZLEY[2], M. H. JAMES[3], G. S. ASTON-JONES[1]
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Abstract: Neurons in lateral septum (LS) promote anxiety-like behaviors, as well as motivation to seek natural and drug rewards. Although it is unclear how LS mediates such diverse behaviors, its behavioral role appears to require signaling to the hypothalamus. Rostral LS projects to neurons containing the hypothalamic neuropeptide orexin, and these LS projections to lateral hypothalamus (LH) orexin neurons are necessary for cocaine conditioned place preference (Sartor & Aston-Jones, 2012). Our laboratory recently implemented a behavioral economics (BE) paradigm that uniquely assesses cocaine demand including demand elasticity, a quantitative measure of motivation. We found that knockdown of LH orexin neurons in this paradigm reduces motivation for cocaine (James et al. *manuscript in preparation).* Therefore, we sought to determine if LS input to these neurons was necessary to drive cocaine motivation. Adult male Sprague-Dawley rats were sacrificed 90 min after the point of maximum effort (Pmax) in our BE paradigm, and sections were processed for Fos immunohistochemistry. Fos expression in LS

neurons increased at Pmax, and the number of Fos+ neurons correlated with demand elasticity (alpha) and Pmax. Infusion of the GABA agonists baclofen-muscimol (B-M) into LS reduced motivation for cocaine without affecting baseline consumption, locomotor activity, or fixed-ratio responding for sucrose. These effects were not observed with aCSF injections into LS, or B-M injections 2 mm dorsal to LS (controls). Intra-LS B-M injections also increased total center time during locomotor testing, and animals' percent increase in center time following intra-LS B-M correlated with their percent decrease in motivation during BE. These results indicate that LS inhibition may reduce cocaine motivation by decreasing anxiety. To determine if these effects were due to LS signaling to LH orexin neurons, we used a bilateral disconnection approach. Orexin A antisense morpholino was infused unilaterally into LH, leading to selective knockdown of LH orexin neurons six days post-infusion (Sartor & Aston-Jones, 2012). On the sixth day, animals received a unilateral infusion of B-M or aCSF into contralateral LS prior to BE or locomotor testing. We hypothesized that disconnection of the LS-to-LH orexin circuit would reduce motivation for cocaine during BE and increase total center time during locomotor testing, consistent with our observations following bilateral LS inhibition.

Disclosures: C. Pantazis: None. **B.S. Bentzley:** None. **M.H. James:** None. **G.S. Aston-Jones:** None.

Poster

244. Motivation: Neural Circuits I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 244.02/NN6

Topic: G.02. Motivation

Support: R01-MH092868 (GAJ)

NHMRC CJ Martin 1128089 (HEB)

NHMRC CJ Martin 1072706 (MHJ)

Title: Chemogenetic activation of a retinal circuit that activates locus coeruleus neurons prevents the development of light-deprivation induced depression-like behavior

Authors: *H. E. BOWREY[1], M. H. JAMES[2], A. MOHAMMADKHANI[2], M. OMRANI[2], G. KANE[2], G. ASTON-JONES[2]
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Abstract: Introduction: Chronic light-deprivation induces a depressive-like phenotype via a locus coeruleus norepinephrine (LC-NE)-dependent mechanism (Gonzalez and Aston-Jones, 2008). Suprachiasmatic nucleus (SCN) provides indirect circadian input onto LC via dorsomedial hypothalamus (DMH) (Aston-Jones et al 2001). SCN is therefore in a key position

to integrate light information with LC via the pathway: retina→SCN→DMH→LC. We refer to this pathway as the Photic Regulation of Arousal and Mood (PRAM) pathway. We tested the hypothesis that increasing PRAM pathway activity prevents darkness-induced depression-like behavior. **Methods:** *Expt 1.* Sprague Dawley rats received intraocular injections of excitatory hM3Dq DREADD (AAV2-hSyn-hM3D(Gq)-mCherry) control virus (AAV2-hSyn-EGFP) or no virus. Rats were placed in continuous darkness for 8 weeks, and those that received virus were concurrently subjected to daily intraperitoneal injections of clozapine-*N*-oxide (CNO; 2 mg/kg), the DREADD-activating ligand. Rats were then subjected to assays of mood (saccharin preference test, elevated plus maze and forced swim test) or vision (electroretinagram: ERG). LC tissue was stained for Poly ADP ribose polymerase (PARP, a marker of apoptosis) and tyrosine hydroxilase (TH). *Expt 2.* To determine the retinal cell-type responsible for depression-like behavior, intrinsically photosensitive retinal ganglion cells (ipRGCs) of animals raised in 12:12 light:dark conditions were ablated using a saporin (SAP) toxin that selectively eliminates melanopsin-expressing cells (Mel-SAP). Two control groups received intraocular injections of vehicle and were kept in either continuous darkness or in 12:12 light:dark conditions. Ten weeks later, rats were subjected to identical analyses as those in *Expt 1.* **Results:** *Expt 1.* ERG analysis showed that CNO-activation of retinal DREADDs increased RGC activity. Constant darkness induced a depression-like phenotype in control animals, which was prevented by daily activation of retinal DREADDs by CNO. *Expt 2.* Mel-SAP induced a depression-like phenotype in animals maintained in normal light-dark conditions. This was also associated with increased apoptosis in LC-NE cells as seen with PARP staining. **Conclusion:** Dysregulation of the PRAM pathway may induce neural damage in LC-NE neurons that is associated with a depressive behavioral phenotype. DREADD-induced activation of RGCs can prevent depression-like behaviors that normally occur in rats kept in chronic darkness. The PRAM pathway presents a novel circuit for the regulation of mood, and thus a possible new direction for the treatment of some forms of depression in humans.

Disclosures: H.E. Bowrey: None. **M.H. James:** None. **A. Mohammadkhani:** None. **M. Omrani:** None. **G. Kane:** None. **G. Aston-Jones:** None.

Poster

244. Motivation: Neural Circuits I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 244.03/NN7

Topic: G.02. Motivation

Support: PHS DA016511

NIEHS 4T32ES007148

Title: Sex differences in motivation for cocaine: Role of oxytocin

Authors: *B. LIN[1], A. S. KOHTZ[3], G. S. ASTON-JONES[2]
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Abstract: Cocaine demand can be measured by the price a subject is willing to pay to consume the drug. Demand is quantified using behavioral economics (BE) procedures in both humans and animals, and we have implemented this procedure in rats. A key feature of cocaine addiction is pathologically high demand for cocaine, wherein addicts increase drug consumption despite high prices. This analysis provides quantitative measures of drug demand that predict several key addiction behaviors. We previously reported that male rats display inherent trait differences in demand for cocaine, such that they can be split by α into distinct high-demand and low-demand groups, similar to population differences in male human subjects. In addition, prior reports show that oxytocin (OTC), a neurohormone that regulates stress responses, decreases demand for cocaine in male rats. In contrast, no studies to date have identified individual variations in cocaine demand among women or female rodents. However, many studies indicate that women in the luteal menstrual phase (when endogenous progesterone (P4) levels are high) have decreased desire for cocaine compared to those in a low progesterone (follicular) phase. Here we investigated demand for cocaine in female rodents across the estrous cycle. We show that overall, females have greater demand than do males. However, we also show that rats in the high progesterone phase of the estrous cycle (proestrous) have decreased motivation for cocaine (high demand elasticity; α) compared to females in other cycle phases. We hypothesize that the variability accounted for by estrous cycle phase (state) summates with individual (trait) variability. We then investigated the effects of systemic administration of oxytocin on demand across the estrous cycle. We find that there are substantial dose-dependent effects of oxytocin to decrease cocaine demand in female rats, where in doses as low as 0.1mg/kg oxytocin can decrease demand for cocaine. The present studies extended prior studies on individual (trait) differences in cocaine abuse in males to female rats, and examined the role also of hormonal (state) factors. Results of these studies can provide biomarkers that will predict effectiveness of sex-specific OXT-based therapies to treat addictive disorders.

Disclosures: B. Lin: None. **A.S. Kohtz:** None. **G.S. Aston-Jones:** None.

Poster

244. Motivation: Neural Circuits I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 244.04/NN8

Topic: G.02. Motivation

Title: Inhibiting orexin-1 receptor signaling in ventral pallidum decreases demand for the opioid remifentanil

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Abstract: The orexin/hypocretin system has been implicated in motivation for drug reward and relapse. Orexin neurons of the hypothalamus send widespread axonal efferents to many reward-associated regions of the brain such as ventral pallidum (VP). Several studies have investigated the involvement of orexin signaling in motivation for cocaine, but little is known about the role of orexin signaling in motivation for opioids. Previously our lab showed that systemic blockade of orexin-1 receptors (Ox1Rs) decreases motivation for the potent and short-acting opioid remifentanil (Porter-Stransky et al., 2015). Previous studies also found that VP is an important site for the reinforcing effect of opiates and cocaine self-administration, as well as for reinstatement of drug seeking (Hubner and Koob, 1990; Mahler et al., 2014). However, it is unclear if orexin signaling in VP contributes to remifentanil demand. This study sought to determine whether intra-VP orexin signaling contributes to remifentanil demand and cue-induced reinstatement. We used a within-session behavioral economic (BE) paradigm in which remifentanil price (responses/µg iv remifentanil) was sequentially increased throughout the session. Rats were implanted with bilateral cannulae into VP, through which microinjections of SB334867 (SB; Ox1R antagonist) were given prior to BE testing. Rats were then extinguished and subjected to cue-induced reinstatement following intra-VP SB microinjection. We found that inhibition of OxR1 signaling in VP reduced motivation (increased demand elasticity) for remifentanil without affecting baseline consumption, cue induced reinstatement or general locomotor activity. These effects were not observed with aCSF injections into VP or SB injections 2 mm dorsal to VP (controls). These behavioral results provide evidence for orexin signaling in VP in motivation for the opioid remifentanil.

Disclosures: A. Mohammadkhani: None. **C. Pantazis:** None. **G. Aston-Jones:** None.

Poster

244. Motivation: Neural Circuits I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 244.05/NN9

Topic: G.02. Motivation

Support: R01 DA006214-25S1

Title: The role of medial hypothalamus orexin circuits in prescription opioid abuse

Authors: *J. E. FRAGALE[1], K. A. PORTER-STRANSKY[3], A. MOHAMMADKHANI[4], C. PANTAZIS[2], M. H. JAMES[5], G. S. ASTON-JONES[2]

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Abstract: Prescription opioid abuse is a chronic and relapsing disorder that is marked by an excessive motivation for the abused drug. Although rates of prescription opioid abuse are high, not all individuals prescribed an opioid become addicted. Motivated drug taking can be assessed using a behavioral economics (BE) task that our lab has used to measure the rate of consumption as the effort to maintain the desired drug concentration increases (Bentzley et al., 2013; 2014). The BE measure Q_o describes the theoretical consumption of a drug when no effort is required and is a measure of hedonic set point. The BE parameter α is a measure of demand elasticity (price sensitivity; inverse of motivation) and is a quantitative measure of motivation. The orexin/hypocretin system is implicated in motivated drug taking and we showed that the orexin-1 receptor (Ox1R) antagonist SB-334867 (SB) decreases hedonic set point and increases demand elasticity for the prescription opioid remifentanil on our BE task (Porter-Stransky et al., 2015). In this study, we investigated the relationship between individual differences in remifentanil demand and orexin neuron activity. Rats were trained to self-administer remifentanil, tested on BE, and sacrificed 90 min after the point of maximum responding (Pmax). Double-labeled immunohistochemistry for Fos and orexin somata in hypothalamus was performed. We found that the percentage of Fos-expressing orexin neurons in dorsal medial hypothalamus (DMH), but not in perifornical (PeF) or lateral hypothalamus (LH), correlated with Q_o. Specifically, subjects with a greater percentage of Fos-expressing orexin neurons had a greater Q_o (higer hedonic setpoint). Correlations were not observed between the percentage of Fos-expressing orexin neurons and demand elasticity (α). Additionally, relationships were not observed between total number of orexin neurons in DMH, PeF, or LH, and Q_o or α. These results indicate that DMH orexin neurons may contribute to prescription opioid abuse by regulating an individual's hedonic set point for the drug. We are currently assessing Fos activation in regions densely innervated by DMH orexin neurons to identify downstream targets of orexin neurons that might contribute to these results.

Disclosures: J.E. Fragale: None. **K.A. Porter-Stransky:** None. **A. Mohammadkhani:** None. **C. Pantazis:** None. **M.H. James:** None. **G.S. Aston-Jones:** None.

Poster

244. Motivation: Neural Circuits I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 244.06/NN10

Topic: G.02. Motivation

Support: PHS DA016511

NIDA DA006214

NIEHS 4T32ES007148

Title: Attenuating locus coeruleus norepinephrine signaling on extinction day 1 prevents cocaine relapse in female rats

Authors: *A. S. KOHTZ, J. F. CATUZZI, G. ASTON-JONES
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Abstract: There is growing evidence for sex differences in cocaine abuse with clear treatment implications. Abundant reports indicate that women progress more quickly from casual drug use to dependence, have greater difficulty quitting, and have shorter periods of abstinence that are exacerbated by stress. Rodent models of addiction/relapse recapitulate these sex differences. Female rats more readily and rapidly acquire cocaine self-administration, and demonstrate greater cocaine-primed and stress-induced reinstatement than males. Female rats also respond more than male rats during initial abstinence (extinction day 1, ED1) after cocaine self-administration, a notably stressful event involving abstinence from drug. Notably, cravings during this period in humans and rodents can predict later relapse in both species, indicating that ED1 may be a critical time point for targeting treatment in addiction. We previously showed that ED1 drug-seeking can be ameliorated by systemically administering “anti-stress” drugs on ED1, including beta-adrenergic antagonists, CRF-1 antagonists, or oxytocin. In addition, we identified sex-specific recruitment of stress sensitive brain regions on ED1, including locus coeruleus norepinephrine (LC-NE) neurons and dorsal hippocampus pyramidal neurons (dHPC). Here, we microinfused a cocktail of beta-adrenergic antagonists (betaxolol plus ICI-118,551) or saline into dHPC on ED1, and observed drug-seeking behavior on ED1 as well as following 2 weeks of forced abstinence. In females only, beta-adrenergic antagonists reduced drug-seeking on ED1; these animals also showed persistently decreased cocaine-seeking following 2 weeks of home-cage abstinence, compared to rats administered saline on ED1. As seen with Fos induction, LC-NE neurons were more sensitive to ED1-stress in females compared to males. Thus, we then further investigated the role of stress reactivity in LC by microinfusing the CRF-1 antagonist CP-154,526 into LC on ED1. Finally, using chemogenetic techniques we targeted LC-NE projections to dHPC. Given the efficacy of beta-adrenergic antagonists in the dHPC to attenuate cocaine seeking in females persistently, we propose that LC projections to dHPC CA1 may be a crucial circuit for targeting cocaine-seeking behaviors, particularly in females. This work was supported by PHS DA016511 and DA006214 to GAJ and NIEHS 4T32ES007148 to ASK.

Disclosures: **A.S. Kohtz:** None. **J.F. Catuzzi:** None. **G. Aston-Jones:** None.

Poster

244. Motivation: Neural Circuits I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 244.07/NN11

Topic: G.02. Motivation

Support: IRP/NIH

Title: Dorsal raphe dual serotonin-glutamate neurons drive dopamine release and reward

Authors: *H.-L. WANG[1], J. QI[2], R. CACHOP[3], C. MEJIAS-APONTE[2], C. PALADINI[5], J. GOMEZ[5], G. BEAUDOIN[5], J. F. CHEER[4], M. F. MORALES[6]
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Abstract: Serotonin neurons from the dorsal raphe nucleus (DR) play a role in reward-related behaviors. However, the mechanism by which DR serotonin neurons participate in these behaviors is unclear. DR serotonin neurons heavily innervate the VTA (Bobillier et al., 1976; Pierce et al., 1976), the origin of the mesolimbic dopamine system, a network of known importance for reward and motivational function (Wise, 2004). Our recent tracing studies have demonstrated that DR neurons expressing serotonergic markers (serotonin-only neurons), vesicular glutamate transporter type 3 (VGluT3, VGluT3-only neurons) or co-expressing serotonergic markers and VGluT3 (dual serotonin-VGluT3 neurons) target the VTA in the rat and mouse (Qi et al., 2014), and make synapses on dopamine neurons (see Zhang et al., SfN 2017). The major input from DR to VTA is from VGluT3-only neurons that utilize glutamate as a signaling molecule. We also have demonstrated that VTA glutamate release from DR VGluT3-fibers induces the release of dopamine in the nucleus accumbens (nAcc) and has reinforcing effects (Qi et al., 2014). In the present study, to determine the role of serotonergic inputs to VTA in behavior, we used an optogenetic approach in which we drove the expression of Channelrhodopsin-2 in DR serotonin transporter positive (SERT) neurons. We found that (1) VTA optical activation of SERT-fibers promoted conditioned placed preference (CPP), which was mediated by both AMPA- and serotonin receptors; (2) VTA optical activation of SERT-fibers evoked excitatory currents on dopamine neurons; and (3) VTA optical activation of SERT-fibers promoted nAcc dopamine release, which involved both AMPA- and serotonin receptors. In comparing these results to the nAcc dopamine release and reinforcement produced by glutamate released from DR VGluT3-fibers (Qi et al., 2014), we found that the amounts of dopamine release and CPP induced by VTA activation of serotonin-fibers was lower than that induced by VGluT3-fibers, but that the CPP induced by activation of SERT-fibers was more extinction-resistant. In conclusion, we provide evidence for a serotonergic-glutamatergic DR → VTA mesoaccumbens dopamine pathway that participates in reward processing. These findings open new avenues to study the possible participation of this pathway in mental disorders involving alterations in serotonergic function and reward-related processing.

Disclosures: H. Wang: None. **J. Qi:** None. **R. Cachop:** None. **C. Mejias-Aponte:** None. **C. Paladini:** None. **J. Gomez:** None. **G. Beaudoin:** None. **J.F. Cheer:** None. **M.F. Morales:** None.

Poster

244. Motivation: Neural Circuits I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 244.08/NN12

Topic: G.02. Motivation

Support: NIH/NIDA

Title: Electrophysiological and pharmacological characterization of Dorsal Raphe glutamatergic neurons

Authors: *J. A. MIRANDA-BARRIENTOS[1,2], M. F. MORALES[3]
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Abstract: The Dorsal Raphe (DR) provides a major source of serotonergic inputs to different brain regions. In addition to serotonergic neurons, the DR contains different types of neurons, including neurons that express the vesicular glutamate transporter 3 (VGluT3) (Gras et al., 2002; Herzog et al., 2004; Jackson et al., 2009). A subpopulation of DR VGluT3 neurons co-expresses serotonergic markers, indicating heterogeneity among the DR VGluT3 neurons. We had recently demonstrated that the DR VGluT3 neurons establish excitatory synapses on dopamine neurons of the ventral tegmental area(VTA) (Qi et al., 2014). We had also showed that VTA photoactivation of DR VGluT3 fibers induces the firing of dopamine neurons, increases the release of dopamine in nucleus accumbens, and is rewarding (Qi et al., 2014). To have a better understanding of the neuronal mechanisms that participate on the regulation of the circuitry involving DR VGluT3 neurons mesoaccumbens dopamine neurons, we began to characterize the electrophysiological and pharmacological properties of DR VGluT3 neurons. By *in vitro* electrophysiological recordings of genetically identified VGluT3 neurons, we analyzed the intrinsic passive and active membrane properties of these neurons. We found that although there were not distinct electrophysiological properties among VGluT3 and non-VGluT3 neurons, the VGluT3 neurons exhibited shorter after hyperpolarization potentials than the serotonin neurons. In addition, we determined that some VGluT3 neurons had high excitability and others had low excitability. Because DR neurons have been shown to contain corticotrophin-releasing factor (CRF) receptors, we determined the effects of CRF on VGluT3 neurons, and found that CRF increased the firing rate of VGluT3 neurons with high excitability, without affecting those with low excitability. From these findings, we concluded that the release of glutamate by a subset of DR VGluT3 neurons is regulated by CRF.

Disclosures: J.A. Miranda-Barrientos: None. **M.F. Morales:** None.

Poster

244. Motivation: Neural Circuits I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 244.09/NN13

Topic: G.02. Motivation

Support: NIDA-IRP

Title: Dual serotonin-glutamate neurons establish synapses on ventral tegmental area dopamine neurons hat innervate the nucleus accumbens

Authors: *S. ZHANG[1], H.-L. WANG[2], M. F. MORALES[3]
[1]Natl. Inst. of Health, Natl. Inst. on Drug Abuse, IRP, Baltimore, MD; [2]IRP/NIDA/NIH, Baltimore, MD; [3]Cell Neurobiol Res. Br., IRP, NIDA, NIH, Baltimore, MD

Abstract: Serotonin neurons from the dorsal raphe nucleus (DR) play a role in reward-related behaviors. We have found that ventral tegmental area (VTA) photoactivation of fibers from DR expressing Channelrhodopsin-2 under the regulation of the serotonin transporter (SERT) induces (1) conditioned place preference (CPP) and (2) dopamine release in the nucleus accumbens (nAcc), both mediated by postsynaptic activation of serotonin and glutamate receptors (Wang et al., SfN 2017). In addition, we have demonstrated that DR neurons including serotonin-only neurons, vesicular glutamate transporter 3 (VGluT3)-only neurons, or dual serotonin-VGluT3 neurons target the VTA (Qi et al., 2014). In the present study, we directly examined the ultrastructural and molecular characteristics of the synaptic connectivity between DR serotonin neurons and VTA neurons. By immunofluorescence, we detected in VTA axon terminals expressing SERT, VGluT3, or both SERT and VGluT3. By quantitative analysis of the DR terminals within the VTA (11,725 terminals), we found that 23.16 ± 1.61% expressed SERT, 64.92 ± 0.71% expressed VGluT3 and 11.92 ± 0.92% co-expressed SERT-VGluT3. By electron microscopy, we found that most of the dual SERT-VGluT3 terminals (69.43 ± 1.01%) established asymmetric synapses on tyrosine hydroxylase (TH)-positive dendrites, and about one third (30.57 ± 1.01%) on TH-negative dendrites. In contrast, SERT-only terminals established symmetric synapses mostly on TH-negative dendrites (68.65 ± 0.73%), and one-third on TH-positive dendrites (31.35 ± 0.73%). Moreover, we found that almost all SERT-positive neurons establishing asymmetric synapses on VTA TH-positive neurons co-expressed VGluT3 (98.46 ± 0.89%). These findings suggest that the majority of DR serotonin neurons innervating the TH-positive neurons are endowed with the capability to co-release serotonin and glutamate from axon terminals expressing VGluT3. We next determined whether SERT-VGluT3 terminals synapse on TH neurons that innervate the nucleus accumbens (mesoaccumbens neurons). We injected in the nAcc of SERT-ChR2-mCherry mice the retrograde tract tracer Fluoro-Gold. By VTA immunofluorescence, we observed that SERT-fibers targeted dendrites from

mesoaccumbens neurons. By electron microscopy, we found that dual SERT-VGluT3 axon terminals made asymmetric synapses on mesoaccumbens neurons. Together these findings indicate that dopamine mesoaccumbens neurons located in the VTA are a major target of dual DR serotonergic-VGluT3 neurons. These findings provide evidence suggesting an excitatory control of mesoaccumbens VTA dopamine neurons by SERT-VGluT3 afferents from DR neurons.

Disclosures: S. Zhang: None. **H. Wang:** None. **M.F. Morales:** None.

Poster

244. Motivation: Neural Circuits I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 244.10/NN14

Topic: G.02. Motivation

Support: NIH/NIDA-IRP

Title: Diverse functions of ventral tegmental area VGluT2 neurons

Authors: *D. H. ROOT, R. J. JUZA, M. MORALES
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Abstract: The ventral tegmental area (VTA) plays fundamental roles in motivated behaviors, including those associated with addiction and depression. In recent years it has become appreciated that the VTA contains genetically-distinct neuronal phenotypes that exhibit unique neuronal networks and influences on motivated behaviors. Among the most recently identified VTA neurons are those that express vesicular glutamate transporter 2 (VGluT2) and release the excitatory neurotransmitter glutamate. Optogenetic studies have shown that VTA-VGluT2 neurons are capable of participating in reward or aversion. However, our understanding of the specific functions of VTA-VGluT2 neurons is limited by the lack of information on specific environmental stimuli or behaviors in which these neurons are responsive. To address this issue, we genetically tagged VTA VGluT2 neurons by injecting a Cre-dependent vector encoding channelrhodopsin2 tethered to eYFP into the VTA of VGluT2::Cre mice, and implanted electrodes in the VTA three weeks after viral injections. We delivered into the VTA brief pulses of 473 nm light, and VTA neurons responding with high-fidelity short-latency spikes were considered as VGluT2 neurons. These VTA identified VGluT2 neurons were recorded during a Pavlovian sucrose reward task and during the receipt of a mildly aversive airpuff stimulus. Prior to recordings, mice learned to discriminate reward port entries between the conditioned stimulus tone paired with sucrose and the conditioned stimulus tone paired with no reward delivery. We identified VTA-VGluT2 neurons that were sensitive to rewarding or aversive stimuli. In order to determine the contributions of VTA-VGluT2 neuron modulations towards performance in the

Pavlovian sucrose reward task, we injected a Cre-dependent vector encoding halorhodopsin3.0 tethered to eYFP into the VTA of VGluT2::Cre mice. Into the VTA of these mice, we delivered brief pulses of 532 nm light to inhibit VTA-VGluT2 neurons specifically during behaviors in which VTA-VGluT2 neurons showed increases in firing rate. Preliminary results suggest that VTA-VGluT2 neuron firing participates in both reward-seeking behavior and aversive signaling. These *in vivo* recording data provide new insights on the participation of newly-identified VTA-VGluT2 neurons in different aspects of motivated behaviors.
This work was supported by NIDA/NIH.

Disclosures: D.H. Root: None. **R.J. Juza:** None. **M. Morales:** None.

Poster

244. Motivation: Neural Circuits I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 244.11/NN15

Topic: G.02. Motivation

Support: NIH Grant DA015188

NIH Grant MH63649

NIDA T32DA007281

Title: Optogenetic stimulation of the medial amygdala generates motivation for natural and drug rewards

Authors: *E. E. NAFFZIGER, S. M. WARLOW, K. C. BERRIDGE
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Abstract: The medial amygdala (MeA) is a striatal-level structure in the medial subdivision of the extended amygdala system (EAS), paralleling the central amygdala (CeA), which belongs to the lateral subdivision of the EAS. While the MeA has been studied extensively in relation to sex and aggression, it has been neglected in addiction neuroscience. Previous research in our lab has shown that optogenetic stimulation of the CeA can substantially bias choice and generate motivation for a photostimulation-paired reward over an identical, non-photostimulation-paired reward. These findings were specific to the CeA, as analogous photostimulation of the basolateral amygdala did not produce these effects. Recently it has been found that channelrhodopsin (ChR2) stimulation of the MeA, has an equal capacity to focus pursuit for a sucrose reward in an instrumental task. Given substantial overlap between neural circuits for natural and drug rewards, it can be hypothesized that MeA may equally generate motivation for a ChR2-paired drug reward (cocaine infusion) or another conspecific paired with ChR2. Indeed, preliminary evidence suggests that in an instrumental task responding for a cocaine reward, rats

elicit a bias for the MeA ChR2 paired cocaine nose port. However, in a separate task in which MeA ChR2 stimulation is paired with another conspecific, rats spend less time interacting and following when receiving MeA ChR2. Together this data suggests that the MeA can focus pursuit for a ChR2-paired sucrose and cocaine reward, but may inhibit social behavior toward a same-sex conspecific.

Disclosures: E.E. Naffziger: None. **S.M. Warlow:** None. **K.C. Berridge:** None.

Poster

244. Motivation: Neural Circuits I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 244.12/NN16

Topic: G.02. Motivation

Support: NIH Grant

DA015188

T32 Grant DC00011

Title: Dangerous desire: Optogenetic central amygdala stimulation amplifies attraction towards rewarding and aversive stimuli

Authors: *S. M. WARLOW, E. E. NAFFZIGER, K. C. BERRIDGE
Psychology, Univ. of Michigan, Ann Arbor, MI

Abstract: Previous research has shown that optogenetic stimulation of the central nucleus of amygdala (CeA) simultaneously narrows and amplifies motivation for sensory rewards such as sucrose and cocaine. However, in all cases, CeA laser by itself was worthless to the same rats, as rats would not self-stimulate laser alone. Here we presented rats with an opportunity to a) choose between two sensory rewards (natural sucrose vs. intravenous cocaine), or b) touch an aversive shock prod that delivers a mild, low-intensity shock to the paw or snout when touched. First, CeA channelrhodopsin (ChR2) stimulation when paired with earning either sucrose or cocaine, made rats intensely prefer that paired reward almost 10-fold compared to an alternative reward not paired with CeA stimulation. Second, when CeA ChR2 stimulation was paired with touching an aversive shock prod, control inactive virus rats, upon touching the prod, learned very quickly to avoid it (spent more time on the opposite side of the chamber) and even elicited anti-predator defensive treading towards it. However, in CeA ChR2 rats, pairing CeA stimulation with touching the shock-delivering prod made the prod more attractive to rats, as they spent more time on that side of the chamber and engaged in biting and sniffing of the prod. In these same rats, CeA ChR2 laser failed to support self-stimulation in a location-based task. Further, we measured and compared Fos protein expression in CeA output circuitry (such as lateral hypothalamus,

ventral pallidum, periaqueductal gray, and ventral tegmental area). Our findings suggest that CeA ChR2 stimulation recruits mesocorticolimbic circuitry to amplify attraction toward rewarding events and to transform avoidance of an aversive event into attraction towards it, but needs a motivationally salient event (whether rewarding or aversive) on which to act.

Disclosures: S.M. Warlow: None. **E.E. Naffziger:** None. **K.C. Berridge:** None.

Poster

244. Motivation: Neural Circuits I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 244.13/NN17

Topic: G.02. Motivation

Support: MH063649

DA015188

DA007268

Title: Optogenetic excitation of the ventral pallidum promotes motivation towards natural rewards

Authors: *J. OLNEY, K. C. BERRIDGE
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Abstract: The ventral pallidum (VP) is a basal forebrain structure whose connectivity with other limbic circuitry makes it ideally positioned to influence reward-related behaviors. Accordingly, previous studies have demonstrated that pharmacological excitation of the VP can enhance food 'wanting' and 'liking.' The present study sought to extend upon these findings by demonstrating that optogenetic excitation of the VP via channelrhodopsin (ChR2) amplifies and narrows the focus of incentive motivation toward a natural reward (i.e. sucrose or food) across a wide variety of paradigms. Here, rats were presented with the choice between two equal sucrose rewards. One reward was paired with optogenetic activation of the VP while the other was not. Preliminary results indicate that rats display a robust bias for the VP ChR2 laser-paired sucrose reward over an identical sucrose reward without laser. Furthermore, similar excitation of the VP produces enhanced motivation to work for a laser-paired reward in a progressive ratio task. Interestingly, rats with ChR2 in the posterior portion of the VP displayed increased motivation to work for a sucrose reward relative to those with ChR2 in the anterior VP regardless of whether or not the reward was paired with laser. In self-stimulation tasks, some rats showed signs that such photoactivation was reinforcing alone as some rats self-stimulated VP laser by touching an object and/or displayed a preference for a laser-paired side of a real-time place preference chamber. These data suggest that photoexcitation of at least some sites within the VP are capable

of producing rewarding effects independent of an external reward, but that such reinforcing effects of laser stimulation are not required to produce a preference for a laser paired reward. Finally, in some rats, VP ChR2 stimulation also caused a significant increase in food intake- a finding consistent with previous pharmacological investigations of the VP. Notably, none of these effects were not observed to vary as a function of sex. As a whole, these data suggest that VP optogenetic excitation bolsters reward-motivated behaviors. These findings may prove beneficial in our understanding of neuropsychological disorders characterized by pathological motivation, such as drug addiction. (Supported by NIH grants MH063649, DA015188, and DA007268).

Disclosures: J. Olney: None. **K.C. Berridge:** None.

Poster

244. Motivation: Neural Circuits I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 244.14/NN18

Topic: G.02. Motivation

Support: NIH Grant MH063649

NIH Grant DA015188

Title: Investigating corticotropin releasing factor in mediating appetitive behavior

Authors: *H. M. BAUMGARTNER[1], J. J. OLNEY[1], S. M. WARLOW[1], J. SCHULKIN[2], K. C. BERRIDGE[1]
[1]Psychology, Univ. of Michigan, Ann Arbor, MI; [2]Dept. of Neurosci., Georgetown Univ., Washington, DC

Abstract: Corticotropin releasing factor (CRF) is well known for its involvement in stress and anxiety, but may also play a role in reward seeking. The current study uses optogenetics in CRH-Cre rats to further understand the role of CRF in reward and motivated behaviors through selectively stimulating CRF neurons in targeted brain areas known to contain CRF neurons. Using ChR2 to stimulate CRF neurons in CRH-cre rats was evaluated in a variety of reward-related tasks including real-time place preference and laser self-stimulation. We targeted CRF neurons in brain regions including 1) the central amygdala (CeA), 2) bed nucleus of the strias terminalis (BNST), 3) ventral tegmental area, or 4) nucleus accumbens. Preliminary data suggest that some individuals will seek out self-stimulation of CRF neurons in the CeA as well as BNST at 3 second laser duration at 10Hz frequency but not 40Hz frequency. This research suggests that CRF may have a more general role in reward and motivated behavior outside of its stress-related

effects. We would like to thank Dr. Robert Messing at the University of Texas for sharing these animals. (Supported by NIH grants MH063649 and DA015188).

Disclosures: H.M. Baumgartner: None. **J.J. Olney:** None. **S.M. Warlow:** None. **J. Schulkin:** None. **K.C. Berridge:** None.

Poster

244. Motivation: Neural Circuits I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 244.15/NN19

Topic: G.02. Motivation

Support: NIDA IRP

Title: Red nucleus to VTA glutamatergic pathway: A newfound link between motor and reward circuits

Authors: *Y. HE, G. MADEO, H. SHEN, H.-Y. ZHANG, G.-H. BI, E. GARDNER, A. BONCI, Z.-X. XI
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Abstract: The central nervous system controls many functions essential to survival, such as feeding, territoriality and reproduction. Hence being physically active is regarded as an “evolutionary force” to aid survival. Thus, physical activity has become an intrinsic motivation. A typical example is exercise reward, which is a euphoric state often induced by intensive running (the “runner’s high”) and is considered to be associated with activity in multiple components of the reward system, such as dopamine, opioids and endocannabinoids. However, little is known as to whether a motor to reward pathway exists between the two systems to activate the reward networks. Although research into the ventral tegmental area (VTA) and its adjacent motor structure red nucleus (RN) has proceeded independently, it is noteworthy that the rubrospinal tract originating in the RN is the only descending motor pathway traveling through VTA. More interestingly, midbrain dopamine (DA) neurons and RN neurons share the same developmental origin. Here we provide evidence that RN neurons have an anatomic and functional connection to VTA DA neurons. We show that VTA DA neurons can be activated by selectively stimulating the RN-VTA glutamatergic projection pathway, which consequently produced reward-seeking behavior in mice as assessed by optical self-stimulation and conditioned place preference. Strikingly, wheel-running also activated the RN-VTA glutamatergic pathway and attenuated cocaine self-administration, and optogenetic activation of the RN-VTA glutamate pathway produces a similar reduction in cocaine self-administration. These results provide strong evidence of an anatomic and functional connectivity between the RN and the VTA - which is a newfound internal pathway by which the motor system may boost

activity within the reward networks to support exercise reward. It also provides solid neuroanatomic evidence that exercise could be a healthy innate reward that may compete with reward-related psychiatric disorders characterized by anhedonia. (Supported by NIDA IRP)

Disclosures: **Y. He:** None. **G. Madeo:** None. **H. Shen:** None. **H. Zhang:** None. **G. Bi:** None. **E. Gardner:** None. **A. Bonci:** None. **Z. Xi:** None.

Poster

244. Motivation: Neural Circuits I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 244.16/NN20

Topic: G.02. Motivation

Support: R15 DA041694

R01 DA09397

Title: Operant responding for optogenetic excitation of LDTg inputs to the VTA requires D1 and D2 dopamine receptor activation in the NAcc

Authors: ***S. STEIDL**[1], S. O'SULLIVAN[1], D. PILAT[1], N. BUBULA[2], J. BROWN[2], P. VEZINA[2]
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Abstract: Evidence from anesthetized rat and mouse preparations indicates that the laterodorsal tegmental nucleus (LDTg) regulates mesolimbic dopamine (DA) signaling via projections to the midbrain ventral tegmental area (VTA). It remains unknown however whether intracranial self-stimulation (ICSS) of LDTg inputs to the VTA requires activity in this ascending DA pathway. To address this question, rat LDTg neurons were transfected with adeno-associated viral vectors encoding channelrhodopsin2 and eYFP (ChR2) or eYFP only (eYFP). As we have shown previously, ChR2, but not eYFP, rats subsequently acquired a lever pressing response to obtain VTA photostimulation of LDTg inputs. During ICSS, DA overflow in the nucleus accumbens (NAcc) core showed maximal increases of approximately 240% of baseline levels. Based on these findings, we next tested the contribution of NAcc core D1 and D2 DA receptors to the reinforcing effects of optogenetic excitation of LDTg inputs to the VTA. Microinjection of SCH23390 or raclopride, D1 and D2 DA receptor antagonists respectively, into the NAcc core each significantly reduced operant responding for this stimulation. Identical effects were observed following microinjection of either SCH23390 or raclopride into the NAcc medial shell. Together these results demonstrate for the first time that optogenetic ICSS of LDTg inputs to the

VTA increases DA overflow in the NAcc and that the reinforcing effects of ICSS depend on the activation of D1 and D2 DA receptors in this site.

Disclosures: **S. Steidl:** None. **S. O'Sullivan:** None. **D. Pilat:** None. **N. Bubula:** None. **J. Brown:** None. **P. Vezina:** None.

Poster

244. Motivation: Neural Circuits I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 244.17/NN21

Topic: G.02. Motivation

Support: SFRH/BD/51992/2012

SFRH/BD/98675/2013

SFRH/BD/90374/2012

SFRH/BD/89936/2012

IF/00883/2013

ON.2 – O Novo Norte

QREN

Title: Impairments in laterodorsal tegmentum to VTA projections underlie glucocorticoid triggered reward deficits

Authors: *B. COIMBRA[1,2], C. SOARES-CUNHA[1,2], S. BORGES[1,2], N. A. VASCONCELOS[1,2], N. SOUSA[1,2], A. J. RODRIGUES[1,2]
[1]Life and Hlth. Sci. Res. Inst. (ICVS), Braga, Portugal; [2]ICVS/3B's–PT Government Associate Lab., Braga/Guimarães, Portugal

Abstract: Ventral tegmental area (VTA) activity is critical for motivated behaviours and reinforcement. Importantly, VTA activity is tightly modulated by afferents arising from the laterodorsal tegmentum (LDT). Disruption of this circuit can ultimately increase the risk for the development of neuropsychiatric disorders, including those associated with reward deficits, such as depression, anxiety, obsessive-compulsive disorder, obesity, addiction or antisocial behaviour. Additionally, the VTA region is particularly vulnerable to the effects of stress/glucocorticoids (GCs). Previous studies revealed that in utero exposure to glucocorticoids (iuGC) triggers prominent reward deficits later in life but nothing is known about the impact of this exposure in the LDT-VTA circuit. Here, we show that iuGC animals have long-lasting changes in the

expression of cholinergic markers in the LDT, and in vivo singe-cell electrophysiology revealed that LDT basal activity was decreased. Interestingly, we observe a bidirectional effect in LDT-VTA inputs: upon LDT stimulation, iuGC animals present a decrease in the magnitude of excitation and an increase in the magnitude of inhibition in the VTA. While in control animals most of the inhibitory responses arise from putative GABAergic neurons, in iuGC group there is a shift in the type of cells presenting inhibitory responses, with a significant increase in the number of dopaminergic neurons. In agreement with LDT-VTA dysfunction, we show that iuGC animals present motivational deficits that are rescued by selective optogenetic activation of this pathway. Importantly, we also show that LDTVTA optogenetic stimulation is reinforcing, and that iuGC animals are more susceptible to the reinforcing properties of LDT-VTA stimulation.

Disclosures: B. Coimbra: None. **C. Soares-Cunha:** None. **S. Borges:** None. **N.A. Vasconcelos:** None. **N. Sousa:** None. **A.J. Rodrigues:** None.

Poster

244. Motivation: Neural Circuits I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 244.18/NN22

Topic: G.02. Motivation

Support: Volkswagen Stiftung Freigeist Fellowship: 88216

Title: Playback of ultrasonic vocalizations modulates firing patterns of single neurons recorded in VTA of male rats

Authors: *M. VAN WINGERDEN, M. VAN BERKEL, S. VAN GURP
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Abstract: Rodents, including rats, use ultrasonic vocalisations (USVs) in their social communication. These USVs are thought to convey the affective state of the animal and are traditionally categorized in two broad subtypes. Longer (about 1s) vocalizations in a tight frequency band centred on 22 kHz occur in response to negative situations. Higher-frequency calls (typically called '50 kHz'), shorter in duration and potentially frequency-modulated, occur in appetitive situations (Burgdorf et al., 2011). Previous research has shown that rats show approach behavior to the playback of recorded 50 kHz but not 22kHz USVs and that perception of these 50 kHz USVs activates brain areas related to the processing of reward (Seffer et al., 2014; Willuhn et al., 2014).
However, the neural processing of these 50 kHz USVs at the single cell level remains unclear. As reporeted by Willuhn et al. (2014), playback of recorded USVs induces the release of dopamine (DA), a neurotransmitter intimately involved in reward and motivation (Schultz, 2016), in the Nucleus Accumbens (NAcc), a brain region implicated in the processing of non-

social and social value in many species, including humans (Haber and Knutson, 2010). A major source of DA in the NAcc is thought to be the ventral tegmental area (VTA), an area in the midbrain that reacts to primary reward delivery (Cohen and Uchida, 2012; Takahashi et al., 2016). Importantly, activating specifically the VTA-NAcc DA projections was shown to enhance social exploration in mice (Gunaydin et al., 2014) and optogenetic stimulation of DA-producing cells in the midbrain induced 50kHz USV production in rats. Given these results, we hypothesized that firing patterns of single cells in the VTA of rats would be modulated by the playback of USVs.
We therefore implanted hyperdrives holding 12 tetrodes in 2 bilateral bundles aimed at the VTA of male rats. In a novel Jukebox task, rats could choose between two compartments over several trials. In each compartment, a sugar pellet reward was given. Before reward delivery, however, a sound stimulus with (50 vs 22) or without (control) ultrasonic components was played back. Rats preferred the compartment with playback of 50 kHz over a matched control stimulus; no preference for or avoidance of the 22kHz stimulus over its control stimulus was found. Indeed, we have found that a subset of isolated VTA single cells respond to the playback of 50kHz, to primary reward delivery, but not to playback of 22kHz vocalizations, suggesting that these appetitive social communication signals indeed carry a reward signal.

Disclosures: **M. van Wingerden:** None. **M. van Berkel:** None. **S. van Gurp:** None.

Poster

244. Motivation: Neural Circuits I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 244.19/NN23

Topic: G.02. Motivation

Title: Systemic and intra-VTA administration of leptin enhances social behavior

Authors: J. LIU, X. ZHOU, *X.-Y. LU
Univ. of Texas Hlth. Sci. Ctr. at San Antonio, San Antonio, TX

Abstract: Impairment of social behaviors and disruptions of social relationships have been implicated in several neuropsychiatric disorders, such as autism, schizophrenia and depression. Leptin is an adipocyte-derived hormone that regulates motivational and emotional behaviors. The aim of this study was to determine if leptin regulates social motivation and social novelty. In the three-chamber social approach test, systemic administration of leptin increased total time spent in the chamber with a novel mouse. When tested for social memory and novelty, leptin treatment did not show a significant effect on the preference of a new stranger mouse over the familiar mouse. Given the important role of the ventral tegmental area (VTA) in social behavior, we determined if infusion of leptin into the VTA regulates sociability and social novelty. Mice with intra-VTA infusion of leptin showed a significant increase in the chamber time and sniffing

time spent for a novel mouse compared to mice with the vehicle treatment. Our studies indicate that leptin enhances sociability, possibly through acting on its target neurons in the VTA.

Disclosures: J. Liu: None. **X. Zhou:** None. **X. Lu:** None.

Poster

244. Motivation: Neural Circuits I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 244.20/NN24

Topic: G.02. Motivation

Support: NIH Intramural Research Program (NIDDK)

Title: Overconsumption of high-fat diet leads to chow devaluation

Authors: *W. FOBBS, A. KRAVITZ
NIDDK, NIH, Bethesda, MD

Abstract: Even though feeding mechanisms evolved to be regulated by hunger, satiety, and energy demand, humans and other animals find it difficult to maintain calorically-balanced diets when presented with highly palatable, calorie-dense foods. When such foods are constantly available, as is the case in our modern food environment, most individuals maintain a state of caloric surplus and some individuals overconsume calories to the point of developing obesity or metabolic syndrome. Although lower calorie options are readily available and there is growing awareness of the detrimental effects of caloric overconsumption, individuals often find it difficult to switch their diets and reduce their overconsumption. Little is known about the neural and metabolic mechanisms that drive and maintain overconsumption, but the behavioral pattern suggests that not only are there mechanisms that encourage palatable food overconsumption but there are also those that discourage or devalue consumption of less-palatable food. We have begun to explore the neural and metabolic basis of less-palatable food under-consumption using a mouse model. In our model, mice given continuous access to high-fat diet (60% fat) for 3 days consume fewer calories of chow on the subsequent day than they did prior to high-fat diet exposure. Interestingly, this effect is not simply driven by the hedonic qualities of the food since 3-day exposure to calorie-matched high-fat diet does not reduce subsequent chow consumption. Given that the dopamine system is implicated in signaling reward value and adaptations of the dopamine system have been linked to cravings for and compulsive consumption of palatable foods in obese individuals, we are also exploring whether and how dopamine signals are altered during chow devaluation.

Disclosures: W. Fobbs: None. **A. Kravitz:** None.

Poster

244. Motivation: Neural Circuits I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 244.21/NN25

Topic: G.02. Motivation

Support: NIH/NIDA R21-DA031577

Title: Optogenetic activation of the lateral preoptic area excites dopamine neurons, supports self-stimulation, and elicits “positive affect” ultrasonic vocalizations

Authors: A. G. GORDON[1], V. RAMACHANDRA[2], N. MITTAL[2], C. L. DUVAUCHELLE[2], *M. MARINELLI[2]
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Abstract: The lateral preoptic area (LPO) is a hypothalamic region whose function is largely unknown. The LPO sends strong projections to the ventral tegmental area (VTA), a key member of the brain-reward system. Therefore, in a first set of experiments, we tested the physiological relevance of this connectivity. We recorded the firing activity of VTA neurons while optogenetically stimulating the LPO or the LPO-VTA pathway. Optogenetic stimulation of the LPO (20-40Hz, 1-10s trains) strongly inhibited the majority of VTA GABA neurons and moderately excited the majority of VTA dopamine neurons. Similar results were obtained with optogenetic stimulation of the LPO-VTA pathway. These results suggest that the LPO sends functional inhibitory projections to GABAergic neurons of the VTA, thereby increasing the activity of dopamine neurons of the VTA. In a second set of experiments, we tested the behavioral relevance of LPO stimulation. We examined if rats respond to optogenetically stimulate their LPO (i.e. intracranial self-stimulation of the LPO) and if they show real-time place preference or avoidance of optogenetic stimulation of the LPO. All rats nose-poked to optogenetically stimulate their LPO (40Hz, 1-10s trains). Average self-stimulation rates were one self-stimulation every 20s for the 1s-long trains and one self-stimulation every 40s for the 10s-long trains. This indicates that 1-10s long stimulation of the LPO supports self-stimulation. These same rats that self-stimulated their LPO with 1-10s trains showed discrepant responses in the real-time place preference/aversion test. In this test, rats received continuous 40Hz optogenetic stimulation of the LPO every time they entered one of two compartments. A minority of rats spent more time in the compartment paired with stimulation of the LPO (i.e. showed real-time place preference), whereas the majority of rats spent less time in that compartment. Despite spending less time in that compartment, all rats showed a higher number of visits in that compartment compared with control rats, and visits were ~10s long. Stimulation of the LPO also elicited 50kHz ultrasonic vocalizations, which are thought to reflect “positive affect”. The nature of these differences between self-stimulation and real-time place

preference/avoidance is unclear, but they suggest that only brief (1-10s) periods of LPO stimulation are rewarding. Additional studies are underway to test the effects of activating the LPO for periods of different duration. Overall, these data support a role for the LPO as a novel structure involved in modulating VTA neuron activity and reward.

Disclosures: A.G. Gordon: None. **V. Ramachandra:** None. **N. Mittal:** None. **C.L. Duvauchelle:** None. **M. Marinelli:** None.

Poster

244. Motivation: Neural Circuits I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 244.22/NN26

Topic: G.02. Motivation

Support: RO1/8A351

Title: Mechanisms of the rostromedial tegmental nucleus (RMTg) responses to aversive stimuli

Authors: *H. LI, P. VENTO, D. PULLMANN, M. EID, T. JHOU
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Abstract: The rostromedial tegmental nucleus (RMTg) is a GABAergic nucleus that sends strong inhibitory projections to DA neurons, thus acting as a “braking” system for DA neurons. RMTg neurons encode negative reward prediction errors (RPEs), i.e. they are activated by aversive stimuli and by cues that predict aversive outcomes, and inactivation or lesions of the RMTg greatly reduce many behavioral responses to these stimuli. Because RPE signals in the RMTg strongly resemble responses of the lateral habenula (LHb), it had been assumed that the LHb drives most of these responses, but using *in vivo* electrophysiology recording and Ca^{2+} imaging, we found that these RPEs (preferentially found in VTA-projecting neurons) are not the only types of aversion-related signals encoded by the RMTg, and that overall RMTg responses to aversive stimuli and cues are driven by a variety of different afferents. Temporal inactivation of the LHb with GABA agonists eliminated surprise-driven activations of RMTg responses to aversive stimuli, while temporal inactivation of the mPFC reduced the RMTg responses to shock-predictive cues. Additionally, optogenetic inhibition of PBN terminals in the RMTg attenuated shock-induced responses of RMTg neurons. In ongoing studies, we will evaluate the contribution of these distinct RMTg afferents to punishment resistance.

Disclosures: H. Li: None. **P. Vento:** None. **D. Pullmann:** None. **M. Eid:** None. **T. Jhou:** None.

Poster

244. Motivation: Neural Circuits I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 244.23/NN27

Topic: G.02. Motivation

Support: DA033533 (N.S)

DA037294 (N.S.)

AA023183 (N.S.)

AA022082 (F.W.)

DA0398210 (F.W.)

Title: Addiction-linked drug history results in compulsive appetite for food in males and female rats

Authors: *A. LAQUE[1], A. MATZEU[1], G. E. WAGNER[1], G. DE NESS[1], T. KERR[1], A. CARROLL[1], T. C. JHOU[2], R. C. RITTER[3], F. WEISS[1], N. SUTO[1]
[1]Neurosci., The Scripps Res. Inst., La Jolla, CA; [2]Med. Univ. of South Carolina, Charleston, SC; [3]Dept. of Integrative Physiol. and Neurosci., Washington State Univ., Pullman, WA

Abstract: Obesity and pathological overeating have received increasing recognition as disorders of “food addiction”. While the applicability of this nosology remains controversial, striking similarities in behavioral manifestations and neurobiological underpinnings do exist between certain forms of maladaptive eating habits and drug addiction. We hypothesized that addiction-linked drug history, known to result in addiction-like brain changes and drug motivation, would result in similar addiction-like motivation for food. We tested this hypothesis in separate cohorts of male and female rats each with an extensive history of cocaine intake (6 hr/day or “long access [LgA]”) - an animal model of cocaine addiction. As a measurement of addiction-like food motivation, all rats were tested for their willingness to self-administer sweetened condensed milk despite an adverse consequence (foot-shock punishment). LgA cocaine history in both males and females resulted in a heightened resistance to punishment without significantly affecting routine feeding and bodyweight gain. This lack of overeating and excess weight gain suggests that addiction-like food motivation or “compulsive appetite” is due to dysregulation in the non-homeostatic mechanisms. In line with this premise, LgA cocaine history also resulted in compulsive appetite for non-caloric saccharin in male and female rats and upregulated mGluR2/3 in medial prefrontal cortex (mPFC) and amygdala (regions implicated in non-homeostatic control of food intake). Extensive but passive administration of cocaine also resulted in compulsive appetite for saccharin. Thus, the pharmacological action of cocaine, rather than the

act of cocaine intake or maladaptive learning per se, likely triggers addiction-linked brain changes that result in compulsive appetite. Moreover, addiction-linked history of alcohol (either via alcohol vapor chamber or liquid diet) and obesogenic diet both resulted in a similar compulsive appetite for saccharin. In contrast, an extensive history of caffeine (a substance with low addiction liability and putative anti-obesity properties) did not. Taken together, the nosology of food addiction is most applicable to the phenotypes of eating disorders characterized by compulsive appetite such as binge-eating disorder and bulimia nervosa. Overlapping neurobiological dysregulations in the non-homeostatic brain system likely mediate compulsive appetite - a shared ramification of addiction-linked drug and obesogenic diet history.

Disclosures: **A. Laque:** None. **A. Matzeu:** None. **G.E. Wagner:** None. **G. De Ness:** None. **T. Kerr:** None. **A. Carroll:** None. **T.C. Jhou:** None. **R.C. Ritter:** None. **F. Weiss:** None. **N. Suto:** None.

Poster

244. Motivation: Neural Circuits I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 244.24/NN28

Topic: G.02. Motivation

Support: DA035371

DA041482

AA017656

Title: A circuit-based mechanism underlying familiarity signaling and the preference for novelty

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Abstract: Preference for novelty over familiarity (or novelty preference (NP)) is an evolutionarily conserved, essential survival mechanism which is also dysregulated in neuropsychiatric disorders such as attention hyperactivity deficit disorder and addiction. NP is mediated, in part, by a motivational dopamine signal that increases in response to novel stimuli thereby driving exploration. However, the mechanism by which once novel stimuli transitions to familiar stimuli is unknown. Here we describe a neuroanatomical substrate for familiarity signaling, the interpeduncular nucleus (IPN) of the midbrain, which is activated as novel stimuli become familiar with multiple exposures. Optogenetic silencing of IPN neurons increases salience of and interaction with familiar stimuli without affecting novelty responses; whereas,

photo-activation of the same neurons reduces exploration of novel stimuli mimicking familiarity. Bi-directional control of NP by the IPN depends on familiarity- and novelty-signals arising from excitatory habenula and dopaminergic ventral tegmental area inputs, which activate and reduce IPN activity, respectively. These results demonstrate that familiarity signals through unique IPN circuitry that opposes novelty seeking to control NP.

Disclosures: S. Molas: None. **R. Zhao-Shea:** None. **L. Liu:** None. **S. DeGroot:** None. **P.D. Gardner:** None. **A.R. Tapper:** None.

Poster

244. Motivation: Neural Circuits I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 244.25/NN29

Topic: G.02. Motivation

Support: CONACYT 220772

Title: Changes in the activity of ventral tegmental area glutamatergic neurons associated to copulation

Authors: *N. YAÑEZ RECENDIS[1], E. SANCHEZ JARAMILLO[1], G. RODRIGUEZ-MANZO[2]
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Abstract: Male rats allowed to freely copulate with a single sexually receptive female will ejaculate repeatedly until becoming sexually exhausted. The main outcome of copulation to satiety is the instatement of a long lasting sexual behavior inhibition (at least 72h) that requires a 15-day period of sexual rest for full recovery of the males' initial ejaculatory capacity. Copulation is a rewarding behavior activating the mesolimbic dopaminergic (DA) system (MLD). The MLD consists of DA neurons originating in the ventral tegmental area (VTA) that project rostrally mainly to the nucleus accumbens (NAcc), the amygdala and the medial prefrontal cortex. Glutamatergic nerve endings at the VTA release glutamate in response to rewarding stimuli, stimulating DA neurons' activity. Glutamatergic transmission in the MLD circuit has been associated with the induction of synaptic plasticity as a result of neuronal repeated activation. During copulation to satiety, the MLD is continuously activated, as evidenced by a sustained increase in NAcc DA levels, and the resulting long lasting sexual inhibition is indicative of brain plasticity. Besides, systemic administration of glutamate AMPA, NMDA and mGluR5 receptor antagonists reverse the sexual inhibition of sexually satiated rats. Together these data suggest that glutamatergic transmission at the VTA might play a role in sexual satiety. Thus, we decided to determine if there were changes in the activity of

glutamatergic neurons that innervate DA soma at the VTA. To this aim, using ISH we searched for changes in the mRNA for the vesicular glutamatergic transporter (VGlut2) in the VTA, as an indicator of the activity of these neurons. The brains of following groups of animals were obtained (n=5-6, each): 1) sexually naïve rats, 2)sexually experienced males not copulating on that day, 3) males ejaculating once and 4) males that copulated to satiety 24 h earlier. Coronal sections (20 μm) were obtained of the region encompassing the VTA. The sections were incubated with a VGlut2 cDNA probe marked with ^{35}S, at 54°C during 13 h. The magnitude of the mark was evaluated with the Image J program. Preliminary results show a clear tendency to an increase in mRNA for VGlut2 in the groups that had sexual activity prior to sacrifice, suggesting that copulation promotes the transcription of the VGlut2 genes.

Disclosures: N. Yañez Recendis: None. **E. Sanchez Jaramillo:** None. **G. Rodriguez-Manzo:** None.

Poster

244. Motivation: Neural Circuits I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 244.26/NN30

Topic: G.02. Motivation

Support: NIH Grant R01 MH104559

NIH Grant R01 MH090264

NIH Grant T32 MH096678

NIH Grant F31 MH111108

Title: A novel lateral habenula microcircuit mediating appetitive aggression

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Abstract: Elevated aggression and violence is a common symptom of multiple neuropsychiatric disorders and represents a significant global health issue that lacks both sufficient therapeutic strategies and satisfactory understanding of relevant neuropathologies. Recent imaging studies in humans suggest that aggression in psychiatric patients may result, in part, from the inappropriate activation of reward circuitry in social contexts. Orexins have been implicated in a broad array of motivational behaviors, including conditioned responses to rewarding or aversive stimuli like

drugs of abuse and social stress. Here, we have characterized a novel orexin circuit between the lateral hypothalamus (LH) and the lateral habenula (lHb) that controls the valence of aggressive social interactions. Using the fiber photometry, we found that highly aggressive mice displayed markedly decreased lHb activity when fighting a subordinate intruder. These same mice displayed increased lHb activity when fighting a dominant intruder. Interestingly, non-aggressive mice displayed increased lHb activity in response to a subordinate conspecific. These data suggest that the lHb encodes the valence of aggressive interactions. Following fighting, aggressive mice also displayed increased lHb orexin receptor 2 (OxR2) mRNA relative to non-aggressors. We then determined that that this increase in OxR2 mRNA occurred specifically in a novel population of GAD65-expressing lHb neurons. Furthermore, the peptide orexin-A physiologically depolarizes these GAD65-expressing lHb neurons. Next, we found that inhibition of OxR2 increased overall lHb calcium activity during the resident intruder task, suggesting that OxR2 signaling dampens lHb activity in this context. Finally, shRNA-mediated knockdown of lHb OxR2 decreased both aggressive behavior and its rewarding components as determined by an adapted model of conditioned-place preference (CPP). The results of this investigation provide compelling evidence for the existence of a novel circuit between LH orexin neurons and lHb GAD65 neurons that serves to indirectly reduce the activity of lHb principal neurons during aggression to signal the positive valence of “winning” a fight.

Disclosures: **M. Flanigan:** None. **H. Aleyasin:** None. **B.A. Matikainen-Ankney:** None. **A. Takahashi:** None. **E.S. Calipari:** None. **S.A. Golden:** None. **C. Menard:** None. **M.L. Pfau:** None. **G.E. Hodes:** None. **S. Russo:** None.

Poster

245. Affective Disorders: Human Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 245.01/NN31

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: Cerebrospinal fluid progranulin in depressive disorder

Authors: L. FRÖMEL, V. BITTNER, H.-J. HEINZE, P. KÖRTVELYESSY, *D. M. BITTNER
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Abstract: Introduction Progranulin (PGRN) is involved in modulation of inflammation as well as lowered levels are found in mutation carriers with frontotemporal dementia. The latter may suggest, that an adequate expression of PGRN is essential for successful aging. In bipolar disorders a decreased plasma level of PGRN has been described, however so far studies of cerebrospinal fluid (CSF) PGRN are still lacking.
Material and Methods It were 39 controls (66.3 ± 9.8 years) and 32 patients with major

depression (MD) (62.7 ± 10.9 years) that underwent lumbar puncture. PGRN and other neurodegenerative markers were estimated. In MD patients an extensive neuropsychological test battery was applied.
Results There were no differences in basic demographic variables between both groups, nor were there differences in the basic CSF analysis. While there were no differences found for ptau, htau and beta-amyloid(1-42), PGRN was significantly decreased in MD (p=.007). Correcting for age, CSF protein and CSF albumin ratio PGRN showed a trend for an association with absolute cell count in CSF (p=.07). A relation to cognition was observed with psychomotor speed (p=.01) and naming (p=.05) revealing an U-shape association. Higher CSF hTau showed a correlation to a worse verbal memory free recall (p=.03) and beta-amyloid(1-42) to visuell memory recall (p=.04), visuell short term (p=.006) and working memory (p=.004).
Discussion In our sample of MD suffering from memory complaints PGRN was decreased in CSF. Moreover there was an U-shape association to more fronto-executive function. Lower PGRN levels have been found in serum of patients with bipolar disorder and may reflect impaired neuroprotective mechanisms. That higher PGRN levels are also deleterious may rely in part to some kind of neuroinflammation

Disclosures: **L. Frömel:** None. **V. Bittner:** None. **H. Heinze:** None. **P. Körtvelyessy:** None. **D.M. Bittner:** None.

Poster

245. Affective Disorders: Human Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 245.02/DP12/NN32 (Dynamic Poster)

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIMH Fellowship F30MH109412

NIMH Grant R01MH40695

NIMH Grant P50MH062185

NIMH Grant R01MH074813

NIMH Grant R01MH090276

NIMH Grant K01MH091354

Clinical and Translational Science Award from Columbia University

Title: Relating cortical thickness, serotonin 1a receptor density, and structural connectivity: A multimodal imaging study

Authors: *R. L. PILLAI[1], *R. PILLAI[1], A. MALHOTRA[2], D. D. RUPERT[3], B. WESCHLER[3], J. C. WILLIAMS[3], M. ZHANG[4], J. YANG[5], J. MANN[6], M. A. OQUENDO[6], R. V. PARSEY[1], C. DELORENZO[1]
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Abstract: Serotonin and serotonin 1A (5-HT_{1A}) receptors play a direct role in neuronal development, cell proliferation, and dendritic branching. We hypothesized that variability in 5-HT_{1A} density can affect cortical thickness, and may account for a subtype of major depressive disorder (MDD) in which both are altered. To evaluate this, we measured cortical thickness from structural magnetic resonance imaging (MRI) and 5-HT_{1A} density by positron emission tomography (PET). To examine a range of 5-HT_{1A} density and cortical thickness values, we recruited both healthy controls and patients with MDD (25 and 19, respectively). We hypothesized that increased 5-HT_{1A} density in the raphe nucleus (RN) would be negatively associated with cortical thickness due to reduced serotonergic transmission. Contrary to our hypothesis, we found raphe 5-HT_{1A} binding was positively correlated with cortical thickness in right posterior cingulate cortex (PCC) and right temporal cortex across all participants. We further hypothesized that the strength of 5-HT_{1A}-cortical thickness correlation depends on the number of axons between the raphe nucleus and a given region. To explore this we related 5-HT_{1A} - cortical thickness correlation coefficients to the number of tracts connecting that region and the raphe, as measured by diffusion tensor imaging (DTI) in an independent sample. The relationship between 5-HT_{1A} binding and cortical thickness correlated significantly with the number of tracts to each region, supporting our hypothesis. We posit a defect in the raphe may affect the default mode network in MDD through serotonergic fibers, resulting in increased ruminative processing.

Disclosures: R. Pillai: None. **A. Malhotra:** None. **D.D. Rupert:** None. **B. Weschler:** None. **J.C. Williams:** None. **M. Zhang:** None. **J. Yang:** None. **J. Mann:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Qualitas Health. Other; Research Foundation for Mental Hygiene. **M.A. Oquendo:** D. Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus); Pfizer, Astra-Zeneca, Bristol Myers Squibb, Eli Lilly, Janssen, Otsuko, Sanofi-Aventis, Shire. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Bristol Myers Squibb. **R.V. Parsey:** None. **C. DeLorenzo:** None.

Poster

245. Affective Disorders: Human Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 245.03/NN33

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIH/NCATS UL1 TR000433

Dept. of Anesthesiology, University of Michigan

Dept. of Integrative Biology & Physiology, UCLA

Title: A comparison of sleep spindles in major depressive disorder and healthy adults

Authors: *B. A. GROSS[1], G. R. POE[2], L. M. SWANSON[3], J. ARNEDT[4]
[1]Anesthesiol., [2]Dept. of Integrative Biol. and Physiol., UCLA, Los Angeles, CA; [3]Psychiatry, [4]Univ. of Michigan, Ann Arbor, MI

Abstract: Sleep disturbances and cognitive deficits are prominent characteristics of major depressive disorder (MDD). Sleep spindle activity (e.g. power, duration, and density), presumed to reflect neural plasticity, has been shown to be strongly associated with performance on declarative learning in healthy humans. A reduction in sleep spindle activity has been suggested as a possible sleep-related mediator of cognitive deficits in MDD; however, it remains unclear if any exist due to inconsistent results among previous studies, which may have been confounded by the use of unreliable automated spindle detection and by not controlling for the effects of age, sex, and the menstrual cycle in female subjects on sleep spindles. We aimed to definitively determine if there are differences in sleep spindle activity between MDD and healthy adults by controlling for these potential confounds. We manually identified sleep spindles in both depressed and healthy adults and compared sleep spindle activity across the night between groups separated by sex. We selected adults from an age range (18-31 years old) known for stability in sleep spindle activity, and female subjects were included if they were not menstruating. We found that MMD men and women have shorter lasting spindles with lower max peak-to-peak amplitude and power than their HC counterparts. These differences were significant for women across the night except for spindle duration in the first non-REM period; however, they were only significant for men in the latter half of the night. In conclusion, after controlling for the aforementioned confounds, MDD subjects have specific lower baseline measures of sleep spindle activity than healthy controls, which may be associated with a decrease in cognitive ability.

Disclosures: B.A. Gross: None. **G.R. Poe:** None. **L.M. Swanson:** None. **J. Arnedt:** None.

Poster

245. Affective Disorders: Human Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 245.04/OO1

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: Structural connectivity of the optimal tractography - guided area within subcallosal cingulate cortex of patients with severe major depression treated with electroconvulsive therapy

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Abstract: ***Introduction***
Abnormalities of the subcallosal cingulate cortex (SCC) are well documented in major depression and are shown to relate to antidepressant response[1,2]. We used a tractography-guided optimized target (TOT) centered in the SCC[3] to determine whether SCC structural connectivity varies with short and longer-term clinical outcome in patients treated with electroconvulsive therapy (ECT).
Methods
MR diffusion data from 30 patients with major depression was acquired prior to, directly after, and within 6 months of an ECT treatment index series. The SCC TOT area was identified in each subject and probabilistic tractography determined connectivity across the whole brain and with target regions-of-interest (ROIs) including the bilateral medial prefrontal cortex (mPFC), ipsilateral ventral striatum (Vst) and the dorsal anterior cingulate (dACC). Common whole brain probabilistic tractography maps were created for ECT responders (patients with >50% change in mood scores over the ECT index) who either maintained clinical response or relapsed within 6 months and for ECT non-responders. Connectivity metrics, including probability of connectivity (Prob) and average fractional anisotropy (FA) for the TOT to each target ROI were compared between clinically-defined response or relapse groups at each study time point and within groups across time points using nonparametric Kruskal Wallis and Friedman tests.
Results
Group-based tractography maps at baseline and after the ECT index showed a greater probability of TOT connectivity with Vst and mPFC regions bilaterally in ECT responders compared to non-responders. A similar pattern was observed at 6 months in ECT responders who maintained response compared to those that relapsed or did not respond. Assessed at baseline, statistical analysis of TOT to target ROI metrics revealed greater structural connectivity with the Vst in responders who maintained clinical response at 6-months compared to non-responders (FA, p=.004; Prob, p=.003). At the end of the ECT index, greater TOT to Vst connectivity was observed in responders who maintained clinical response compared to non-responders (Prob, p=.046). Significant changes in TOT to Vst connectivity pre-to-post ECT occurred only in responders who maintained response at 6-months (Prob, p=.033).
Conclusion
Differences in TOT-targeted SCC and Vst and mPFC structural connectivity distinguish patients who respond to ECT and stay well from those who do not respond or later relapse. These findings support that SSC to Vst and mPFC connectivity might serve as a biomarker of long-term clinical outcome and may be important for patient selection or tracking response to therapy.

Disclosures: E. Tsolaki: None. **K. Narr:** None. **G. Hellemann:** None. **R. Espinoza:** None. **N. Pouratian:** None.

Poster

245. Affective Disorders: Human Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 245.05/OO2

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: R01 MH109544

Title: Fronto-limibic connectivity alterations in patients with major depressive disorder

Authors: *J. W. RUTLAND[1], J. W. MURROUGH[2,3], R. O'HALLORAN[1], P. BALCHANDANI[1]
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Abstract: Major Depressive Disorder (MDD) is a mood disorder with a lifetime prevalence of approximately 20% in the US [1]. MDD is characterized by persistent feelings of sadness and apathy not attributable to any apparent external causes [1]. Fronto-limbic circuits play a role in motivation and affect, thus understanding changes in these circuits is important [1,2]. Functional magnetic resonance imaging (fMRI) studies have found both attenuated and increased connectivity between certain limbic and frontal structures [1,2]. Structural connectivity may underpin functional changes that exist in MDD. In this study we aim to quantify alterations in fronto-limbic structural connectivity in MDD. We hypothesize that abnormal connectivity fronto-limbic will be observed in patients with MDD.
8 healthy controls and 6 MDD patients were scanned using a 7T whole body scanner (Siemens Magnetom) under an approved IRB protocol. The MRI protocol consisted of high-resolution diffusion-weighted dMRI (1.05 mm isotropic resolution, 68 directions) and T1-weighted imaging. Cortical and subcortical segmentations were obtained using FreeSurfer software. Whole brain tractography was performed using spherical deconvolution. Total connectivity, or degree, of hippocampus, amygdala, NAc, and thalamus were calculated by determining the total number of connecting streamlines. Connectivity between limbic structures and vPFC, rostral middle frontal, superior frontal, dlPFC, and ACC were also determined.
In MDD patients, the degree of left hippocampal connectivity (M = 65005.72) was significantly less than that of the healthy controls (M= 74956.76), $p < .05$. Of the fronto-limbic tracts analyzed, reduced connectivity was found between left hippocampus and left vPFC, $p = .08$. Increased connectivity was found between the left NAc and right ACC ($p=.05$) as well as between right NAc and right vPFC, $p <.05$. A number of other limbic regions displayed increased connectivity to the ACC, a region that is implicated in MDD. Total limbic connectivity to the left ACC was greater in MDD than in controls, $p = .08$. This study adds to evidence of altered connectivity in MDD, and identifies potential structural substrates of these abnormalities.

Future work will include expanding the sample size and correlating with clinical MDD symptoms.

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2. Beauregard, M., Paquette, V., & Levesque, J. (2006). Dysfunction in the neural circuitry of emotional self-regulation in major depressive disorder. NeuroReport, 17(8), 843-846.

Disclosures: J.W. Rutland: None. **J.W. Murrough:** None. **R. O'Halloran:** None. **P. Balchandani:** None.

Poster

245. Affective Disorders: Human Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 245.06/OO3

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIH Grant K01MH096175-01

NARSAD Young Investigator Award

The William K Warren Foundation

Title: Examining insula activity during interoceptive recall among individuals diagnosed with major depressive disorder

Authors: *D. DEVILLE[1,2], J. A. AVERY[4], K. L. KERR[4,2], K. BURROWS[1], J. BODURKA[5,4], M. P. PAULUS[1,3], K. SIMMONS[4,3]

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Abstract: Theoretical accounts of interoception suggest that the perception and integration in the insula of viscerosensory signals allows humans to form associations between interoceptive signals and co-occurring external stimuli. The subsequent recall of these associations later facilitates the selection of behaviors that meet homeostatic needs and benefit physical health. It has been recently proposed that major depressive disorder (MDD) is associated with abnormal insula activity that interferes with the formation of viscerosensory associations, thereby undermining the selection of health-related behaviors. To examine interoceptive recall among individuals diagnosed with MDD, we developed the Interoceptive Encoding and Recall (IER) task. During the encoding phase of the IER task, subjects were intermittently exposed to an

inspiratory breathing load (ranging from 10 to 50 cmH2O/L/sec), an aversive interoceptive stimulus, while viewing one of 3 abstract geometric symbols. As an exteroceptive control, subjects viewed 3 different geometric symbols while aversive auditory screams are played at varying volumes. Later, subjects performed an incidental (i.e., unexpected) recall task while undergoing fMRI. During the recall task, subjects saw the geometric symbols that were presented during the encoding phase and were instructed to recall the intensity of the stimulus associated with each shape. Our lab previously demonstrated that interoceptive recall results in activation of the primary viscerosensory cortex within the mid to posterior insula in psychiatrically healthy subjects.In the current study, we examined the process of interoceptive encoding and recall in depressed (N = 20) and healthy (N = 21) individuals. HC and MDD groups were matched for age, sex, and BMI. An ANOVA demonstrated a significant group (MDD vs. HC) by condition (interoceptive vs. exteroceptive recall) interaction in the right dorsal-mid insula. Analyses of the effects underlying this interaction indicate that MDD subjects failed to activate the insula during recall of interoceptive stimuli. Consistent with theoretical models of interoceptive dysfunction in MDD, reduced insula activity during interoceptive recall may reflect an inability to form precise interoceptive representations during encoding, and/or a low fidelity memory of previous interoceptive experiences. For individuals with MDD, this may promote a misrepresentation of the interoceptive consequences associated with external stimuli, resulting in a reduced ability to select behaviors that meet the body's interoceptive needs, thereby undermining physical health.

Disclosures: **D. Deville:** None. **J.A. Avery:** None. **K.L. Kerr:** None. **K. Burrows:** None. **J. Bodurka:** None. **M.P. Paulus:** None. **K. Simmons:** None.

Poster

245. Affective Disorders: Human Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 245.07/OO4

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: American Foundation for Suicide Prevention

Title: Present bias in decision making and suicidal ideation among bipolar patients: An fMRI study

Authors: *J. M. FELICIONE[1], S. WALSH[2], J. LERNER[4], A. S. WIDGE[1], Y. LI[6], F. OR[5], R. MONTANA[2], R. FRANKLIN[1], T. DECKERSBACH[3], A. NIERENBERG[2]
[1]Div. of Neurotherapeutics, Massachusetts Gen. Hosp., Charlestown, MA; [2]Bipolar Clin. and Res. Program, Massachusetts Gen. Hosp., Cambridge, MA; [3]Div. of Neurotherapeutics, Bipolar Clin. and Res. Program, Massachusetts Gen. Hosp., Charlestown, MA; [4]Kennedy Sch. of

Government, Harvard Univ., Cambridge, MA; [5]TH Chan Sch. of Publ. Hlth., Harvard Univ., Boston, MA; [6]Univ. of California, Riverside, Riverside, CA

Abstract: Bipolar disorder (BD) is a chronic psychiatric condition often associated with suicide attempts. The pathophysiology underlying decision making related to suicide is unknown. Present bias (PB) is the tendency to choose less money now rather than (waiting for) more money later. In a non-clinical population, sadness has been shown to increase present bias, creating a phenomenon termed "myopic misery" (Lerner, Li, & Weber, 2013). This effect may be particularly pronounced in bipolar patients with suicidal ideation (SI). Neuroimaging studies show that TD is related to increased ventral striatum, medial frontal gyrus (MFG), and posterior cingulate (PCC) activation in response to immediate rewards in healthy individuals. Increased dorsolateral prefrontal cortex and posterior parietal activation is found in response to choosing delayed rewards. In the present study, we examined TD and associated brain activity in suicidal bipolar patients. Fifteen bipolar patients (8 female, M_{age}=37.6 ± 14.3 years) with DSM-IV BD completed a TD paradigm during neutral and sad mood states (Lerner, Li, & Weber, 2013) while undergoing functional magnetic resonance imaging (fMRI) using a Siemens 3.0 Tesla Skyra scanner. Suicidality was assessed using the Columbia Suicide Severity Rating Scale (C-SSRS). Imaging data was processed using SPM8; first level models examined differences between sad and neutral states for both immediate and delayed rewards. Parametric trial by trial regressors were used to represent the utility surplus of the reward chosen (subjective value of the reward not chosen subtracted from the reward chosen). For the second level analysis, the C-SSRS Lifetime Suicidal Ideation Intensity subscale was used as a regressor of interest. Imaging results with a $p\leq$ .01 uncorrected will be reported. Participants showed an increased present bias during sad compared to neutral state (p<.05), reflecting an increased likelihood to choose smaller rewards sooner rather than larger rewards later when sad. Compared to the neutral condition, sad state fMRI results showed that when subjects selected the immediate reward, C-SSRS scores correlated positively with activity in the ACC, precuneus, posterior parietal lobes, and anterior insula and negatively with activity in the MFG, superior frontal gyrus, and PCC. As SI intensity increases, sad mood as opposed to neutral mood in bipolar patients was associated with greater activation in regions related to emotion regulation and reward, and decreased activation in regions involved in decision making. These findings suggest that bipolar patients may be more prone to SI due to biologically driven increases in present bias.

Disclosures: J.M. Felicione: None. **S. Walsh:** None. **J. Lerner:** None. **A.S. Widge:** None. **Y. Li:** None. **F. Or:** None. **R. Montana:** None. **R. Franklin:** None. **T. Deckersbach:** None. **A. Nierenberg:** None.

Poster

245. Affective Disorders: Human Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 245.08/OO5

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: KAKENHI(No.17K01826)

Title: A cohort study on the relationship between the risk of mental health disorders and life habits

Authors: *Y. MASHIO, T. YOSHIZAKI, M. OTA, H. KAWAGUCHI
Toyo Univ., Gunma, Japan

Abstract: Recently, the number of patients with mental health disorders has been increasing. Our previous study revealed that we may be able to predict the risk of mental health disorders by analyzing the temporal information of handwriting using a digital pen that digitizes the handwriting with resolutions of 0.3 mm and 13 ms. To confirm the predictability of the risk and establish a feasible coping strategy at an individual level in a high-risk group, the aim of this study conducted in 2014 was to investigate the differences in life habits between a high-risk group and a low-risk group.

A total of 87 student volunteers (aged 18-22 years; 43 men and 44 women) were recruited for a follow-up cohort study conducted over three years from 2014 to 2016 (once a year in April). The participants voluntarily completed the Uchida-Kraepelin test and a life habit questionnaire, DIHAL.2 (Diagnostic Inventory of Health and Life Habit). The time intervals between the first and second stroke of a number (4, 5, and 7; mean time interval: t_1) and those between the completion of writing a number and the initiation of writing the next number (mean time interval: t_2) were analyzed. The participants were classified into two groups according to the ratio of the mean time intervals (t_2/t_1) in 2014; one group included participants with a t_2/t_1 ratio of ≥ 10 (high-risk group, n = 4), and the other group included participants with a t_2/t_1 ratio of <10 (low-risk group, n = 83). The difference in the scores on the DIHAL.2 scale between these two groups was analyzed in 2014 using the t-test and Mann-Whitney U test. Significant differences were observed with respect to the scores of regular diet and regular sleep in 2014 between the groups ($p < 0.05$). In detail, the deviation of breakfast time and lunch time in the high-risk group was significantly larger than that in the low-risk group ($p < 0.10$ and $p < 0.05$ respectively). In addition, the deviation of sleeping time and wake-up time in the high-risk group was larger than that in the low-risk group ($p < 0.10$). Therefore, these results suggested that the participants in the high-risk group were unable to maintain regular life habits compared with those in the low-risk group.

The protocols used in this study were approved by the Ethics Committee of Toyo University.
This work was supported by KAKENHI (No. 17K01826).

Disclosures: **Y. Mashio:** None. **T. Yoshizaki:** None. **M. Ota:** None. **H. Kawaguchi:** None.

Poster

245. Affective Disorders: Human Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 245.09/OO6

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: Psychological health and ADHD profile of adolescent hockey players are influenced by history of concussion and age

Authors: *W. ARCHAMBAULT[1], J. LEPINE[2], R. D. MOORE[3], G. LAZANIS[2], D. ELLEMBERG[2]
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Abstract: Purpose: To characterize differences in psychological health and ADHD profiles between adolescent hockey players who sustained concussive injuries and their control teammates. **Methods:** The young athletes completed a psycho-affective assessment consisting of the Depression (BDI) and Anxiety scales (BAI) of the Beck Youth Inventory (BYI) while a parent completed the Conner's 3. Only the ADHD specific scales (ADHD Inattentive, ADHD Hyperactivity-Impulsivity and Total ADHD Index) of the Conner's 3 were included in the analysis. All athletes were competing in their teams' activities at the time of testing. Those who scored in the clinical range on any of the DSM-IV scales of the Conner's 3 were excluded from the analyses. Two-Way ANOVAs were conducted with concussion status and age as between group factors. **Results:** For the BDI *t*-scores, there was a significant main effect for history of concussion F (1, 109) = 9.642, p = .002, *means* = 46,33 ± 6,28 vs. 42,91 ± 4,84, with a moderate to strong effect size (partial eta^2 = .081). The interaction between age and history of concussion was not significant. For the BAI *t*-scores, the interaction between age and history of concussion was significant, F (1, 109) = 6.852, p = .010, with a moderate effect size (partial eta^2 = .059). Analysis of simple effects revealed that the mean BAI *t*-score ($\overline{x}$ = 49.15 ± 6.21) for 'Midget/Concussion' participants is significantly greater than that of the other 3 groups. The same was observed for the ADHD Hyperactivity-Impulsivity scale; there was an age x history of concussion interaction, F (1, 109) = 4.790, p = .031, with a moderate effect size (partial eta^2 = .042) and the mean score for the 'Midget/Concussion' group ($\overline{x}$ = 53.76 ± 10.78) was significantly greater than that of the other 3. However, scores were not significantly different for both the ADHD Inattentive (F (1, .109) = .465, p = .497) and Total ADHD Index (F (1, .109) = .052, p = .820) scales. **CONCLUSION:** Compared to their non-concussed teammates, adolescent hockey players reporting concussive injuries present some alterations in their psycho-affective health and ADHD profiles. In addition, it seems that severity of anxiety symptoms and ADHD symptoms of the hyperactive-impulsive category increases with age in adolescent with a prior history of concussion. Additional longitudinal research is necessary to better understand

how those early vulnerabilities evolve over time and in relation with subsequent concussive injuries.

Disclosures: W. Archambault: None. **J. Lepine:** None. **R.D. Moore:** None. **G. Lazanis:** None. **D. Ellemberg:** None.

Poster

245. Affective Disorders: Human Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 245.10/OO7

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: Integrated Research on Depression, Dementia and Development disorders, AMED

Brain/MINDS, AMED

JSPS 17H05921

Title: Functional connectivity between the substantia nigra and ventromedial prefrontal cortex is associated with cognitive function in major depressive disorder

Authors: *S. KOIKE[1], Y. NAKAMURA[2], N. OKADA[3], K. KASAI[3]
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Abstract: The substantia nigra (SNc) is well-known as the origin of nigrostriatal pathway which is assumed to exert motor regulation and cognitive function by dopaminergic neurons. However, little has been known whether the pathway in functional magnetic resonance imaging (fMRI) would be associated with cognitive function in patients with major depressive disorder (MDD) and healthy controls. Here we tested this using resting state fMRI data for 29 patients with MDD (female n=15, mean age=39.4 years) and 61 healthy controls matched for sex, age, handedness, and premorbid IQ. This study was approved by the ethics committee at Department of Medicine, The University of Tokyo, and all participants provided written informed consents. Resting state fMRI data were acquired using a GE Discovery 3T-MRI and a gradient-echo echo-planar imaging sequence (TR=2500 ms, TE=30 ms, 40 slices, 240 image volumes; 10 min 10 sec). A seed-based rsfMRI analysis was then performed using the SNc as a seed. First, the difference in the connectivity maps with the SNc seed was tested between the groups. Second, a sphere with 3mm radius centered on the peak coordinate of the significant region was set as an ROI. Results showed that the patients with MDD showed greater connectivity in SNc - ventromedial prefrontal cortex (peak: [-18, 48, -2]) compare to the controls. The connectivity was associated with the premorbid IQ for all participants (r=.26, p=.014) as well as the MDD and control groups in a trend (r=.24, p=.062; r=.34, p=.069; respectively), while any other association with clinical

demographics was not found. The results suggest that resting state connectivity may be associated with cognitive function and brain pathology in MDD. Future work will be tested for the relationship with specific cognitive domains in details.

Disclosures: S. Koike: None. **Y. Nakamura:** None. **N. Okada:** None. **K. Kasai:** None.

Poster

245. Affective Disorders: Human Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 245.11/OO8

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: A comparative study of resting-state functional connectivity in first-episode drug-naïve adolescents with major depressive disorder

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Abstract: Major depressive disorder (MDD) is a leading cause of disability and frequently emerges during adolescence. Because of the significant brain maturational changes that occur during adolescence, the brain abnormalities in adolescent with MDD are likely to be different from those in adults with MDD. However, neurobiological studies in adolescents are lacking compared to adults. Functional connectivity-based MRI recently has been used to localize functional connectivity abnormalities across a range of psychiatric disorders, and to identify connectivity patterns that predict treatment response, as well as clinical measures of illness severity. We aim to compare the resting-state functional connectivity (RSFC) in adolescents with and without MDD. Resting-state functional magnetic resonance imaging (rs-fMRI) data were acquired from 24 first-episode drug-naïve adolescents aged 13 to 18 years with MDD (male 9, female 15, mean age 15.6) and 24 healthy adolescents with no previous psychiatric diagnoses (male 4, female 20, mean age 15.9). We have only chosen a drug-naïve patient, so that we exclude the effect of unexpected pharmacotherapeutic medications on the brain. Seed-to-voxel and ROI-to-ROI RSFC analyses were performed using the CONN toolbox. This study was conducted from April 2015 to August 2016. The MDD group demonstrated lesser RSFC relative to healthy controls (HC) in medial frontal cortex and right caudate nucleus to regions including both hippocampus and both insular cortex. In contrast, the MDD group had greater RSFC than HC in anterior cingulate cortex to regions including left cerebellum and cerebellar vermis. Our results show that altered RSFC of several regions associated with cognitive, affective, memory and higher cognitive function in first-episode drug-naïve adolescents with MDD. The medial frontal cortex areas are components of the default mode network (DMN). These findings, which

are in alignment with resting-state abnormalities in DMN regions in adolescent MDD patients, support recent models of depression, that emphasize the importance of medial network disturbances. Our findings suggest the possibility that therapeutic interventions that can restore the functional connectivity among these networks to that typical of healthy adolescents might be a fruitful avenue for future research. Further studies using prospective designs are also needed to detect the long-term effect of treatment on the brain of adolescents with mood disorders.

Disclosures: **J. Lee:** None. **Y. Lee:** None. **S. Park:** None. **E. Suh:** None. **J. Lee:** None. **J. Kim:** None. **S. Suh:** None. **M. Lee:** None.

Poster

245. Affective Disorders: Human Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 245.12/OO9

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: Friends of BrainHealth to NAH

Think Ahead Group Research Award to LH

Title: A study of network changes during depressive self-referential processing in never-depressed individuals

Authors: *L. HIMES[1], N. HUBBARD[2], M. P. TURNER[3], C. ROBINSON[4], C. ELLISON[4], R. OPPENHEIMER[4], B. P. RYPMA[5]
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Abstract: Cognitive theories of depression posit a key role for negative self-referential thought. Rumination, repetitive focus upon negative thoughts pertaining to ones' life and self, is strongly related to negative cognitive, emotional, and social outcomes, and is predictive of depression. Specific brain regions have been associated with self-referential processing in persons with depression. However, less is known about the regions involved in depressive self-referential processing in never-depressed individuals. We used functional magnetic resonance imaging to assess differences in functional connectivity (FC) during a non-depressive self-referential processing task and a depressive self-referential processing task (NST and DST, respectively) in 10 never-depressed individuals (Mean age = 25.30 (7.18); 70% female). During scanning, participants viewed either a non-depressive (NST: e.g., "I like to eat meat") or a depressive (DST: e.g., "I have no friends") self-referential statement and indicated whether that statement was representative of him or herself by button press. A global brain connectivity (GBC) coefficient was derived for each voxel of the NST and the DST. This value was calculated using

the aggregate numbers of positive, functional connections each voxel had with all other voxels. Measures of GBC were used to identify hubs during DST and NST in never-depressed individuals. We further assessed brain organization changes between these tasks and how differences in FC between tasks might reflect individual differences in the brooding-component of trait rumination. Hubs identified during the DST were largely in cortical midline structures (CMS), prefrontal, and parietal regions, similar to those observed in studies of depressed individuals. Similar regions acted as hubs during NST. Results showed increased FC during the NST compared to the DST ($k \geq 15$; $FWER\ p \leq .05$). Further, increased FC from the NST to the DST in the CMS, temporal, and limbic regions, was associated with higher levels of brooding rumination ($r = .803$, $p \leq .005$, $k \geq 5$, $FWER \leq .05$). These findings provide evidence for a depressive self-referential network common across healthy and clinical populations. Moreover, this network can be activated in never-depressed individuals when depressive self-rumination is induced in the laboratory. Chronic activation of this network might result in disrupted emotional processing and integration, leading to depression. Future research is needed to understand how activation of this depressive self-referential network contributes to mood-related mental disorders.

Disclosures: L. Himes: None. **N. Hubbard:** None. **M.P. Turner:** None. **C. Robinson:** None. **C. Ellison:** None. **R. Oppenheimer:** None. **B.P. Rypma:** None.

Poster

245. Affective Disorders: Human Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 245.13/OO10

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: T37800

Title: Abnormalities of the fronto-limbic circuit during negative emotion processing in depression

Authors: *S. TAK[1], C.-A. PARK[1], E.-N. CHEONG[2], J.-W. SEOK[1,3], J.-H. SOHN[2], C. CHEONG[1]
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Abstract: A depressive disorder is an affective disorder which is characterized by persistent low mood state and deficits in cognitive functioning. The pathophysiology of depressive disorder has been shown to be associated with the dysfunction of fronto-limbic circuit involved in emotion regulation. In this study, using 7T fMRI and dynamic causal modelling method, we investigated

how effective connectivities among the areas within fronto-limbic circuit are modulated by negative emotion processing, and explored difference in the connectivity between depressed patients and healthy controls.
The present study was conducted in 5 depressed individuals and 8 age-matched healthy controls. All images were acquired using a 7T MRI system (Achieva, Philips Medical Systems). During scanning, subjects underwent event-related fMRI while viewing emotionally negative and neutral pictures. Specifically, pictures from the International Affective Picture System (IAPS) (valence ratings 2-3; arousal ratings < 6) were selected to evoke the negative emotion. Neutral pictures were also selected from the IAPS (valence ratings 4.5-5.5 and arousal ratings < 3). Subjects were instructed to let the feelings elicited by the pictures.
The fMRI data were analyzed using SPM12 software. In DCM analysis, we selected 3 regions of interest, including primary visual cortex (V1), dorsolateral prefrontal cortex (DLPFC), and amygdala (AMYG), based on results of general linear model analysis and findings of previous neuroimaging studies. We then created 3 models which differed in interregional connections modulated by negative emotional stimuli. In all models, V1 activity served as a driving input for the fronto-limbic network. The best model structure across subjects was identified using the fixed effects Bayesian model selection, and group-level parameter estimates were finally obtained by using Bayesian model averaging.
We found increased activation of DLPFC and AMYG in respond to negative emotional stimuli from both depressed patients and healthy controls. However, patterns of modulatory connectivity were significantly different between two groups. Specifically, top-down connectivity from DLPFC to AMYG was greatly reduced in depressed patients relative to healthy controls, while bottom-up connectivity from AMYG to DLPFC was significantly increased. These results may reflect reduced regulatory influence on AMGY by DLPFC and increased sensitivity to change of emotional state in response to negative stimuli.

Disclosures: **S. Tak:** None. **C. Park:** None. **E. Cheong:** None. **J. Seok:** None. **J. Sohn:** None. **C. Cheong:** None.

Poster

245. Affective Disorders: Human Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 245.14/OO11

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIMH Grant RO1 MH069942

Stony Brook Research Foundation

Title: Differential alterations of visual and multiple-demand network functional connectivity in major depressive disorder

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Abstract: Our work recently revealed the neural correlates of visual working memory (WM) deficits in individuals with major depressive disorder (MDD) (Le et al., 2017). While such alterations appear to be limited to a small number regions, previous literature suggests neural dysfunctions in MDD involve multiple brain structures (Zeng et al., 2012). In this study, we examined whether WM impairment in MDD is characterized by altered properties of large-scale networks using a graph theory approach. fMRI data from 18 unmedicated participants with MDD and 21 healthy controls (CTL) were acquired while they performed a visual delayed recognition task with an updating cue. Three cues, Remember Face (Ignore Scene), Remember Scene (Ignore Face) and Remember Both, were used to indicate which one or both of the two memorized stimuli (a neutral face and a neutral scene) would remain relevant for the recognition test. Beta values from the Psychophysiological Interactions analysis were used to estimate the connectivity strength between a set of brain regions, including individually defined face- and scene-processing areas and a group of multiple-demand structures (Fedorenko et al., 2013). Our results revealed a differential pattern of weakened network connectivity strength and altered network properties during visual WM updating in MDD. Compared to the CTL group, MDD subjects showed attenuated within- and between-network connectivity involving the scene-processing and multiple-demand networks. These networks also had diminished global efficiency in MDD. Both within-network connectivity and global efficiency predicted task performance in all subjects. In contrast, network properties for face processing were more comparable between the two subject groups. Graph theoretic measures of functional connectivity including global efficiency and transitivity measures of the face network yielded a significant condition effect, with higher efficiency and transitivity during Remember Face than Remember Scene and Remember Both in all subjects. To rule out possibility that the scene network was inherently impaired in MDD, we calculated graph measures using data from an independent localizer task. No group differences were found, suggesting deficits were likely specific to WM updating processes. In sum, we found evidence for functional connectivity alterations at a network level involving both visual association cortices and frontoparietal regions previously associated with cognitive control. The differentiation in impairments (i.e., in the scene but not the face network) indicates a potential interaction between visual category bias and working memory updating deficit.

Disclosures: T.M. Le: None. **H. Leung:** None.

Poster

245. Affective Disorders: Human Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 245.15/OO12

Topic: G.03. Emotion

Title: Short-term and long-term influences of serotonergic medication on intrinsic functional connectivity

Authors: *H. T. HAMADA[1], Y. SHIMIZU[1], J. ZENG[1], K. HIKISHIMA[1], N. TAKATA[2], K. F. TANAKA[2], K. DOYA[1]
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Abstract: Serotonin plays a pivotal role in multiple functions such as mood, reward/punishment processing, and locomotor activity. Serotonin is also the major target of antidepressant drugs for major depression (MD), notably selective serotonin reuptake inhibitors (SSRIs). While long-term administration of SSRIs reduces anxiety of MD patients, short-term administration sometime worsens their anxiety. Animal behavioral studies also showed that short-term and long-term SSRI applications have different effects on fear conditioning [Burghardt et al., 2013]. In this study, we investigate the short-term and long-term effects of SSRI administrations on functional connectivity (FC) using functional MRI in rodents. We conducted resting-state functional MRI experiments with twelve healthy wild-type mice (C57BL6/J, male, over 15 w.o.) under awake state. We administered escitalopram (10 mg/kg), a SSRI, to one group (n=6) for 19 days although escitalopram was not administered to another group (n=6) as the control group. Multiple imaging sessions (3~5 sessions per day) were performed along different time points of administration (1st, 8th, 15th day). We applied a pattern classification algorithm, group least absolute shrinkage and selection operator (gLASSO), to find a set of functional connectivities that allow discrimination of the acutely SSRI-treated group and the control group. 14 connections are chosen for discrimination, including a corticobasal FC between the insula cortex and the SNr. We also applied group LASSO to the datasets of chronically SSRI-treated group and the control group. The result revealed 9 connections for discrimination, including the FCs between the lateral orbital area and the primary motor area, and the central nucleus of the amygdala and the thalamic reticular nucleus. These connections are known as a motor-related circuit and a punishment-related circuit [Hooks et al., 2013; Zikopoulos et al., 2012]. Furthermore, subsequent behavioral tests also showed significantly higher locomotor activities and lower anxiety level in the chronically SSRI-treated group. These rs-fMRI classification and behavioral results suggest that chronic SSRI administration influences motor-related and axneity-related neural circuits and affect motor behaviors. Significant effect on an anxiety-related circuit is consistent with the effect of serotonin on anxiety. In follow-up analyses, we will further investigate distinct effects of SSRI on the regulation of neural circuits between different time points of administration.

Disclosures: H.T. Hamada: None. **Y. Shimizu:** None. **J. Zeng:** None. **K. Hikishima:** None. **N. Takata:** None. **K.F. Tanaka:** None. **K. Doya:** None.

Poster

245. Affective Disorders: Human Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 245.16/OO13

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: Neuronal and peripheral markers of plasticity dynamics, change concomitantly after sub-anesthetic dose of ketamine in humans

Authors: L. COLIC[1], C. W. MCDONNELL[2], M. LI[3], O. SPECK[4,5,6], B. H. SCHOTT[4,7,6], *M. BIANCHI[2], M. WALTER[8,4,3,9,6]
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Abstract: Sub-anesthetic ketamine elicits rapid antidepressant response in patients via modulation of glutamatergic system and synaptic plasticity. Specifically, 24h after infusion ketamine induces changes in glutamine-glutamate cycling in pregenual anterior cingulate cortex (pgACC) in healthy controls (HC). Microtubule dynamics is essential for neural plasticity and post-translational modifications of α-tubulin are considered markers of microtubule dynamics. Acetylation of α-tubulin (Acet-Tub) associates with less dynamic microtubules and appears involved in the pathogenesis and treatment of depression. Here, we examined Acet-Tub as a peripheral marker of microtubule dynamics and well-established changes in glutamatergic system 24h after infusion. Moreover, we investigated correlations with acute dissociative symptoms. In a placebo-controlled study 81 healthy controls received 40 min infusion of vehicle or 0.5 mg/kg of ketamine. At baseline and 24h post-infusion, glutamate (Glu) levels were assessed in pgACC by 7T magnetic resonance spectroscopy (MRS), and blood was sampled. The dissociative symptoms were evaluated using CADSS right after the infusion. MRS data were processed with LCModel, Glu was normalized to creatine, and grey matter (GM) partial volume was calculated. Plasma Acet-Tub and Transferrin (TRF) expression was analyzed using infrared western blot. RmANCOVA tested Glu and Ace-Tub/TRF change, with treatment, sex as factors, and age, BMI, (GM) as covariates of nuisance. The relationship between relative changes and CADSS was assessed with non-parametric partial correlations in ketamine group. Ketamine effect was present in both Glu (time-by-treatment, p=0.044) and Ace-Tub/TRF (time-by-

treatment-by-sex, p=0.023), where a decrease in pgACC Glu and an increase in Ace-Tub/TRF was observed. Markers of sustained effect were negatively associated with each other only in the ketamine group (p=0.001) vs. vehicle (p=0.20). Marker of acute effect CADSS trend-wise positively correlated to Ace-Tub/TRF (p=0.06) in the ketamine group, but not with pgACC Glu (p=0.21). Results confirm effects of single dose of ketamine on Glu 24h after infusion in the pgACC, a region important for affect processing and neuronal mechanisms of depression. In parallel, plasma Acet-Tub increased suggesting peripheral decreased microtubule dynamics which may be reflected centrally. The neuronal representation of ketamine was negatively associated with Acet-Tub/TRF, indicating similar time-frame of plasticity processes in brain and blood. Interestingly, only Acet-Tub/TRF was positively associated with degree of acute dissociative symptoms.

Disclosures: L. Colic: None. **C.W. McDonnell:** A. Employment/Salary (full or part-time):; Transpharmation Ireland Limited. **M. Li:** None. **O. Speck:** None. **B.H. Schott:** None. **M. Bianchi:** A. Employment/Salary (full or part-time):; Transpharmation Ireland Limited. 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.; Transpharmation Ireland Limited. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Transpharmation Ireland Limited. **M. Walter:** None.

Poster

245. Affective Disorders: Human Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 245.17/OO14

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: P30GM103328

P20GM104357

P20GM103476

Title: Neuroinflammatory gene expression in hippocampus in major depressive disorder

Authors: G. J. MAHAJAN[1], E. J. VALLENDER[1], M. R. GARRETT[2], L. CHALLAGUNDLA[3], J. C. OVERHOLSER[5], G. J. JURJUS[7], L. DIETER[5], H. BENGHUZZI[4], *C. A. STOCKMEIER[8,6]
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Abstract: Background: Major Depressive Disorder (MDD) is a common psychiatric disease for which available medications are often ineffective. Decreases in hippocampal volume with increasing duration of depression suggest altered gene expression. Methods: Tissue punches from the dentate gyrus were collected from 23 subjects (MDD, psychotropic medication-free; no psychoactive drugs) and 23 normal controls. Of the 23 subjects with MDD, 17 died by suicide, 17 had multiple and 6 had single depressive episodes. Total RNA was isolated (Invitrogen PureLink RNA Mini kit) with RNA Quality Index > 6. Whole transcriptome paired-end RNA-sequencing was performed using an Illumina NextSeq 500. Results: For each sample, raw RNA-seq reads (adapter-trimmed fastq files) were aligned to the Ensembl GRCh38 human reference genome using GSNAP (Genomic Short-read-Nucleotide Alignment Program). About 100 million reads and 90-95 percent mapping to the human genome was obtained for nearly all samples. 'Cuffdiff' analysis in the Tuxedo Suite revealed 30 genes differentially expressed in all MDD compared to control subjects (Lumenogix™, FDR < 0.05). In all MDD, genes downregulated included several with inflammatory function (*ISG15, IFI44L, IFI6, NR4A1*) and *GABBR1*. Genes upregulated in all MDD included those with cytokine function (*CCL2/MCP-1*), inhibiting angiogenesis (*ADM, ADAMTS9*), and the *KANSL1* gene, a histone acetyltransferase. Ingenuity Pathway Analysis revealed a significant over-representation of gene pathways vs. all controls as follows: 1) single episode MDD (n=6) in the ERK/MAPK, TNF-R1/2, glucocorticoid receptor signaling, and retinoic acid receptor activation; 2) multiple episode MDD (n=17) in thioredoxin (redox reactions) and the IL-6, IL-17, and IL-22 signaling; and 3) MDD/non-suicide (n=6) in STAT3 pathway affecting phosphoinositide metabolism and interferon signaling; MDD/suicide (n=17) in the thioredoxin and inflammation-related pathways. Conclusion: Inflammatory and neurogenesis-related (ERK/MAPK) signaling pathways are significantly altered in the hippocampal dentate gyrus in MDD, with cytokine signaling and inflammatory pathways preferentially altered in MDD/suicide vs. MDD/non-suicide. Neuro-inflammation in the hippocampal dentate gyrus, potentially mediated by microglia and astrocytes, may play a crucial role in major depressive disorder.

Disclosures: G.J. Mahajan: None. **E.J. Vallender:** None. **M.R. Garrett:** None. **L. Challagundla:** None. **J.C. Overholser:** None. **G.J. Jurjus:** None. **L. Dieter:** None. **H. Benghuzzi:** None. **C.A. Stockmeier:** None.

Poster

245. Affective Disorders: Human Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 245.18/OO15

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: T32MH067631-12

1RO1MH106565

Title: Epigenetic regulation of glucocorticoid receptor exon 1f in teenage suicide

Authors: *H. S. RIZAVI, D. R. GRAYSON, H. ZHANG, G. N. PANDEY
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Abstract: Impaired hypothalamic-pituitary-adrenal (HPA) function is linked to depression and increased susceptibility to suicide. Dysregulation of HPA axis function observed in depression and suicide may be due partially to a disturbed feedback inhibition by endogenous corticoids. Glucocorticoid receptors (GR) play an important role in the regulation of stress response when endogenous levels of glucocorticoids are high. Our goal was to investigate the role of DNA methylation and hydroxymethylation in regulating GR1F expression by examining GR1F promoter. In addition, we examined the expression of genes that control DNA methylation, DNA methyltransferases (DNMTs), and genes involved in demethylation, ten-eleven translocation proteins (TETs). Gene expression and methylation levels were measured in prefrontal cortex (PFC) of 22 suicide and 22 normal control teenage subjects. We found that DNMT1 and DNMT3a expression was increased with no change in DNMT3b and expression of TET1 and TET2 was decreased with no change in TET3 in teenage suicide victims as compared to normal controls. Also when analyzing $GR1_F$ promoter specifically, methylation levels were increased and hydroxyl-methylation levels were decreased. Additionally $GR1_F$ expressing was significantly downregulated in teenage suicide victims as compared to normal controls. This study provides strong evidence that epigenetic variations caused by aberrant regulation of DNMT and TET lead to higher $GR1_F$ promoter methylation and decreased expression. This study underlines the relevance of understanding epigenetic mechanisms involved in adolescence and its significance to understanding the molecular pathology of teenage suicide.

Disclosures: H.S. Rizavi: None. **D.R. Grayson:** None. **H. Zhang:** None. **G.N. Pandey:** None.

Poster

245. Affective Disorders: Human Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 245.19/OO16

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: Pritzker Neuropsychiatric Research Consortium

Title: Neuropeptide processing enzymes of the regulated secretory pathway are decreased in the anterior hippocampus of postmortem depressed subjects

Authors: *M. WASELUS[1], A. MEDINA[1], C. A. TURNER[1], W. E. BUNNEY JR[2], R. M. MYERS[3], A. F. SCHATZBERG[4], J. D. BARCHAS[5], H. AKIL[1], S. J. WATSON, Jr.[1]
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Abstract: Numerous neuropeptides have been implicated in the pathophysiology of major depressive disorder (MDD). Unlike the biosynthesis of classical neurotransmitters, neuropeptides must go through a series of processing steps to release active neuropeptide(s) from their larger, inactive precursors.
The first enzymatic step in this process is carried out by a family of proprotein/prohormone convertases (PCs), which typically cleave inactive peptide precursors C-terminal to paired basic amino acid residues (e.g., Lys/Arg). Two members of the PC family, PC1/3 and PC2, are stored in secretory granules and act on peptide precursors that are processed in the regulatory secretory pathway. Early in the secretory pathway, the activity of PC1/3 and PC2 can be modified when bound by their associated binding proteins, proSAAS (PC1/3) and 7B2 (PC2). We have previously shown that 7B2 was decreased in specific posterior hippocampal subregions of depressed subjects compared to controls. Here, we extended these studies to examine the distribution and expression of these enzymes in the anterior hippocampus of both control and depressed subjects. Frozen 10µm sections through the anterior hippocampus were processed for in situ hybridization using radiolabeled cRNA probes for PC1/3, PC2, proSAAS and 7B2, with subsequent quantification of mRNA expression measured in the dentate gyrus (DG), hippocampus proper (CA1, CA2, CA3, and CA4) and subicular complex (prosubiculum, subiculum and presubiculum). Decreased expression of PC1/3 and PC2 was identified within specific subregions of the typical component (Ding and Van Hoesen, 2015) of the anterior hippocampus in depressed subjects. Differences in the expression of proSAAS and 7B2 between control and MDD subjects were not detected in any region examined. Unfortunately, it is difficult to predict and/or determine with certainty the specific complement of peptides that may be impacted by these decreases in PC1/3 and PC2 due to the indiscriminate nature of these enzymes. However, given that PC1/3 and PC2 are the primary endopeptidases responsible for neuropeptide processing in the regulated secretory pathway, our findings suggest that there may be widespread dysregulation in the early processing steps of regulated neuropeptides, specifically in the anterior hippocampus, in depressed subjects. Furthermore, together with our previous findings of decreased 7B2 expression in the posterior hippocampus, it is apparent that there exists both molecular and anatomical specificity in the dysregulation of neuropeptide processing enzymes in the postmortem hippocampus of depressed individuals.

Disclosures: M. Waselus: None. **A. Medina:** None. **C.A. Turner:** None. **W.E. Bunney Jr:** None. **R.M. Myers:** None. **A.F. Schatzberg:** None. **J.D. Barchas:** None. **H. Akil:** None. **S.J. Watson:** None.

Poster

245. Affective Disorders: Human Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 245.20/OO17

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: Funded by the FRM (Fondation pour la Recherche Biomédicale)

Title: Clinical subgroups of patients with bipolar disorder and white matter microstructure: An enigma bipolar disorder fractional anisotropy dti working group mega-analysis

Authors: *M. E. PAULING[1], *M. E. PAULING[1], ***M. E. PAULING**[1], *M. E. PAULING[2], C. HENRY[3], S. SARRAZIN[2,4], J. HOUENOU[2,3,4]
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Abstract: Introduction: Using diffusion tensor imaging (DTI), connectivity differences between patients with bipolar disorder (BD) and healthy controls can be explored by looking at white matter microstructure. The mega-analytic methods used in this study increase the power of the analysis, and that, along with sub-group comparisons among patients with differing clinical presentations of the disease, seek to harmonize the heterogeneity of results seen across previous studies. Heterogeneity can Methods: We analyzed data from 18 sites part of the ENIGMA BD DTI consortium, gathering 2804 (1501 female, 1303 males) adult subjects (1345 patients, 1459 controls), ages 18 to 65 (M= 37.25, SD= 12.40). All subjects underwent a DTI acquisition, and data was processed according to the ENIGMA DTI pipeline utilizing TBSS within FSL. This harmonizes data processing across sites. For each subject we calculated average FA values across 42 regions of interest (ROI). Using a linear mixed model, we compared FA between patients and controls, including age and sex as fixed factors and site as a random effect. Results: Using a likelihood ratio test, Bonferonni corrected for multiple comparisons, we saw statistically decreased FA in patients compared to controls within 29 of the 42 ROI: Anterior corona radiata right/left, Body of corpus callosum, Cingulum (cingulate gyrus) left/right, Corona Radiata left/right, External capsule left/right, Genu of corpus callosum, Posterior thalamic radiation left/right, Splenium of corpus callosum, Superior fronto-occipital fasciculus left/right, Sagittal stratum left/right, Uncinate fasciculus left/right (for all proceeding, $p<.001$), Anterior limb of internal capsule left/right ($p=.004$, $p=.012$), Fornix (cres)/Stria terminalis right ($p=.013$), Inferior fronto-occipital fasciculus left/right ($p=.019$, $p<.001$), Posterior corona radiata left/right ($p=.045$, $p=.005$), Superior longitudinal fasciculus left ($p= 0.007$), Superior corona radiata right ($p=.004$), Average FA ($p=.004$). We did not find any significant increase in FA. Conclusions: Our results confirm and extend previous results from smaller studies. They highlight the importance of fronto-limbic dysconnectivity but also point towards the implication of other networks.

Disclosures: **M.E. Pauling:** None. **C. Henry:** None. **S. Sarrazin:** None. **J. Houenou:** None.

Poster

245. Affective Disorders: Human Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 245.21/OO18

Topic: I.05. Biomarker and Drug Discovery

Support: NIH Grant MH111099

NIH Grant GM076990

NSERC Discovery grant RGPIN-2016-05991

NeuroDevNet Grant

UBC bioinformatics graduate training program

CIHR post-doctoral fellowship

Title: Concordant alterations of brain cell-type specific genes in four cohorts of neuropsychiatric patients

Authors: *L. TOKER, O. B. MANCARCI, S. TRIPATHY, P. PAVLIDIS
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Abstract: High-throughput expression techniques are widely used to study neuropsychiatric and neurodevelopmental disorders. A major challenge of these studies is understanding the biological impact of the identified genes. Researchers often struggle with questions such as - which cells are expressing the affected genes? Moreover, it is unclear what part of the transcriptional pattern is driven by changes in cellular abundance (e.g, due to cellular death or inflammation) and which part can be attributed to regulatory events. Therefore, identifying the affected cell-types is crucial for the analysis and interpretation of transcriptomic data.
We used NeuroExpresso - a rigorously curated database of brain cell-type expression data maintained in our lab, to identify marker-genes for 35 cell-types brain-wide. We next analyzed the marker-gene expression profiles in bulk-tissue data from neuropsychiatric patients to estimate changes in the relative abundance of neuronal and glial cell types in bipolar-disorder and schizophrenia.
We analyzed publically available datasets from four different cohorts of subjects with bipolar disorder and schizophrenia, including ten datasets of cortical samples, two datasets of hippocampal samples and one dataset of cerebellar samples. Strikingly, in each of the cortical datasets we observed a significant decrease in marker-gene profiles of fast-spiking PV

interneurons and an increase in marker-gene profiles of astrocyte in subjects with both psychiatric disorders. Based on analysis of mouse and human developmental data, we demonstrate that the changes in fast-spiking PV interneurons are not likely to represent defects in maturation of these cells.
The changes in astrocyte marker gene profiles were specific to cortical samples, since no changes in astrocyte marker-gene profiles were observed in the cerebellar and hippocampal datasets originating from the same subjects. In addition, we report a robust decrease in Reelin positive interneurons in the hippocampus of subjects with schizophrenia.
Our results suggest that the pathophysiology of bipolar-disorder and schizophrenia involves changes in marker-gene profiles of cortical astrocytes and fast-spiking PV interneurons. Cautiously, these changes can be attributed to alterations in the relative abundance of these cells, and should be accounted for when analyzing and interpreting transcriptomic data.

Disclosures: L. Toker: None. **O.B. Mancarci:** None. **S. Tripathy:** None. **P. Pavlidis:** None.

Poster

245. Affective Disorders: Human Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 245.22/OO19

Topic: G.03. Emotion

Support: JSPS KAKENHI Grant 15K00210.

Title: Olfactory impairment and sleep disorder may provide early indication of neurodegeneration

Authors: *Y. MASAOKA[1], M. KAWAMURA[2], M. YOSHIDA[5], N. KOIWA[6], A. YOSHIKAWA[3], M. IDA[7], K. ONO[2], A. PHILLIPS[8], M. IZUMIZAKI[4]
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Abstract: There is evidence that impaired human cognitive abilities are reflected by loss of olfactory abilities. Declining olfactory perception may be a biomarker for impairment of cognitive function and of impending illnesses in neurodegenerative disorders. In this study, we examined possible relationships between age and olfactory abilities in healthy subjects (controls) over a wide range of ages and compared this relationship with that observed in Parkinson's disease (PD) and rapid eye movement (REM) sleep behavior disorder (RBD) that has been

reported having a risk to develop to a parkinsonian disorder. We also performed further analysis to see brain activities during olfactory stimuli in controls, PD and RBD using electroencephalogram (EEG) dipole modeling analysis (EEG/DT) and fMRI. All controls and patients were provided written informed consent, and the study was approved by the Ethics Committee of the Showa University School of Medicine. The authors declare that they have no conflict of interests. Ability to detect odors was generally intact in PD and RBD, however, we found that the abilities of individuals in the PD and RBD populations to recognize odors were impaired relative to control subjects. RBD were divided into two conditions: RBD with normal odor recognition and RBD with impaired odor recognition (RBD-impaired odor). EEG/DT and fMRI showed olfactory limbic areas including the amygdala (AMG), entorhinal cortex (ENT), hippocampus (HI), and orbitofrontal cortex (OFC) were less activated during olfactory stimuli in PD and RBD-impaired odor compared with controls, especially activations in the OFC were not observed in two groups. RBD with normal olfactory recognition ability showed normal activations in AMG, ENT, HI and OFC as normal controls. RBD is characterized by dream-enacted behavior associated with skeletal muscle atonia during REM sleep. REM sleep is mediated by a distributed network within the brainstem, hypothalamus and limbic regions, including a key role for the amygdala in the regulation of REM sleep. Pathophysiological changes within the AMG may contribute to abnormality in both RBD and olfaction. We found some RBD-impaired odor had symptoms of PD at this stage. It is tempting to speculate that both these impairments in olfaction and RBD may reflect common mechanisms of neurodegeneration of PD. This study is supported by a JSPS KAKENHI Grant Number 15K00210.

Disclosures: **Y. Masaoka:** None. **M. Kawamura:** None. **M. Yoshida:** None. **N. Koiwa:** None. **A. Yoshikawa:** None. **M. Ida:** None. **K. Ono:** None. **A. Phillips:** None. **M. Izumizaki:** None.

Poster

245. Affective Disorders: Human Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 245.23/OO20

Topic: I.05. Biomarker and Drug Discovery

Title: Pharmacological MRI platform for pre-clinical CNS drug discovery

Authors: *A. SHATILLO, T. MIETTINEN, J. KEINÄNEN, A. J. NURMI
Charles River Discovery, Kuopio, Finland

Abstract: Pharmacological MRI (phMRI) is a versatile and powerful MRI technique for in-vivo non-invasive mapping of the effects (direct and indirect target engagement) of the pharmacological test compounds in the brain. High temporal and spatial resolution, whole brain coverage and controlled environment render phMRI an invaluable tool for pre-clinical drug

testing, allowing fast screening of the novel compounds for modulating neuronal metabolism and hemodynamic response in the brain. Most widely used phMRI modalities are blood oxygen level-dependent (BOLD) signal and regional cerebral blood volume (rCBV) measurements. Multiple experimental paradigms (e.g. acute dosing vs. pretreatment-challenge) combined with different approaches to data analysis gives flexibility to look into specific aspects of test molecule's action. Deliverables include multiple quantitative temporal (time to peak, full width at half-maximum, area under the curve, amplitude etc.) and spatial (statistical parametric maps of activity) characteristics.
Here we present our further development of the pharmacological MRI platform in high field for pre-clinical drug testing, focusing on rCBV measurements of rat brain response to commonly used psychoactive compounds, such as amphetamine, S-ketamine, phencyclidine and yohimbine. Pretreatment with corresponding antagonists was used to show sensitivity of the method as well as presence of the detection window for the modulatory effects of the test compounds.
Functional data were acquired using 7T or 11.7T Bruker MRI system, with T2-weighted TurboRARE sequence featuring 30 seconds time resolution and 300 micrometers in-plane resolution with slice thickness of 1-1.5 mm. Battery of anesthetic protocols, including Isoflurane, Urethane and Medetomidine was used depending on the experiment. Typical duration of single experiment was 1 hour with 10 min pre-contrast baseline, intravenous contrast agent administration (20 mg/kg Fe content), 20 min post-contrast baseline and drug challenge with 30 min follow-up. Every phMRI session was accompanied with physiological monitoring including pulse oximetry, respiration, temperature, arterial blood gas analysis and in some cases - continuous blood pressure measurements, which provides additional information about the drug's systemic effects.
Results are shown as individual or group-level statistical maps and signal time-series from selected region of interests (ROI). Provided data and methodology established within this study, demonstrates extensive drug testing capabilities using phMRI in various pre-clinical rat and mouse models.

Disclosures: **A. Shatillo:** None. **T. Miettinen:** None. **J. Keinänen:** None. **A.J. Nurmi:** None.

Poster

245. Affective Disorders: Human Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 245.24/OO21

Topic: A.09. Adolescent Development

Title: Orbitofrontal gray matter and sulcogyral pattern differences in bipolar disorder

Authors: *B. BLASS[1,2], V. TROIANI[1]
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Abstract: The orbitofrontal cortex (OFC) is known for its role in goal-directed behavior, emotion processing, and decision-making. A finite number of sulcogyral patterns are formed by the medial and lateral OFC sulci, frequently referred to as the H-sulcus. While the Type I H-sulcus pattern is most common in the general population (~50-75%), less common patterns (Type II,Type III) have been associated with schizophrenia. Additional variance across individuals exists in the presence and number of posterior orbital sulci (POS). To date, no study has examined OFC sulci differences in bipolar disorder (BP).
Here, we investigate the relationship between H-sulcus pattern type, POS subtype (absent, single, double), and gray matter (GM) volume in the posterior orbital gyrus (POG). Anatomical MRI scans of BP patients (N=46, 19 females, mean age=35) and healthy controls (N=56, 14 females, mean age=36) were characterized using a previously published classification rubric. Voxel-based morphometry (VBM) was also performed to assess POG GM volumes.
We find higher frequencies of atypical H-sulcus patterns in the left hemisphere of the BP group compared to controls (χ^2=11.632; p=0.009). VBM results indicated that BP subjects had significant GM volume reduction in POG relative to controls (L: p=0.005; R: p=0.023).
These results indicate that OFC H-sulcal patterns are relevant to BP. Furthermore, these results suggest that GM differences may exist in the absence of overt morphological differences, such as the presence of additional sulci.

Disclosures: B. Blass: None. **V. Troiani:** None.

Poster

246. Animal Models for Affective Disorders: Mechanisms II

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 246.01/OO22

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: Hope for Depression Research Foundation

ONR N00014-15-1-2224

NIH 5R01MH104261-04

Title: Selectively bred high responder and low responder rats show sex differences in the development of novelty seeking and adult emotional reactivity

Authors: *E. K. HEBDA-BAUER, A. V. STEFANOV, S. J. WATSON, Jr., H. AKIL
Univ. of Michigan, Ann Arbor, MI

Abstract: Selectively bred High-Responder (bHR) and Low-Responder (bLR) rats, a unique animal model of mood disorders, consistently show differences in novelty-seeking and emotional reactivity. Since mood disorders are more common in women than men, we examined sex differences in the HR/LR locomotor activity phenotype from weaning to young adulthood and in adult anxiety-like behaviors. Male and female rats from generation F50 were tested in locomotor activity boxes for 60 minutes on postnatal days (PND) 22, 42, and 62. As young adults, rats were exposed to a novel rat for 5 minutes in a 1-day social interaction (SI) test, followed by elevated plus maze (EPM) testing several days later. To determine the role of environmental familiarity, a second cohort of F50 rats was tested in a 2-day SI test, which consisted of exposure to an empty open field (OF) on day 1, followed by exposure to a novel rat in the OF on day 2. We detected HR/LR locomotor activity differences right after weaning on PND22, with activity levels increasing with age in bHRs and bLRs. Male and female bHRs exhibited 20% of their young adult (PND62) activity levels on PND22 and 75% by adolescence (PND42). In contrast, male and female bLRs both exhibited 10% of their adult activity levels at PND22 and males 85% and females 50% at PND42. Further, early age prediction of locomotor activity is stronger in bLRs than bHRs. bHRs exhibited more SI behavior than bLRs, as expected, and environmental familiarity enhanced this HR/LR difference since male and female bLRs interacted less with a novel rat in a familiar environment than a novel environment. Female bHRs interacted more with a novel rat in a novel environment than did male bHRs, but this sex difference did not exist in a familiar environment or among bLRs in either environment. As expected, bHRs traveled more distance at a higher speed than bLRs in the OF periphery. Females were quick to escape from the center to the periphery, while males traveled more distance at a slower speed in the center. Although bLRs exhibited more anxiety-like behavior than bHRs in the EPM, as expected, female bHRs spent more time in the open arms and female bLRs entered the open arms more than their corresponding male counterparts. In conclusion, the HR/LR locomotor activity phenotype is clearly evident at weaning and the prediction of adult locomotor activity levels during adolescence is most promising among bLRs, especially males. The degree of environmental familiarity modulates the magnitude of HR/LR differences and the detection of sex differences in SI behavior. In the presence of the expected HR/LR emotionality differences, females show more anxiety-like behavior than males in the OF, but less in the EPM.

Disclosures: E.K. Hebda-Bauer: None. **A.V. Stefanov:** None. **S.J. Watson:** None. **H. Akil:** None.

Poster

246. Animal Models for Affective Disorders: Mechanisms II

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 246.02/OO23

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: R01MH090264

5F30MH100835

Title: Modulation of neuroligin-2 in the nucleus accumbens alters stress and dominance behaviors

Authors: *M. HESHMATI[1], H. ALEYASIN[1], C. MENARD[3], D. J. CHRISTOFFEL[5], M. FLANIGAN[3], M. L. PFAU[3], P. H. GOFF[3], G. E. HODES[1], A. TAKAHASHI[1], A. LEPACK[2], L. BICKS[1], R. CHANDRA[6], M. LOBO[7], I. MAZE[4], S. A. GOLDEN[8], S. J. RUSSO[1]
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Abstract: Behavioral coping strategies are critical for active resilience to stress and depression; here we describe a novel role for neuroligin-2 (NLGN-2) in the nucleus accumbens (NAc). Neuroligins (NLGN) are a family of neuronal postsynaptic cell adhesion proteins that are constituents of the excitatory and inhibitory synapse. Importantly, NLGN-3 and NLGN-4 mutations are strongly implicated as candidates underlying the development of neuropsychiatric disorders with social disturbances such as autism, while the role of NLGN-2 in neuropsychiatric disease states is unclear. We show a reduction in NLGN-2 gene expression in the NAc of patients with major depressive disorder. Reverse translation of this finding in chronic social defeat stress, an animal model of depression that enables investigation of both susceptibility and resiliency mechanisms, uncovers an important functional role for NAc neuroligin-2 in stress susceptibility. Chronic social defeat stress in mice decreases NLGN-2 selectively in dopamine D1-positive cells, but not dopamine D2-positive cells, within the NAc of stress susceptible mice. Functional NLGN-2 knockdown produces bidirectional, cell type-specific effects: knockdown in dopamine D1-positive cells promotes subordination and stress susceptibility, while knockdown in dopamine D2-positive cells mediates active defensive behavior. These findings establish a behavioral role for NAc NLGN-2 in stress and depression, provide a new basis for targeted, cell-type specific therapy, and highlight the role of active behavioral coping mechanisms in stress susceptibility.

Disclosures: M. Heshmati: None. **H. Aleyasin:** None. **C. Menard:** None. **D.J. Christoffel:** None. **M. Flanigan:** None. **M.L. Pfau:** None. **P.H. Goff:** None. **G.E. Hodes:** None. **A. Takahashi:** None. **A. Lepack:** None. **L. Bicks:** None. **R. Chandra:** None. **M. Lobo:** None. **I. Maze:** None. **S.A. Golden:** None. **S.J. Russo:** None.

Poster

246. Animal Models for Affective Disorders: Mechanisms II

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 246.03/OO24

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: MH077681

MH105824

DA033945

Title: Modulation of anxiety- and depression-like behaviors by α7 subunit-containing nicotinic acetylcholine receptors in GABAergic neurons of the basolateral amygdala

Authors: *S. T. PITTENGER, T. N. MOSE, Y. S. MINEUR, M. R. PICCIOTTO
Yale Sch. of Med., New Haven, CT

Abstract: Heightened levels of the neurotransmitter acetylcholine (ACh) have been correlated with depressive symptoms in both preclinical and human clinical studies. The amygdala is a critical node in the neuronal circuits involved in behavioral responses to stress. In particular, the basolateral amygdala (BLA) receives substantial cholinergic input and is involved in aversive learning and anxiety-like behaviors in animal models. Previous studies have shown that decreasing nicotinic acetylcholine receptor (nAChR) activity in BLA, either by local infusion of the nAChR antagonist mecamylamine or following viral-mediated knockdown of the β2 or α7 nAChR subunits, reduces depression- and anxiety-like phenotypes. The role of cholinergic innervation of specific neuronal subtypes in BLA, and therefore the structure of the microcircuit regulated by ACh, is still unknown, however. We have begun to address these questions by knocking down the β2 or α7 nAChR subunit in specific cell types in the BLA using AAVs harboring CRE-dependent small hairpin RNAs in transgenic mice expressing Cre recombinase under the control of the CaMKII, vGlut2 (glutametergic neurons), or GAD65 (GABAergic neurons) promoters. Fourteen days after stereotaxic surgery, mice were tested in the light-dark box, tail suspension test, forced swim test, and social defeat paradigm to evaluate their performance in tests of depression- and anxiety-like behaviors. Compared to control mice, α7 knockdown in BLA of GAD65-CRE mice significantly increased the amount of time spent in the light side of the light-dark box, suggesting an anxiolytic-like response. GAD65-CRE mice with α7 knockdown also spent less time immobile in the tail-suspension test compared to control mice, suggesting an antidepressant-like effect; although there were no significant changes in the other tests of antidepressant-efficacy evaluated. Knockdown of either the β2 or α7 nAChR subunit in CamKII- or vGlut2-CRE mice resulted in no significant changes in any of the behavioral tasks tested. These findings suggest that expression of β2 or α7 nAChR subunits on

glutamatergic neurons alone is not sufficient to mediate the array of anxiolytic- and antidepressant-like effects we have observed previously following constitutive knockdown of these subunit in BLA; however, α7 nAChR signaling in GABAergic cells does contribute to baseline behaviors related to anxiety and depression. The effects observed following cell-type selective α7 nAChR knockdown in BLA were limited to specific tasks, suggesting that additional cell types likely contribute to behavioral effects of nAChR signaling in the amygdala.

Disclosures: S.T. Pittenger: None. **T.N. Mose:** None. **Y.S. Mineur:** None. **M.R. Picciotto:** None.

Poster

246. Animal Models for Affective Disorders: Mechanisms II

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 246.04/OO25

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: This work was supported by the Natural Science Foundation of China (no. 81171251).

Title: Effects and underlining mechanisms of short photoperiod on emotions of rats

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Abstract: Objective: Photoperiod can lead to a range of effects on the person's psychological and physiological functions, a typical example is seasonal affective disorder, with which a vary of changes in circadian rhythm was found. In addition, environmental factors, particularly stressful life events, are important risk factors for depression. However, the underlied molecular mechanism of the effects of photoperiod on the emotion is still unclarified. **Methods**: We established a winter depression animal model, 21-day of short photoperiod combine with 16-day of subchronic unpredictable mild stress (SCUS). After stress, behavioral tests, including sucrose preference test (SPT), open field test (OFT), elevated plus maze test (EPT) and forced swimming test (FST), were performed to assess depression - like and anxiety - like behaviors. Thereafter, the CRF system and NPY system was detected by using western blotting. **Results**: Compared to rats in 12:12 CON group, rats in 8:16 SCUS group showed a significant decrease of values of sucrose preference. Rats in 12:12 SCUS or 8:16 CON group did not show a significant decrease in values of sucrose preference. Rats in each group did not exhibit a significant difference in

immobility time in FST. Rats in 8:16 SCUS group also showed a significant dicrease in the horizontal crossing distance in OFT. As for the anxiety - like behaviors, rats in 12:12 SCUS, 8:16 CON and 8:16 SCUS group exhibited a significant decrease of time at center in OFT, the ratio of residence time in the open arms in EPT, compared to rats in 12:12 CON group. For NPY system: it is short photoperiod condition but not SCUS significantly decreased the expression of NPY and NPY1-R in mPFC. SCUS induced a significant reduction of the expression of NPY and short photoperiod condition induced a significant decrease in the expression of NPY1-R in BLA. It is short photoperiod condition but not SCUS induced a significant increase in the expression of NPY1-R in CeA and DG. For CRF system: It is short photoperiod condition can induce a significant increase in the expression of CRFand CRF1-R in CA1, while SCUS can induce a significant increase in the expression of CRF but not CRF1-R in CA1. It is short photoperiod condition can induce a significant decrease in the expression of CRF1-R but not CRF and SCUS can induce a significant increase in the expression of CRF1-R but not CRF. **Conclusion**: The short photoperiod condition make adolescent rats more sensitive to stress. The imbalance between NPY system and CRF system in emotion regulation related brain areas may be involved in the more susceptible to stress in adolescent rats.

Disclosures: **S. Li:** A. Employment/Salary (full or part-time):; National Institute on Drug Dependence, Peking University, Beijing, China. **M. Yuan:** None. **L. Lu:** None.

Poster

246. Animal Models for Affective Disorders: Mechanisms II

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 246.05/OO26

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIH MH103322

MH10332S1

Title: Effects of short-term inhibition of kappa-opioid receptor on prevention and reversal of depression-like behavior

Authors: *A. WILLIAMS[1], A. LAMAN-MAHARG[2,3], C. V. ARMSTRONG[1], B. C. TRAINOR[1,2,3]
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Abstract: Stressful experiences are a risk factor for the development of mood disorders such as depression and anxiety. Kappa opioid receptors (KOR) play an important role in mediating behavioral responses to stress and are thought to represent a new target for antidepressants. Social defeat stress (SDS) activates KOR through the action of dynorphin, which in turn

promotes aversion and depression-like behaviors. Previous research targeting KOR as a therapeutic option have focused on long-acting antagonists that are present weeks after a single administration. The long-acting properties of these drugs has made it unclear whether the changes observed following stress are due to KOR inhibition exclusively during a stressful experience, or if continuous inhibition of KOR is necessary for efficacy. Two experiments were run to answer this question. First we examined the effect of a short-acting antagonist (AZ-MTAB) administered before exposure to SDS on the development of depression-like behavior. Second we examined whether treatment with AZ-MTAB after SDS reverses depression-like phenotypes that typically arise after stress. Both experiments were done in male and female California mice (*Peromyscus californicus*). In both experiments mice underwent three episodes of SDS or control conditions and were treated with either a 10mg/kg dose of AZ-MTAB or vehicle. In experiment 1 treatment was prior to each episode of SDS (3 times). In experiment 2 treatment was 2 hours before behavioral observations that took place two-weeks following SDS. Autogrooming behavior was observed prior to the first and last SDS episode in experiment 1. In both experiments behavior was observed two weeks following stress; a sucrose anhedonia test was done in both sexes and a social interaction test was done in females. Inhibition of KOR immediately before stressful experiences reduced autogrooming before the last episode of defeat. In addition, pre-stress AZ-MTAB treatment reduced long-term increases in anhedonia and social withdrawal. These results show that short-term inhibition of KOR during stress is sufficient to prevent the development of long-lasting increases in depression-like behavior. Preliminary results from experiment 2 indicate that treatment with AZ-MTAB after stressful experiences does not reverse behavioral changes induced by stress. We are currently analyzing RNAseq data from the nucleus accumbens of control and stressed California mice to identify transcripts that are affected by stress. We will test whether AZ-MTAB treatment prior to defeat can block these changes.

Disclosures: **A. Williams:** None. **A. Laman-Maharg:** None. **C.V. Armstrong:** None. **B.C. Trainor:** None.

Poster

246. Animal Models for Affective Disorders: Mechanisms II

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 246.06/OO27

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: KBRI basic research program Grant No. 17-BR-03

NRF basic research program Grant No. 2015R1D1A1A01059602

Title: Gadd45b mediate depressive-like role through DNA demethylation

Authors: *Y. JEONG[1], B. LABONTÉ[2,3], O. ENGMANN[3], O. ISSER[3], R. BAGOT[3], K.-A. CHO[1], E. NESTLER[3], J. KOO[1]
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Abstract: Animal studies using chronic defeat stress, an ethologically validated model of depression in mice, showed that brain-derived neurotrophic factor (BDNF) signaling in the mesolimbic dopamine (DA) pathways is important for the development of social aversion. However, the downstream molecular targets after BDNF release from ventral tegmanetal area (VTA) are not known. Here we present the data showing that depressive-like behaviors induced by chronic social defeat is mediated GADD45b, which is downstream of BDNF signaling in nucleus accumbens (NAc). We showed that Gadd45b mRNA is increased in susceptible mice but not in resilient mice. Intra-NAc infusion of BDNF and optical stimulation of mesolimbic DA pathway also enhanced the Gadd45b mRNA levels in NAc. Importantly, GADD45b knock-down reversed the impaired social interaction in susceptible mice and also blocked a social avoidance 5 days after the last defeat in resilient mice. These data suggest that GADD45b mediates the susceptible phenotype. In addition, we checked the function of GADD45b as a DNA demethylation agent at the CpG islands of the representative targets such as Bdnf, Dlx5, Gad67, and Crh, which have been involved in a depressed phenotype in humans and in animal depression models. We found that GADD45b knock-down induced the levels of DNA methylation in a phenotype-, gene-, and promoter (locus)-specific ways. Together, these data indicate the novel role of GADD45b in chronic defeat-induced depressive-like behaviors. Further, we suggest that lower DNA methylation levels by GADD45b in some stress-related genes such as Crh may affect development of susceptibility to chronic defeat stress.

Disclosures: Y. Jeong: None. **B. Labonté:** None. **O. Engmann:** None. **O. Isser:** None. **R. Bagot:** None. **K. Cho:** None. **E. Nestler:** None. **J. Koo:** None.

Poster

246. Animal Models for Affective Disorders: Mechanisms II

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 246.07/OO28

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIH Grant R01 MH090264

NIH Grant P50 MH096890

NIH Grant P50 AT008661-01

NIH Grant T32 MH087004

NIH Grant T32 MH096678

NIH Grant F31 MH105217

Title: Establishment of a repeated social defeat stress model in female mice

Authors: *J.-R. CHUNG[1], A. TAKAHASHI[2], S. ZHANG[1], H. ZHANG[1], Y. GROSSMAN[1], H. ALEYASIN[1], M. FLANIGAN[1], M. PFAU[1], C. MENARD[1], D. DUMITRIU[1], G. HODES[1], B. MCEWEN[3], E. NESTLER[1], S. J. RUSSO[1], M.-H. HAN[1]
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Abstract: Numerous studies have employed repeated social defeat stress (RSDS) to study the neurobiological mechanisms of depression in rodents. An important limitation of RSDS studies to date is that they have been conducted exclusively in males due to the difficulty of initiating attack behavior directed toward females. Here, we establish a female mouse model of RSDS by inducing male aggression toward females through chemogenetic activation of the ventrolateral subdivision of the ventromedial hypothalamus (VMHvl). We demonstrate that females susceptible to RSDS display social avoidance, anxiety-like behavior, reduction of body weight, and elevated levels of circulating Interleukin 6. In contrast, a subset of mice we term resilient only display anxiety-like behaviors after RSDS. This model allows for investigation of sex differences in the neurobiological mechanisms of defeat–induced depression–like behaviors. A robust female social defeat model is a critical first step in the identification and development of novel therapeutic compounds to treat depression and anxiety disorders in women.

Disclosures: J. Chung: None. **A. Takahashi:** None. **S. Zhang:** None. **H. Zhang:** None. **Y. Grossman:** None. **H. Aleyasin:** None. **M. Flanigan:** None. **M. Pfau:** None. **C. Menard:** None. **D. Dumitriu:** None. **G. Hodes:** None. **B. McEwen:** None. **E. Nestler:** None. **S.J. Russo:** None. **M. Han:** None.

Poster

246. Animal Models for Affective Disorders: Mechanisms II

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 246.08/OO29

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: Bilateral transection of hypoglossal nerves increased anxiety- and depression-like behaviors in rats

Authors: *J. JAHNG, S. CHUNG, D. KIM, J.-H. LEE
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Abstract: It has been reported that oral sensory and motor stimulations are necessary to maintain normal function of hippocampus. In rodent models, disrupted oral sensory relay to brain increased depression-like behaviors with a hippocampal dysfunction, and oral motor dysfunctions impaired hippocampus-dependent cognitive function. Hippocampus exerts negative feedback regulation on the hypothalamic-pituitary-adrenal (HPA) axis, and the HPA axis dysfunction has been implicated in psycho-emotional disorders. Hypoglossal nerve controls tongue movements and damages of it result in difficulty mastication and deglutition. We have examined if tongue motor loss with bilateral transection of hypoglossal nerves (Hx) induces psycho-emotional adversities in relation with a HPA axis dysfunction. Male SD rats were subjected to elevated plus maze (EPM) or forced swim tests at two weeks after the Hx or sham surgery. The hypothalamic phosphorylated extracellular signal-regulated kinase (pERK) and the pituitary pro-opiomelanocortin (POMC) expressions were examined by western blot analysis, and the plasma corticosterone by ELISA. Open arm stay was decreased, but closed arm stay increased, in Hx rats during EPM test. Immobility duration of Hx rats during swim test was increased and struggling decreased. Increases in the plasma corticosterone levels and adrenal hypertrophy were observed in Hx rats. The hypothalamic pERK and the pituitary POMC expressions were decreased in Hx rats. Results suggest that bilateral transection of hypoglossal nerves increases anxiety-/depression-like behaviors in rats, possibly in relation with the HPA axis dysfunction.

Disclosures: J. Jahng: None. **S. Chung:** None. **D. Kim:** None. **J. Lee:** None.

Poster

246. Animal Models for Affective Disorders: Mechanisms II

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 246.09/OO30

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: Spanish Ministry of Economy and Competitiveness, SAF2015-68346-P (FA) and SAF2016-75797-R (AB)

Instituto de Salud Carlos III PI13/01390 (AB) co-financed by the European Regional Development Fund “A way to build Europe”

Title: Murine model of depression: Astroglial glutamate transporter knockdown in infralimbic cortex induces a depressive phenotype

Authors: N. FULLANA[1], E. RUIZ-BRONCHAL[2], A. FERRÉS-COY[1], A. BORTOLOZZI[2], *F. ARTIGAS[3,4]
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Abstract: Emerging evidence suggests that dysregulations of glutamatergic neurotransmission in prefrontal cortex are involved in the pathophysiology of depression. Astrocytes regulate excitatory neurotransmission by removing synaptic glutamate via GLAST and GLT-1 transporters. We demonstrated that unilateral knockdown of GLAST and GLT-1 in mouse infralimbic (IL) cortex induced by the local micro-infusion of small interfering RNAs (siRNA) targeting either transporter evoked a depressive-like phenotype. Conversely, intra-prelimbic (Prl) cortex microinfusion of both siRNAs did not affect behavioral responses despite comparable reductions of GLAST and GLT-1-1 expression in both PFC subdivisions. Downregulation of GLAST and GLT-1 remained diminished for at least 3 day and recovered 7 days post-administration. The depressive-like phenotype induced by reducing GLT-1 and GLAST expression in IL may be due to a hypoactive serotonergic (5-HT) system since it was reversed by the antidepressant drug citalopram. Likewise, microdialysis experiments revealed that siRNA-treated mice exhibited a reduced basal 5-HT release in the dorsal raphe nucleus (DRN) compared with controls, and a similar effect of veratridine in both experimental groups, indicating a similar intracellular 5-HT content. Further, local infusion of the $GABA_A$ receptor antagonist bicuculline increased DRN-5-HT release more markedly in siRNA-treated mice, suggesting a greater inhibition of 5-HT neurons via $GABA_A$ receptors. However, local downregulation of both transporters in PrL did not alter baseline 5-HT in DRN not the effect of bicuculline on 5-HT release. Taken together, these observations suggest that 1) an alteration of astroglial glutamate uptake in ventral PFC regions (IL) evokes downstream changes in 5-HT function, associated to a depressive-like phenotype in mice, and 2) the regional specificity of the effect suggests a differential functional connectivity between PrL/IL and DRN 5-HT neurons. In addition, this potential new model of MDD shows several physio pathological markers observed in patients: reduced expression of GFAP, a smaller number of astrocytes in mPFC, as well as a decreased BDNF expression in mPFC and the hippocampal formation, which is highly and significantly correlated with the degree of glutamate transporter knockdown in IL, indicating a direct relationship between both processes. Overall, these findings improve our understanding of the pathophysiology of depression and could help to identify novel targets in antidepressant drug development, since this potential new MDD model mimics many of the functional and molecular alterations observed in MDD patients.

Disclosures: N. Fullana: None. **E. Ruiz-Bronchal:** None. **A. Ferrés-Coy:** None. **A. Bortolozzi:** None. **F. Artigas:** None.

Poster

246. Animal Models for Affective Disorders: Mechanisms II

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 246.10/OO31

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: Japanese Ministry of Education, Culture, Sports, Science and Technology

Title: Molecular biological analysis of the de novo mutations found in the bipolar disorder patients

Authors: *T. NAKAMURA[1,2], K. NAKAJIMA[1], T. TSUBOI[2], T. KATO[1]
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Abstract: Bipolar disorder (BD) is a common neuropsychiatric disorder characterized by manic and depressive episodes with around 1% life time prevalence as well as schizophrenia. Although the pathogenesis of BD remains unclear, recent studies have shown that genetic factors are known to be important for the development of the disease. Recently, a trio-based exome sequencing study for BD has reported that *de novo* mutations have physiological importance in BD. In this study, we investigated functional consequences of the gene-disrupting *de novo* mutations found in *EHD1*, *MACF1* and *KMT2C*. These three genes have high scores in two indices, Residual Variation Intolerance Score (RVIS) which represents an intolerance to protein altering mutation, and probability of Loss-of-Function intolerance (pLi) which means an intolerance to loss-of-function mutation. First, we investigated the function of the *de novo* frameshift mutation in *EHD1* at cellular level because the mutation existed in the last exon. This mutation generates stop codon on the last exon, and a truncated EHD1 protein is predicted to be expressed in organs of the patient, escaping nonsense-mediated mRNA decay. The truncated EHD1 lacks almost all of the EH domain which includes the EF-hand calcium binding domain. EHD1 reportedly plays important roles in neurite outgrowth and endocytosis at the cellular level. In the present study, we investigated functional significance of the mutant EHD1 protein on those functions using PC12 cells. We found that overexpression of the wild type EHD1 significantly enhanced neurite outgrowth induced by nerve growth factor in PC12 cells. This effect was not detected using the mutant EHD1. We also detected that the mutant EHD1 significantly inhibited endocytosis in PC12 cells mediated by endogenous EHD1 suggesting a dominant negative effect of the mutant protein. To study the effect of the mutations *in vivo*, we are generating genome-edited mice for *Ehd1*, *Macf1* and *Kmt2c* using CRISPR/Cas9 system in order to perform behavioral analysis. We designed single guide RNAs to cleave the DNA double strand at each locus and detected cleavage activity of each single guide RNA by Surveyor assay. We injected those designed CRISPR/Cas9 sets into the fertilized eggs of mice. The present study

will shed light on the pathophysiological mechanisms of BD at the cellular and organism levels in terms of the *de novo* mutations.

Disclosures: **T. Nakamura:** None. **K. Nakajima:** None. **T. Tsuboi:** None. **T. Kato:** None.

Poster

246. Animal Models for Affective Disorders: Mechanisms II

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 246.11/OO32

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIH Grant MH105482

Title: Orphan receptor GPR158 modulates intrinsic excitability of layer 2/3 neurons in prelimbic cortex by regulating A-type potassium current

Authors: *C. SONG, C. ORLANDI, L. P. SUTTON, K. A. MARTEMYANOV
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Abstract: G protein coupled receptors (GPCRs) are a large and diverse family of receptors that have become the most important targets in modern pharmacology. Growing evidence suggests that GPCRs play critical roles in mood disorders and their treatments. We have recently found that the orphan receptor GPR158 plays a role in emotional control and is highly expressed in the prefrontal cortex. The current study aimed at determining the cellular mechanisms of GPR158 action underlying behavioral effects. We utilized whole-cell patch-clamp recordings to examine the effect of GPR158 deletion (KO) on electrophysiological properties of pyramidal neurons in prelimbic (PL) area. We focused on these neurons because this area is critical for emotional control. We first determined that GPR158 KO does not significantly change electrophysiological properties of layer 5 PL neurons. In contrast, layer 2/3 neurons were significantly affected. Analysis of the data revealed that the intrinsic excitability was significantly increased in GPR158 KO neurons compared to wild type (WT) neurons ($p < 0.01$), as evidenced by KO neurons firing more spikes in response to depolarizing current injection (all neurons were held at -70 mV). In addition, GPR158 KO neurons displayed larger input resistance and lower rheobase current ($p < 0.05$ for both measurements). Furthermore, increase intracellular cAMP levels by adding Sp-cAMPs into the internal solutions for WT but not KO neurons mimicked the effect of GPR158 KO, suggesting GPR158 suppresses intrinsic excitability through modulating intracellular cAMP level. These results also suggest that some potassium channels are inhibited in GPR158 KO neurons through cAMP-PKA pathway. Interestingly, voltage-clamp recordings of barium-sensitive current suggested that the outward-rectifying but not inward-rectifying potassium current was inhibited in GPR158 KO neurons. Under voltage clamps in brain slice, we further demonstrated that A-type potassium current was inhibited in GPR158 KO neurons. Taken

together, these data suggest that GPR158 modulates intrinsic excitability of L2/3 pyramidal neurons in prelimbic area, and may be a potential target for novel anti-depressants.

Disclosures: C. Song: None. **C. Orlandi:** None. **L.P. Sutton:** None. **K.A. Martemyanov:** None.

Poster

246. Animal Models for Affective Disorders: Mechanisms II

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 246.12/OO33

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: CIHR grant MOP142308

Title: Selective activation of estrogen receptors alpha and beta under chronic stress: Implications for depressive-like phenotypes

Authors: *R. MAHMOUD, J. A. CHAITON, C. CHOW, S. E. LIEBLICH, L. A. M. GALEA
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Abstract: Chronic stress has profound effects on the brain and is associated with the development of neuropsychiatric disorders including depression and anxiety. Sex differences exist in the outcomes of chronic stress exposure, and prior research indicates that females may be resilient to some of the deleterious effects of chronic stress. While estradiol may afford resilience against stress, the molecular mechanisms underlying this effect are poorly understood; in part due to the complexity of estradiol signaling. The aim of this study was to dissect the contribution of estrogen receptor (ER) subtypes to depressive-like outcomes of chronic stress exposure in female mice. Adult mice (C57BL/6) were ovariectomized or sham-operated, then chronically treated with the ERα-selective agonist propylpyrazole-triol (PPT), ERβ-selective agonist diarylpropionitrile (DPN), estradiol (E2), or vehicle (Oil). Mice from each treatment group were assigned to Chronic Unpredictable Stress (CUS) or non-CUS conditions. All mice were assessed for depressive- and anxiety-like behaviour (forced swim test, tail suspension test, and novelty suppressed feeding), hippocampal neurogenesis, hippocampal cytokine levels, and neuroendocrine function (dexamethasone suppression test). Preliminary results suggest that the ERβ-selective agonist DPN may alleviate depressive-like behaviour in the tail suspension test. Further, CUS increased hippocampal interleukin-6 in ovariectomized mice, but this effect was prevented by E2 or PPT treatment, indicating that ERα activation may ameliorate inflammation in the hippocampus under chronic stress. Thus, estrogen receptor subtypes differentially contribute to the protective effects of estradiol under chronic stress, shedding light on the potential cellular mechanisms of estradiol-mediated stress resilience.

Disclosures: **R. Mahmoud:** None. **J.A. Chaiton:** None. **C. Chow:** None. **S.E. Lieblich:** None. **L.A.M. Galea:** None.

Poster

246. Animal Models for Affective Disorders: Mechanisms II

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 246.13/OO34

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: CNPQ 465550/2014-2

FAPESP 2017/06100-8

Title: Brain expression of 5-HT_6 receptor in adolescent male mice susceptible or resilient to the effects of prolonged social defeat stress

Authors: *S. CHIAVEGATTO, L. S. RESENDE, M. A. METZGER, J. F. S. CARRILLO, P. E. N. S. VASCONCELOS
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Abstract: Social stress is an important trigger factor for developing depression especially in adolescence, when the brain is not completely developed. It is unclear why some individuals are more susceptible than others. Studies show that expression changes of 5-HT6 serotonin receptor (5-HT6R) could have an important role on cognition, memory and mood disorders, but a putative role on resilience and susceptibility to chronic stress on adolescence is not known. Thus, the aim of this study was to investigate the brain expression 5-HT6R in the resilience and susceptibility phenomena under the negative effects of social defeat (SD) in adolescent male mice. 30 day-old C57BL/6 were subjected to daily bouts of SD with an aggressive adult male CD-1 mouse for 10 days. Control mice were exposed to the same situation without the aggressive encounter. Twenty-four hours after the last defeat episode, mice were evaluated in the social interaction and sucrose preference tests. Our behavioral data showed the occurrence of anhedonic and social avoidance behaviors in one part of the defeated animals (~50-60%): the susceptible subgroup ($p<0.001$). The other animals (~40-50%) did not develop these behaviors: the resilient subgroup. Brain tissues [prefrontal cortex (PFC), hippocampus (HC), dorsal striatum (DS) and hypothalamus (HYP)] were collected for molecular analyses. The protein expression of 5-HT6R, quantified by immunoblot, was not changed in any brain area studied ($p>0.05$). 5-HT6R gene expression was decreased in the DS ($p<0.05$), in both resilient and susceptible subgroups, whereas in the HYP there was a decrease only in the susceptible subgroup, ($p<0.01$). Regarding the brain localization of 5-HT6R by immunohistochemistry, were found immunorreactive neurons in the paraventricular nucleus of the hypothalamus and the olfactory bulb, where the stains were found in neuronal cilia. Our data suggest that prolonged psychosocial stress induces

depressive and social anxiety like-behaviors, moreover, we showed a possible relation between the gene expression of the 5-HT6R, in the DS and HYP, and the resilience and susceptibility phenomena in adolescent male mice.

Disclosures: S. Chiavegatto: None. **L.S. Resende:** None. **M.A. Metzger:** None. **J.F.S. Carrillo:** None. **P.E.N.S. Vasconcelos:** None.

Poster

246. Animal Models for Affective Disorders: Mechanisms II

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 246.14/OO35

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NSFC grant 81070888

NSFC grant 81230025

NSFC grant 81200862

NIMH grant MH092306

NIMH grant MH051399

Title: Circadian modulation of the paraventricular thalamic nucleus in susceptibility to repeated social stress

Authors: *H. ZHANG[1], M. SCHNEEBERGER[3], Y. ZHU[5], X. LIU[5], Z. CHEN[6], A. R. NECTOW[7], N. RENIER[4], D. CHAUDHURY[8], P. J. KENNY[9], J. FRIEDMAN[10], M.-H. HAN[5], J.-L. CAO[2]
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Abstract: Circadian rhythm influences animal behaviors. Circadian disruption leads to mood disorders, including depression, suggesting that neural substrates regulating circadian rhythm contribute to susceptibility to depression. Depressive symptoms exist day and night, yet a same neural substrate might display different mechanism-based circadian activities. Utilizing a repeated social defeat stress (RSDS) mouse model of depression, our brain-wide screening study with newly-developed iDISCO+/ ClearMap technique revealed a significantly increased Fos

protein expression in the paraventricular thalamic nucleus (PVT) from depressed susceptible mice when compared with their stress naïve control littermates. PVT is one of the circadian rhythm-related nuclei in the brain, and has been implicated in a variety of depression-related functions, notably vigilance, stress and motivated behaviors. However, the role of PVT in mediating social stress-related depressive-like behaviors remains unknown. In this study, we then observed circadian Fos protein expression in the PVT following RSDS as PVT neurons display well-known circadian variations in neuronal activity based on different mechanisms. Immunofluorescent staining indicates that the susceptible mice have an increased PVT Fos protein expression at both day (11:30 am - 13:30 pm) and night time (11:30 pm - 1:30 am) points as compared with their controls. Consistently, our electrophysiological recordings further confirmed an elevated firing rate of PVT neurons in susceptible mice at day time, and an increasing trend in firing activity at night hours, when compared with their controls. Leveraging circuit-specific molecular profiling, electrophysiology and optogenetics combined with pharmacological approaches, we will further investigate and manipulate diurnally different circuitry/ionic/molecular targets that underlie the hyperactivity of PVT neurons in regulating depressive-like behaviors. Collectively, our study might identify a novel depression center in the brain, and importantly, provide diurnally different translational targets/strategies for depression treatment.

Disclosures: H. Zhang: None. **M. Schneeberger:** None. **Y. Zhu:** None. **X. Liu:** None. **Z. Chen:** None. **A.R. Nectow:** None. **N. Renier:** None. **D. Chaudhury:** None. **P.J. Kenny:** None. **J. Friedman:** None. **M. Han:** None. **J. Cao:** None.

Poster

246. Animal Models for Affective Disorders: Mechanisms II

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 246.15/OO36

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: F31MH108326

R21MH112081

Title: Extrinsic modulation of midbrain dopamine neurons in stress-induced depression

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Abstract: Major depression is a highly prevalent mental disorder with an increasing social burden. Current antidepressant therapies are not efficacious in approximately 30% of depression patients, highlighting a crucial need to develop better treatments. Clinical studies and preclinical models of depression have highlighted the mesolimbic reward circuitry as a possible mediator of depression symptoms. In particular, our laboratory has identified the ventral tegmental area (VTA) as a key substrate for mediating susceptibility or resilience to chronic social defeat stress. VTA dopamine (DA) neurons have been shown to be functionally heterogeneous; we have shown that the VTA DA neurons projecting to the nucleus accumbens (NAc) exhibit a pathological hyperactivity that is specific to susceptibility and social avoidance behaviors. Although we previously characterized the intrinsic mechanisms supporting this hyperactivity, we hypothesize a concomitant alteration of the GABAergic tone onto VTA DA neurons. Using the chronic social defeat stress model for depression and electrophysiological techniques, we have investigated the involvement of GABA in the expression of depressive behaviors. Elucidating the contribution of GABA neurotransmission onto VTA DA neurons towards stress-induced depression may provide highly novel information for better therapeutic strategies.

Disclosures: **S.M. Ku:** None. **C. Morel:** None. **H. Zhang:** None. **B. Juarez:** None. **R.E. Mesias:** None. **K. Devarakonda:** None. **J.J. Walsh:** None. **D. Chaudhury:** None. **A.K. Friedman:** None. **M. Han:** None.

Poster

246. Animal Models for Affective Disorders: Mechanisms II

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 246.16/PP1

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NARSAD

NIGMS SC2GM122646

NIMHD MD007599

Title: Sex and coping strategy dependent plasticity of midbrain dopamine neurons mediates response to repeated variable social stress

Authors: *M. SHANLEY[1,2], A. SEIDENBERG[1], M. VAYSBLAT[1], T. FUNG[1], C. GUEVARA[3], A. K. FRIEDMAN[1]
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Abstract: Social stress induces a wide variety of behavioral responses in humans. Some individuals successfully employ active coping strategies in response to stress and become

resilient. In others, social stress can precipitate long-lasting psychiatric dysfunction, such as major depressive disorder (MDD). Coping mechanisms are known to be crucial for the maintenance of healthy mental functioning. Males and females demonstrate different social stress coping strategies, suggesting potential non-overlapping neural circuitry adaptations. While a successful coping strategy decreases the impact of stress, and protects from long-term pathological states, there is less known about the neurophysiological basis of how this occurs. Previous work has demonstrated importance of maintaining healthy activity of dopamine (DA) neurons in the ventral tegmental area (VTA), which project to the nucleus accumbens (NAc), in regulating decision-making and mood. Thus, we are exploring this circuit for novel therapeutic targets to promote stress-resilience. To identify the unique neural adaptations that occur during social stress-induced depression and resilience in both males and females, we have established a repeated variable social stress (RVSS) mouse model. This model exploits the innate social needs of both male and female mice by inducing home-cage instability, social overcrowding, witness restraint stress, and predator odor stress. We found that the inbred strain of C57BL/6J male and female mice exhibit a spectrum of behavioral responses, ranging from depressive-like to stress resilient. To evaluate the behavioral phenotype following the 10 day RVSS, we used a social interaction test, a social preference sociability test, and sucrose preference test. Interestingly, similar to human population, we found more females were susceptible to stress induced by RVSS and developed depressive symptoms. Using slice electrophysiology, we have characterized differences in firing activity in the VTA between resilient and susceptible mice in both males and females in response to RVSS. Importantly, we found an increase in the in vitro firing activity of VTA dopamine neurons of male and female mice that exhibit social avoidance, reduced social preference, and passive coping strategies. Our research explores the neurophysiological mechanisms of active stress coping strategies, and how they enhance resilience to stress induced depression. This may provide novel pharmacological targets to enhance coping skills and reverse depressive symptoms.

Disclosures: **M. Shanley:** None. **A. Seidenberg:** None. **M. Vaysblat:** None. **T. Fung:** None. **C. Guevara:** None. **A.K. Friedman:** None.

Poster

246. Animal Models for Affective Disorders: Mechanisms II

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 246.17/PP2

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIMH

HDRF

Title: Sex-specific effects of brain extracellular matrix genes in major depressive disorder

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Abstract: The extracellular matrix (ECM) of the brain is a highly complex network of proteoglycans, glycoproteins, fibrous glycoproteins, and hyaluronic acid that surround neurons and glial cells. In the brain, the ECM is essential in providing structural support, driving developmental decisions, guiding cell migration, promoting cell maturation and differentiation, ensuring cell survival, and facilitating synaptic plasticity. Major Depressive Disorder (MDD), a costly and burdensome mood disorder poised to be the leading cause of disability in the world, is known to cause structural alterations throughout the brain. Despite this, the role of the brain ECM in MDD is poorly understood. In order to identify possible MDD-associated alterations in the ECM, we analyzed transcriptional profiles from the nucleus accumbens (NAc) and prefrontal cortex (PFC) in postmortem brain tissue of humans with MDD. In parallel, we analyzed RNA sequencing data from male and female mice exposed to chronic variable stress (CVS), a validated stress paradigm. We identified dozens of ECM-specific genes differentially expressed in both data sets. Strikingly, we found little overlap between male and female differentially expressed brain ECM genes. To better understand the functional role of these sex-specific ECM target genes on stress responses, we are investigating their ability to influence stress susceptibility at the behavioral and molecular levels. Together, these findings implicate the ECM of the brain as a potential key mediator of stress responding that is impacted in a sex-specific manner.

Disclosures: E.M. Parise: None. **L.F. Alcantara:** None. **Z.S. Lorsch:** None. **P.J. Hamilton:** None. **B. Labonté:** None. **C.A. Bolanos-Guzman:** None. **E.J. Nestler:** None.

Poster

246. Animal Models for Affective Disorders: Mechanisms II

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 246.18/PP3

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: Sackler Foundation

Spain Science Department Postdocotoral fellowship

NIMH R01MH091844

NIMH RO1 MH91427

Title: Loss of prefrontal cortex 5-HT1A during adolescence results in an adult depression but not anxiety-like phenotype

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Abstract: Serotonin (5-HT) plays an important role refining the formation of brain circuits during developmental time periods. While it is clear that early postnatal manipulations of the 5-HT system in general, and the 5-HT_{1A} receptor in particular, can impact the formation of emotion-related brain circuits, less is known about the role of 5-HT_{1A} receptors during adolescence, a time period of expansive maturation of frontal circuitry as well as vulnerability for the onset of affective disorders.
Despite significant evidence linking 5-HT_{1A} receptor function to depression in humans, 5-HT_{1A} receptor KO mice show a significant anxiety phenotype with no clear depressive phenotype. This might be due to the fact that 5-HT_{1A} receptors exist in two major forms: as an autoreceptor in serotonergic (5-HT) neurons in the raphe nuclei, and as a heteroreceptor in non-5-HT cells in the forebrain. Previous studies from our lab have demonstrated a functional dissociation between 5-HT_{1A} autoreceptors and heteroreceptors, implicating selective loss of autoreceptors in anxiety, while selective loss of heteroreceptors appears to result in increased behavioral despair. Interestingly, we have recapitulated the anxiety phenotype of the whole-brain knockout mice, in mice that loss 5-HT_{1A} receptor signaling during adolescence. Thus, these results raise the possibility that variation in adolescent heteroreceptor function might have lasting effects on adult behaviors distinct from autoreceptor manipulations. In addition, women have higher rates of major depression, yet most studies have excluded female mice.
Here, we used transgenic and viral approaches with temporal and spatial specificity to establish whether adolescence is a period during which circuits contributing to depression are subject to modulation by 5-HT_{1A} heteroreceptor. We demonstrate that mice lacking 5-HT_{1A} heteroreceptors during adolescence (postnatal day (P)35-P50), but not during early-adulthood (P50-P65) display increased behavioral despair and anhedonia while maintaining normal anxiety levels in both male and female mice. We further found that suppression of prefrontal cortex (PFC) 5-HT_{1A} heteroreceptors during adolescence, but not adulthood, is sufficient to confer these behavioral effects in adult male mice.
Our results demonstrate a developmentally mediated adult depression-related phenotype that results from altered PFC 5-HT_{1A} signaling during adolescence.

Disclosures: **A. Garcia:** None. **I. Aly:** None. **A. Dranovsky:** None. **E. Leonardo:** None.

Poster

246. Animal Models for Affective Disorders: Mechanisms II

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 246.19/PP4

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIH Grant 1F30NS101873-01

NIH Grant 1P01NS055976

Title: Neuroinflammation and dorsal raphe neuronal activity associated with depression after spinal cord injury

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Abstract: Depression occurs three times more frequently in spinal cord injured (SCI) individuals than in the general population and only a small percentage receives relief with pharmaceutical treatment. The pathology of depression has been attributed to an imbalance in the neurotransmitter serotonin, with the dorsal raphe nucleus acting as the primary central source. There also is a suggestion that neuroinflammation may have a prominent role in the development and/or persistence of SCI-depression. In this study we used a battery of behavioral tests (sucrose preference, social exploration, open field, novel object recognition, and forced swim) and K-means cluster analysis to identify a depression-like phenotype in approximately 60% of female rats at 4 weeks after a moderate thoracic (T9) contusion injury. SCI-induced changes in electrophysiological activity of serotonergic dorsal raphe neurons and GABAergic interneurons of the dorsal raphe nucleus were detected using whole cell patch clamp techniques 5 weeks after injury. Further, we used immunocytochemistry to measure changes in levels of GLT1 as an indicator of astrocyte glutamate transport activity. ELISA was used to measure levels of TNFα, IL1B, and IL6 as evidence of chronic inflammation in higher brain centers (dorsal raphe, prefrontal cortex and hippocampus) that may contribute to a depressive phenotype in SCI rats. This study begins to elucidate a role for inflammation in the development of depression after SCI which could be instrumental in identifying efficacious treatment strategies for this patient population.

Disclosures: **K. Farrell:** None. **M.R. Detloff:** None. **J.D. Houle:** None.

Poster

246. Animal Models for Affective Disorders: Mechanisms II

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 246.20/PP5

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: R01MH107033

R01MH112076

Title: Network alterations following immune-induced glutamate dysregulation

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Abstract: Mood and anhedonic symptoms are mediated by dysfunctional integration of large-scale networks that regulate affect, cognition, motivation and arousal. Inflammatory molecules impair this neural integration by selectively disrupting the functional activation patterns in key nodes and hubs that integrate network activity. Our earlier published studies demonstrated that inflammation increases concentrations of the excitatory neurotransmitter glutamate in mood-regulating hub regions such as the basal ganglia; which was associated with increases in severity of anhedonic symptoms. The location of the target binding sites engaged by glutamate is critical - with stimulation of the intrasynaptic binding site promoting network plasticity, while excess stimulation of extrasynaptic sites promotes disarrayed, chaotic signaling that disrupts network plasticity. Thus, we hypothesized that loss of coherent, synchronized local hub activity in the basal ganglia region in response to increased extrasynaptic glutamate activity might serve as a biomarker of inflammation-induced circuit decompensation. We measured basal ganglia glutamate concentrations using magnetic resonance spectroscopy (MRS); intrinsic brain activity at local level using spontaneous fluctuations in brain oxygen level dependent (BOLD) signals during resting state functional imaging (rsfMRI) scans; and functional connectivity between basal ganglia and other brain regions using rsfMRI-connectivity metrics along with standardized assessments of behavior and inflammation [as reflected by C-reactive protein (CRP)] in a group of depressed subjects. Synchronized local activity namely Regional Homogeneity (REHO) - a measure of network centrality - was derived from spontaneous fluctuations of BOLD activity. Decreased basal ganglia REHO measures were associated with increased basal ganglia glutamate concentrations, increased inflammation as reflected by CRP, decreased basal ganglia-prefrontal region connectivity measures and with increased severity of self-rated anhedonia symptom

ratings. Recent advances in voxel-level modeling of BOLD fMRI activity have advanced our ability to estimate functional integrity and coherent activity of key hubs targeted by inflammation. The outcome of the study will take us a step closer to treating anhedonic behaviors by targeting either glutamate or inflammation or both by using degree of hub synchrony and coherence as a guide.

Disclosures: E. Haroon: None. **X. Chen:** None. **Z. Li:** None. **X.P. Hu:** None. **J.C. Felger:** A. Employment/Salary (full or part-time):; Emory University. F. Consulting Fees (e.g., advisory boards); Pfizer. **A.H. Miller:** None.

Poster

246. Animal Models for Affective Disorders: Mechanisms II

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 246.21/PP6

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: PhRMA Foundation Starter Grant

Iowa Osteopathic Education and Research Funds

Title: Glucocorticoid signaling regulates activation of hippocampal MKP-1 during stress

Authors: C. LANGRECK, D. NERLAND, B. LAMB, *L. SEMKE, E. WAUSON, V. DURIC
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Abstract: Major Depressive Disorder (MDD) is a commonly occurring and debilitating mental illness characterized by negative changes in mood. The exact etiology of MDD is not well understood, however, clinical and preclinical evidence suggests that prolonged exposure to stress and altered function of limbic brain areas, such as the hippocampus, are key factors that contribute to the development and maintenance of a depressive state. We have previously reported that MAP Kinase Phosphatase 1 (MKP-1), a negative regulator of MAP kinase signaling pathway, is overexpressed within the hippocampal subregions of depressed human brains. Moreover, MKP-1 was found to be both sufficient and necessary for development of depressive-like behaviors in rodent models. In the current study, glucocorticoid receptor (GR) signaling was investigated as a potential regulator of hippocampal MKP-1 expression. Treatment with the GR agonist dexamethasone significantly increased MKP-1 mRNA levels within the rat hippocampus at 1, 2, and 4 hours post treatment. Similarly to dexamethasone, exposure to acute restraint stress (ARS; i.e., 1 hr of immobilization) also evoked upregulation of hippocampal MKP-1 gene expression; however, this upregulation was transient and MKP-1 mRNA levels returned to baseline (i.e., similar to unstressed controls) as early as one hour after the end of ARS. Additionally, we also investigated whether GR blockade could prevent stress-induced

expression of MKP-1. Administration of the GR antagonist mifepristone 30 min before the initiation of ARS produced only a partial blockade of MKP-1 upregulation, suggesting that stress-mediated MKP-1 activation utilizes, in part, molecular mechanisms independent of the GR activation. Ongoing studies are investigating the effects of hippocampus-specific MKP-1 knockdown on the development of depressive-like behavior in response to chronic glucocorticoid exposure.

Disclosures: C. Langreck: None. **D. Nerland:** None. **B. Lamb:** None. **L. Semke:** None. **E. Wauson:** None. **V. Duric:** None.

Poster

246. Animal Models for Affective Disorders: Mechanisms II

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 246.22/PP7

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NSERC DG RGPIN-2011-222912

NSERC DG RGPIN-2015-04276

Title: Parallel effects of cyclical corticosterone administration on depression-like behaviour and the downregulation of reelin in the rat hippocampus

Authors: J. ALLEN[1], K. A. LEBEDEVA[1], R. ROMAY-TALLON[1], E. Y. FENTON[3], *H. J. CARUNCHO[2], L. E. KALYNCHUK[1]
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Abstract: Depression is a complex psychiatric disorder characterized by a cyclical disease course with repeated episode relapses. Rats repeatedly treated with corticosterone (CORT) for one cycle of 21 consecutive days exhibit a depression-like phenotype and a downregulation of hippocampal reelin. Reelin is a large glycoprotein that is known to regulate many forms of hippocampal plasticity, such as dendritic spine formation, synaptogenesis, and the acquisition of LTP. In this experiment, we modelled the episodic nature of depression using repeated cycles of CORT exposure, interspersed with periods of recovery. We reasoned that episode relapse in patients with depression may be due to the individual becoming increasingly sensitized to stress, and that exposing rats to repeated cycles of CORT exposure might be a productive way to examine this idea experimentally.
Long-Evans rats received repeated and intermittent CORT administration (three cycles of 21-days of injections at 20mg/kg, each one followed by a 21-day recovery period). Non-repeated behavioral testing of naïve animals, namely the forced swim test (FST), open field test and

sucrose preference test, was employed to examine depression-like behavior. The expression of reelin in the dentate gyrus sub-granular zone (SGZ) was then measured using immunohistochemistry.
CORT produced an increase in depression-like behavior, evidenced by increases in immobility in the FST and decreased sucrose consumption in the sucrose preference test. Immobility scores of rats that received CORT recovered to baseline levels after the first two recovery periods, but not after the third recovery period. Reelin was downregulated in the SGZ by CORT during the first cycle of treatment and after the 21-day recovery period, and this downregulation was more pronounced in cycle three and after the recovery period. We also noted an important relationship between the number of reelin+ cells and immobility time: Increased immobility was negatively correlated with reelin expression.
Our data provide evidence that reelin downregulation is an important neurochemical event underlying depression-like behavior, and that repeated and intermittent CORT treatment can be used as an animal model of recurrent depression.

Disclosures: **J. Allen:** None. **K.A. Lebedeva:** None. **R. Romay-Tallon:** None. **E.Y. Fenton:** None. **H.J. Caruncho:** None. **L.E. Kalynchuk:** None.

Poster

246. Animal Models for Affective Disorders: Mechanisms II

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 246.23/PP8

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIH Grant MH111276

Title: Decrased daytime illumination impairs male copulatory behavior in a diurnal rodent model of Seasonal Affective Disorder

Authors: *L. YAN[1], K. LINNING-DUFFY[1], J. S. LONSTEIN[2]
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Abstract: Seasonal affective disorder (SAD) in humans is associated with the naturally reduced daytime light intensity and light duration that occurs during fall and winter. Previous work from this group using the diurnal Nile grass rat (*Arvicanthis niloticus*) as a model of SAD has shown that reducing day light intensity alone without modifying day-length produces numerous behavioral changes reminiscent of those seen in SAD patients. Specifically, male grass rats housed for 4 weeks under 12:12 hr dim light:dark conditions (DLD) showed higher depressive-like behaviors in sucrose preference and forced swim tests, and higher anxiety-like behaviors in open field and marble burying tests, compared to males housed under 12:12 hr bright light:dark conditions (BLD). The symptoms of SAD are known to extend to some highly motivated

behaviors, including sexual activity, as men with SAD commonly report a lack of libido. To further validate the grass rat model of SAD by extending the range of motivated behaviors affected by low daytime light intensity, we compared masculine copulatory behavior in gonadally intact male grass rats housed for 4 weeks under DLD or BLD conditions. Subjects were observed during 30-min interactions with estrogen- and progesterone-primed receptive female grass rats, and males were sacrificed immediately afterwards for blood and brain collection. Results indicate that compared to male grass rats housed in bright light during the day (i.e., BLD), male grass rats housed in dim daylight (i.e., DLD) were slower to begin sniffing the hormone-primed females and mounted them less frequently. Frequencies of intromissions did not differ significantly between groups. Because previously reported changes in depressive- and anxiety-like behaviors in DLD male grass rats were associated with reduced orexin levels in the brain, we are currently examining orexin levels in the caudal hypothalamus as well as in brain sites associated with male sexual behavior. We will also examine circulating testosterone levels and the expression of androgen and estrogen receptors in these brain sites to determine if diminished level and/or loss of sensitivity to gonadal hormones after DLD housing could underlie the current behavioral findings.

Disclosures: L. Yan: None. **K. Linning-Duffy:** None. **J.S. Lonstein:** None.

Poster

246. Animal Models for Affective Disorders: Mechanisms II

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 246.24/PP9

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: R00 MH102352 (ZRD)

American Foundation for Suicide Prevention (ZRD)

Title: Generation of a humanized mouse model of rs6295: Assessing the direct contribution of a promoter polymorphism to serotonin 1a receptor expression

Authors: A. M. CUNNINGHAM[1], V. GUTZEIT[2], T. SANTOS[3], R. HEN[4,5], *Z. R. DONALDSON[6]
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Abstract: Mood and anxiety disorders represent the most common and costly psychiatric disorders. A better understanding of the factors that contribute to individual differences in

disease susceptibility may help guide treatment options and preventive strategies. Work in humans and animal models supports a role for the serotonin 1A receptor system in modulating mood and anxiety. In mouse models that enable refined manipulations of receptor levels, it has been repeatedly demonstrated that this system is very sensitive; subtle manipulations of receptor levels are behaviorally significant. This finding suggests that naturally-occurring mechanisms that impact human 1A receptor levels may be behaviorally meaningful and may contribute to individual differences in psychiatric risk. One such mechanism that has been implicated in modulating human receptor levels is a common G/C single nucleotide polymorphism (SNP; rs6295) located ~1000 bp upstream of the human serotonin 1a receptor gene (HTR1A) translation start site. In cell culture, the G and C-alleles drive differential reporter expression, and biochemical assays indicate that this may result from a failure of the G-allele to bind various transcription factors, such as NUDR/Deaf1. To further understand the effects of this SNP, we used a novel bacterial artificial chromosome (BAC) approach to investigate the direct contribution of this polymorphism to gene expression and protein levels within the heterogeneous cellular environment of the mammalian brain. This design enabled us to integrate both human alleles at the same genomic location and embed them within the larger regulatory context of ~180 kb of human DNA. We generated four transgenic mouse lines from independent BAC insertion sites. Upon breeding these lines to HTR1A knockout mice, the only source of serotonin 1a receptor in these animals is from the human transgene. Three of four lines exhibit expression of the human HTR1A receptor with the patterns of expression differing across lines. Ongoing work is examining the impact this polymorphism has on mRNA and protein levels. This work has the potential to elucidate a genetic mechanism postulated to contribute to depression risk in humans and provide insight into how a common genetic variant contributes to individual differences in gene expression.

Disclosures: **A.M. Cunningham:** None. **V. Gutzeit:** None. **T. Santos:** None. **R. Hen:** None. **Z.R. Donaldson:** None.

Poster

246. Animal Models for Affective Disorders: Mechanisms II

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 246.25/PP10

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: JST-CREST

KAKENHI-15H04895

KAKENHI-15K09807

Title: MicroRNA profiling of the ventral hippocampus in stress-resilient and stress-susceptible mice

Authors: *S. UCHIDA, H. YAMAGATA, T. SEKI, K. HARA, A. KOBAYASHI, Y. WATANABE
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Abstract: Chronic stress-induced aberrant gene expression in the brain, and subsequent dysfunctional neuronal plasticity, are implicated in the etiology and pathophysiology of mood disorders. Small, regulatory, noncoding microRNAs (miRNAs) may contribute to the development of depression and its treatment. MiRNAs are known to regulate the expression of approximately half of all protein-coding genes in mammals, and are enriched in the brain regions where they play a role in synaptic plasticity. We previously reported that chronic stress-elicited downregulation of miRNA-124 in the hippocampus is associated with depression-like behavior (Higuchi et al., J. Neurosci 2016). To further understand the effects of stress episodes on the gene expression network, we measured miRNAs levels in the ventral hippocampus of two strains of mice, each of which demonstrated different behavioral responses to stress. We subjected C57BL/6J (B6) and DBA/2 (DBA) mice to subchronic social defeat stress (smSDS) episodes. These episodes consisted of brief confrontations with aggressive male mice over a period of 7 days. Non-defeated control mice were not exposed to the aggressive mice. Two days after the last smSDS session, we evaluated their depression-like behaviors using a social interaction test. We found normal sociality of B6 mice exposed to smSDS, as compared to non-defeated control B6 mice. In contrast, DBA mice exposed to smSDS demonstrated a significantly less social interaction than non-defeated DBA mice. Thus, we developed B6 and DBA mice as stress-resilient and stress-susceptible strains, respectively. We then measured miRNA levels within ventral hippocampus tissues in stressed and non-stressed B6 and DBA mice. MiRNA-seq revealed a unique change in miRNA expression between stress-resilient B6 and stress-susceptible DBA mice. This study suggests that miRNA expression, influenced by genetic and environmental factors, may contribute to behavioral responses to stress.

Disclosures: S. Uchida: None. **H. Yamagata:** None. **T. Seki:** None. **K. Hara:** None. **A. Kobayashi:** None. **Y. Watanabe:** None.

Poster

246. Animal Models for Affective Disorders: Mechanisms II

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 246.26/PP11

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NRF-2016RIA2B3015167

Title: Connective tissue growth factor mediates functional lateralization of mPFC in chronic stress

Authors: *J. HONG[1], S. CHAE[3], K. KANG[4], D. KIM[2]
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Abstract: Chronic stress has known to induce functional laterality in medial prefrontal cortex (mPFC); activity of the left mPFC regulates social behavior of stressed mice whereas the right mPFC mediates acquisition of stress. To elucidate the molecular mechanism involved in this functional asymmetry of the mPFC, we performed microarray analysis in mice subjected to chronic social defeat stress. The profiles of gene expression in both mPFC changed after stress compared to non-stressed control. However, the imbalance in the ratio of mRNA expression between left and right hemispheres was only appeared in susceptible mice, while left and right mPFC of resilient mice showed similar level of gene expression. Among candidate genes which can be involved in functional laterality of mPFC, we targeted connective tissue growth factor (CTGF), growth factor involved in wound healing and cell survival in brain. After chronic social defeat stress, the expression level of CTGF was increased in the right mPFC both in susceptible and resilient mice compared to that of non-stressed mice, whereas only resilient mice showed high expression of CTGF in the left mPFC. Knockout of CTGF in the right mPFC prevented inducing social avoidance and corticosterone increase after chronic social defeat stress, whereas overexpression of CTGF in the right mPFC induced depressive-like behavior and increased corticosterone without stress. Overexpression in the left mPFC induced resilient behavior in stressed mice. Our results show that the laterality of gene expression profile is induced by chronic social defeat stress. Among them, CTGF of the right mPFC mediates perception of chronic stress coincidence with the increase of corticosterone, whereas the left mPFC CTGF induces resilience to chronic stress.

Disclosures: **J. Hong:** None. **S. Chae:** None. **K. Kang:** None. **D. Kim:** None.

Poster

246. Animal Models for Affective Disorders: Mechanisms II

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 246.27/PP12

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: Quinnipiac University School of Health Sciences Faculty Scholarship Grants

Brain and Behavior Research Foundation (NARSAD) Young Investigator Award

Quinnipiac University Startup Funds

Title: Increase in activated GABA neurons co-localized with 5HT1aR in the lateral septum of helpless rats is associated with development of stress and depressive-like behavior

Authors: *C. E. ROSE[1], M. SADOWSKI[2], M. MIRRIONE[1]
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Abstract: The lateral septum is a small area in the brain split into three sub-regions, the lateral septum dorsal (LSD), intermediate (LSI), and ventral (LSV), and has been implicated in the regulation of the hypothalamo-pituitary axis as well as regulation in affect and emotion. The lateral septum has been shown to be heavily involved in mood circuitry, specifically depression, although its exact function and circuitry go unknown. We have shown that the lateral septum plays a key role in depressive-like behavior using neuroimaging research, which displayed an increase in metabolic activity in the lateral septum of helpless rats. Literature shows that the lateral septum contains a large amount of GABAergic neurons and 5HT1a receptors. Twenty rats underwent the inescapable foot shock paradigm, ten were categorized as helpless six as resilient, which model depression and resilient behavior in humans, respectively, and the four rats categorized as intermediate were not evaluated. Rat brains were perfused and sliced for immunofluorescence and visualized with confocal microscopy, and were analyzed using MatLab2014 and Image J. Specifically, this research looked to investigate the amount of activated GABAergic neurons, and activated GABAergic neurons co-localized with 5HT1aR between helpless and resilient rats to help support a hypothesized working circuit model of the lateral septum. c-Fos activation in the LSV was significantly higher than the LSD and LSI regardless of helpless or resilient behavior. Overall, c-Fos activation between helpless and resilient animals was not found to be statistically different, in each septum sub-region. However, between helpless rats and resilient rats there was a statistically significant increase of GABAergic neurons, activated GABAergic neurons, and activated GABAergic neurons co-localized with 5HT1aR in helpless rats. Our results demonstrate how essential it is to identify cell type with transcriptional activation markers to accurately evaluate dysfunctional circuitry. Further investigation could help support a hypothesized circuit model, which would give further insight into a stress response pathway that may be malfunctioning in the development of depression.

Disclosures: **C.E. Rose:** None. **M. Sadowski:** None. **M. Mirrione:** None.

Poster

246. Animal Models for Affective Disorders: Mechanisms II

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 246.28/PP13

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: IBS-R001-D1

Title: Functional proteomics of AMPA receptor complex with the mouse model of depressive spectrum disorder

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Abstract: The a-amino-3-hydroxy-5-methyl-4-isoxazole propionate receptor (AMPA-R) is a major excitatory neurotransmitter receptor in the brain. Modulation of AMPA-R trafficking and activity is known as one of the important mechanisms for synaptic plasticity. Proteomic identification and functional characterization of novel components/interactors of the AMPA-R complex are important not only for the elucidation of the mechanisms underlying synaptic plasticity but also for the development of new therapies for the treatment of various brain disorders caused by abnormal synaptic transmission or plasticity. Recently, AMPA-R has been emerged as a neuronal molecule deeply involved in the pathophysiology of depressive spectrum disorder (DSD). By applying the methodologies developed through proteomic analysis of AMPA-R complex, we have analyzed protein composition changes of the AMPA-R complex in the brain of mice with chronic restraint stress, a popular mouse model of DSD. This functional proteomic approach has uncovered a sets of candidate proteins as a molecules related to the pathophysiology of DSD in the hippocampus and cerebral cortex. Behavioral changes of the mice related to DSD were also analyzed through several behavioral tests. Our study could provide novel insights into the pathophysiology of DSD.

Disclosures: M. Kang: None.

Poster

246. Animal Models for Affective Disorders: Mechanisms II

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 246.29/PP14

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: CSIR-BSC0115/miND

Title: piRNA binding proteins PIWIL1 and 2: Potential role in chronic stress-induced neural, neurogenic and behavioral changes in mouse models of depression and anxiety

Authors: *A. KUMAR[1,2], N. KHANDELWAL[1], P. K. SANT[1], S. KOOTAR[1], S. CHAKRAVARTY[3,2]
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Abstract: Mouse PIWI-like proteins viz. MIWI (PIWIL1), MILI (PIWIL2) and MIWI2 (PIWIL4) are known to be involved in the maintenance of germline stem cells. Neural stem/progenitor cells (NSCs/NPCs) in specific neurogenic niches have been reported to undergo proliferation and differentiation resulting inregular turnover of neural cells in adult mammalian brain and the dysregulation in these dynamic events have been associated with stress, depression, anxiety and related affective disorders. Here, we used chronic social defeat model to investigate the potential role of Piwi-like proteins in the regulation of NSCs/NPCs in mouse brain. Transcriptional profiling showed significant down regulation of Piwil1 and upregulation of Piwil2 in dentate gyrus and sub-ventricular zone, respectively, in depressed mouse. We observed similar results in NPCs/NSCs culture derived from defeated mouse brain. Furthermore, our analysis showed significant increase in Piwil1/2 levels with the differentiation of NSCs/NPCs. Manipulating these proteins using Adeno-Associated Virus-2 system affected proliferation and formation of neurospheres. Besides, there is a study indicating altered transcriptionally repressive epigenetic marks H3K9-K27 dimethylation on their promoters in Nucleus Accumbens (NAc) of depressed mice. We therefore, mapped the expression pattern of these proteins in reward circuitry of defeated/depressed mouse and found that these piRNA binding proteins are differentially regulated. Finally, manipulating one of the PIWI-like proteins in NAc and PFC of a healthy mouse could reproduce similar behavior that was caused by chronic defeat stress. Ours is the first study reporting a substantial role of Piwi-like proteins in brain and behavior disorders.

Disclosures: **A. Kumar:** None. **N. Khandelwal:** None. **P.K. Sant:** None. **S. Kootar:** None. **S. Chakravarty:** None.

Poster

246. Animal Models for Affective Disorders: Mechanisms II

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 246.30/PP15

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: R01 MH108562-01A1

5T32MH065215-13

Title: Role of TREK-1 twin pore K+ channel in the photoperiodic programming of the dorsal raphe serotonin neurons

Authors: *M. A. GIANNONI GUZMAN, N. GREEN, D. G. MCMAHON, H. IWAMOTO
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Abstract: Depression is one of the most common mood disorders globally, with more than 16 million cases reported in 2015. Among the different depression disorders, seasonal affective

disorder manifests in people around the same time every year, most commonly in the winter months when light exposure is lowest during the year. Given that light duration (photoperiod) has been shown to have various effects on the serotonergic system, which plays a role in various mood disorders, understanding the relationship of photoperiod changes to the serotonin system and mood disorders may lead to the development of new therapies to treat this and other disorders. Recent work from our laboratory shows that developmental exposure to different day lengths (photoperiods) has lasting changes in the mouse dorsal raphe serotonergic neurons, such as differences in spontaneous firing rate and depression/anxiety related tasks. Previous studies show that raphe neurons from mice raised in long photoperiods exhibit depolarized resting potentials and increased firing rates while long photoperiod mice exhibit reduced depression-like behaviors. The twin pore K+ channel TREK-1 is expressed in raphe neurons and TREK-1 knockout mice present increased 5-HT firing rate and reduced depression-like behaviors, in a similar manner to our long photoperiod mice. Here, we examine the role of TREK-1 on changes to the spontaneous firing rate of raphe serotonergic neurons. We hypothesized that photoperiod-induced depolarization of 5-HT neurons might result from changes in TREK-1 activity and the pharmacological inhibition of these channels would elicit a significant increase in the firing rate of raphe neurons from short photoperiod and equinox mice, while neurons from long photoperiod mice which phenocopy TREK-1 knockouts would be unaffected. To test this hypothesis, we performed multielectrode array recordings of dorsal raphe neuron slices from short, equinox and long photoperiod mice exposed to different doses of the selective TREK-1 inhibitor Amlodipine. Consistent with our hypothesis, pharmacological inhibition of these channels increases the firing rate of neurons from short, and equinox mice increase in a dose-dependent manner, while the firing rate of neurons from long photoperiod mice remained unchanged. Further analysis indicated that the increase in the short photoperiod mice was significantly lower than in the Equinox cohort, suggesting a lack of plasticity in the neurons in the Short and Long photoperiod groups. Taken together, these results show that changes in TREK-1 play a role in the photoperiodic programming of 5-HT neurons in the dorsal raphe.

Disclosures: M.A. Giannoni Guzman: None. **N. Green:** None. **D.G. McMahon:** None. **H. Iwamoto:** None.

Poster

247. Animal Models of Trauma, Stress, and Anxiety II

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 247.01/PP16

Topic: G.06. Post-traumatic Stress Disorder

Support: NARSAD Young Investigator Grant

NIH P20GM103449

NIH R15DA041618

NIH R01DA037927

NIH P50DA039841

Title: Genome-wide mapping of conditioned fear in the diversity outbred mouse population

Authors: K. E. WILSON[1], D. GATTI[2], T. WILCOX[2], E. F. BUSCH[3], S. FLYNN[3], S. KASPAREK[1], D. KREUZMAN[1], B. MANSKY[1], S. MASNEUF[3], E. SAGALYN[3], K. SHARIF[1], D. TATERRA[1], W. TAYLOR[1], M. THOMAS[1], E. J. CHESLER[2], A. HOLMES[3], *C. C. PARKER[1]
[1]Dept. of Psychology and Program in Neurosci., Middlebury Col., Middlebury, VT; [2]The Jackson Lab., Bar Harbor, ME; [3]Lab. of Behavioral and Genomic Neurosci., NIAAA, Bethesda, MD

Abstract: Mice offer a powerful tool for elucidating the genetic basis of traits relevant to anxiety disorders; yet conventional experimental crosses have only identified large chromosomal regions rather than specific genes. Recent advances have led to genetically diverse, highly recombinant mouse populations. We have taken advantage of the newly developed Diversity Outbred (DO) mice to map narrow QTLs associated with conditioned fear (CF). We phenotyped 587 DO mice for the acquisition, extinction, and renewal of CF using a three-day paradigm. We genotyped a subset of these mice at ~150k markers across the genome and performed high precision QTL mapping using the R program DOQTL. A one-way repeated measures ANOVA found a significant increase in freezing following each tone-shock pairing during acquisition, ($F_{1.8, 892.8}$ = 799.5, $p < 0.0001$; $\eta_p^2 = 0.612$), demonstrating the ability to learn to associate the tone and foot-shock. Freezing behavior in response to the tone significantly decreased across trial-blocks during extinction training ($F_{6.2, 3619.4} = 145.6$, $p < 0.0001$; $\eta_p^2 = 0.199$) suggesting mice were able to successfully extinguish the fearful association over time. On the renewal test, mice displayed less freezing relative to the first trial-block of extinction training ($t(586) = 13.7$, $p < 0.0001$). QTL analyses identified numerous suggestive and significant QTLs associated with CF on chromosomes 2, 3, 7, and 12. With the inclusion of RNA-Seq we will be able to apply a systems genetic strategy to construct the network of correlations that exist between DNA sequence, gene expression values and CF.

Disclosures: K.E. Wilson: None. **D. Gatti:** None. **T. Wilcox:** None. **E.F. Busch:** None. **S. Flynn:** None. **S. Kasparek:** None. **D. Kreuzman:** None. **B. Mansky:** None. **S. Masneuf:** None. **E. Sagalyn:** None. **K. Sharif:** None. **D. Taterra:** None. **W. Taylor:** None. **M. Thomas:** None. **E.J. Chesler:** None. **A. Holmes:** None. **C.C. Parker:** None.

Poster

247. Animal Models of Trauma, Stress, and Anxiety II

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 247.02/PP17

Topic: G.06. Post-traumatic Stress Disorder

Title: Fluoxetine does not prevent increased voluntary ethanol consumption in a predator-based psychosocial stress model of PTSD

Authors: *K. L. ROBINSON, R. M. ROSE, B. A. KOHLS, M. E. HEIKKILA, B. J. HERTENSTEIN, K. E. MUCHER, M. R. HUNTLEY, P. A. D'ALESSIO, W. C. MCCABE, P. R. ZOLADZ
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Abstract: We previously reported that, following exposure to a predator-based psychosocial stress model of PTSD, chronically stressed rats voluntarily consumed significantly more ethanol than controls. Here, we have tested whether chronic fluoxetine treatment would prevent these effects. Prior to the stress manipulations, male Sprague-Dawley rats were given access to either ethanol (10% EtOH + 1% sucrose) or water (1% sucrose) in 12-hr cycles (1930-0730 every night) using a two bottle, free choice test for 20 days. Beginning on the day after this ethanol pre-exposure period, rats were exposed to psychosocial stress or control conditions for 31 days. Stressed rats were given two cat exposures, separated by 10 days, and subjected to daily social instability throughout the paradigm. Control rats were handled daily. One group of stressed rats was also given fluoxetine (140 mg/l) in their drinking water beginning on Day 2 of the stress paradigm and ending on the final day of the stress paradigm (i.e., Day 31). Beginning on Day 32, rats were again given access to either ethanol or water for 20 days, as per the methods described above. The results showed that, in this paradigm, stressed rats consumed significantly more ethanol than control rats following the chronic stress manipulation. Moreover, chronic prophylactic fluoxetine treatment was ineffective at preventing the increased ethanol consumption observed in stressed rats. These findings provide further support that our model of PTSD may be used to further examine the neurobiological mechanisms associated with stress-induced changes in ethanol consumption. They also suggest that chronic stress-induced changes in ethanol intake, at least as a result of this paradigm, are not preventable via a common SSRI.

Disclosures: K.L. Robinson: None. **R.M. Rose:** None. **B.A. Kohls:** None. **M.E. Heikkila:** None. **B.J. Hertenstein:** None. **K.E. Mucher:** None. **M.R. Huntley:** None. **P.A. D'Alessio:** None. **W.C. McCabe:** None. **P.R. Zoladz:** None.

Poster

247. Animal Models of Trauma, Stress, and Anxiety II

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 247.03/PP18

Topic: G.06. Post-traumatic Stress Disorder

Title: Toll-like receptor 4 (TLR4) activation alters anxiety-like behavior in an animal model of post-traumatic stress disorder (PTSD)

Authors: *S. J. NIETO, C. QUAVE, T. A. KOSTEN
Univ. of Houston, Houston, TX

Abstract: There is a growing body of evidence demonstrating the role of inflammation in stress-related disorders. Toll-like receptor 4 (TLR4) is one receptor type involved in innate immune responses to stress and may play a role in some aspects of these disorders. The goal of this study was to determine if TLR4 activation factored into behavioral changes seen in an animal model of post-traumatic stress disorder (PTSD). To test this idea, we examined male and female rats that were either TLR4 gene knockout (KO; n=18) or wild type (WT) controls (n=18). We obtained baseline behavioral measures on three assays of anxiety- and depressive-like behaviors: 1) elevated plus maze (EPM); 2) open field test (OFT); and 3) two-bottle choice sucrose preference test (SPT). We then subjected the rats to a stressor that induces a PTSD-like condition - exposure to predator odor. This exposure was conducted using a conditioned place aversion (CPA) protocol. Rats were confined to one side of a 2-compartment apparatus for 15-min during the morning. That evening, rats were confined to the other distinct compartment and exposed to predator odor (bobcat urine) for 15 minutes. We performed CPA testing 24 hours post-exposure and again at 10 days post-exposure. In these tests, rats had access to both compartments and time spent on the odor-paired side over the 15-min test was tabulated. Rats were re-tested on EPM, OFT, and SPT within 48 hours of predator odor exposure. We observed no group or sex differences in aversion behavior in the CPA tests. Male KOs exhibited heightened anxiety-like behaviors as measured by EPM and OFT compared to male WTs. Female KOs displayed increased anxiety-like behavior on OFT but not on EPM compared to female WTs. Males of both groups showed decreased sucrose preference post-exposure, with male KOs exhibiting increases in stress-induced polydipsia compared to WTs. No effects on sucrose preference were seen in females of either group. These data indicate that TLR4 activation may play a protective role in psychological functioning following exposure to a traumatic stressor.

Disclosures: S.J. Nieto: None. **C. Quave:** None. **T.A. Kosten:** None.

Poster

247. Animal Models of Trauma, Stress, and Anxiety II

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 247.04/PP19

Topic: G.06. Post-traumatic Stress Disorder

Support: NIH Grant MH099345

NIH Grant MH107615

Title: Ketamine metabolite (2R,6R)-HNK reverses behavioral despair symptoms produced by adolescent trauma

Authors: *G. I. ELMER[1], C. L. MAYO[1], P. ZANOS[2], T. D. GOULD[3]
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Abstract: Early life trauma dramatically increases the risk of developing major depressive disorder, generalized anxiety, obsessive-compulsive disorder, substance abuse and psychotic disorders. In addition, early trauma can significantly alter symptom complexity and treatment response within a diagnostic category. In particular, early life trauma markedly decreases adult treatment response to antidepressants. Thus, novel acting antidepressants are required to treat childhood trauma-induced MDD. Recent studies suggest that ketamine is a rapid acting antidepressant and that a metabolite, (2*R*,6*R*)-hydroxynorketamine (HNK), exerts fast- and long-lasting antidepressant effects without ketamine's adverse side-effect profile. The purpose of this study was two-fold: 1) Develop a novel mouse adolescent trauma model which manifests enduring effects later in life, and 2) Determine if the ketamine metabolite (2*R*,6*R*)-HNK would attenuate a behavioral despair phenotype (learned helplessness) induced by adolescent trauma. Male and female C57BL/6J mice were exposed to a live snake or control conditions at post-natal (PND) days 31, 46 and 61. At a minimum of 14 days following the last exposure, mice received inescapable shocks followed the next day by a session with available escape options to assess the enduring consequences of trauma-exposure. One week following testing, mice that manifested enduring escape deficits (learned helplessness; LH) were treated with vehicle or (2*R*,6*R*)-HNK (20 mg/kg, i.p.), 24hr prior to retesting in the LH test. Two key results were found, 1) a significantly greater number of mice developed LH if they had a trauma history and 2) the LH phenotype was reversed in mice treated with (2*R*,6*R*)-HNK. Male and female mice did not differ in the response to trauma exposure or (2*R*,6*R*)-HNK treatment. Early life trauma is established as a pervasive risk factor for the development of mental illness. The trauma model developed in this study provides an opportunity to improve our understanding of the neurobiological substrates impacted by trauma and improve treatment strategies. The demonstrated therapeutic efficacy of

(2*R*,6*R*)-HNK in this model may point to novel therapeutic intervention in a treatment- resistant population.

Disclosures: G.I. Elmer: None. **C.L. Mayo:** None. **P. Zanos:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); PZ is listed as co-inventors on a patent application for the use of ketamine metabolites, (2R,6R)-hydroxynorketamine in the treatment of depression, anxiety, anhedonia, suicidal ideation and. **T.D. Gould:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); TDG is listed as co-inventor on a patent application for the use of ketamine metabolites, (2R,6R)-hydroxynorketamine in the treatment of depression, anxiety, anhedonia, suicidal ideation and.

Poster

247. Animal Models of Trauma, Stress, and Anxiety II

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 247.05/PP20

Topic: G.06. Post-traumatic Stress Disorder

Support: VA Merit Review Grant

Title: Gene expression based measures of chronic stress exposure

Authors: *D. MCKINNON[1,4], M. L. JACOBSON[2], B. ROSATI[3]
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Abstract: The risk of developing post-traumatic stress disorder (PTSD) in response to traumatic stress exposure is thought to be dose-dependent, increasing with both the severity of the traumatic stressors as well as with cumulative exposure to multiple traumatic stressors. The gene regulatory network integrates a large number of different signals and the expression of at least some genes is likely to change in parallel with the degree of exposure to chronic stress. In principle, a relatively small number of genes could be used to create a stress-sensitive gene expression (SSGE) index to measure chronic stress exposure, analogous to the way in which some stock market indexes can capture the mood of the market by sampling only a small subset of the most characteristic stocks.
We tested this idea using male rats that were exposed to one of six different three-week long stress paradigms: social isolation (SI), social defeat (SD), grid housing (GH), social defeat with isolation (ID), chronic variable stress (CVS) and chronic shock (CS). Initially, RNA sequencing was used to measure changes in the transcriptome of the adrenal gland following exposure to the two most intense stress protocols, CVS and CS. Candidate genes from this analysis were tested using real-time PCR in order to identify a small number of genes that were consistently

responsive to stress exposure in these two models and that also had low variability across multiple replicates. The selected genes were used to construct a stress-sensitive gene expression index that was then validated across all six stress models. Although these stress protocols differed markedly in the intensity and nature of the stressors that were used, the index reliably detected every type of stress exposure and quantitated differences in chronic stress exposure in a graded fashion.
We conclude that a sensitive and robust measure of chronic stress exposure can be constructed from gene expression data. Gene expression indexes may prove to be a useful adjunct to behavioral and hormonal measures of stress exposure since they are relatively inexpensive to implement and many steps can be automated so that they can be scaled for large numbers of animals. The results support the hypothesis, derived from psychological studies of chronic traumatic stress exposure in humans, that the response to traumatic stress exposure is dose-dependent with the probability of developing symptoms increasing with increasing 'dose' of stress exposure. In this model no individual has an absolute resilience, only relative resilience that can be overcome with a sufficiently high dose of traumatic stress exposure.

Disclosures: D. McKinnon: None. **M.L. Jacobson:** None. **B. Rosati:** None.

Poster

247. Animal Models of Trauma, Stress, and Anxiety II

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 247.06/PP21

Topic: G.06. Post-traumatic Stress Disorder

Support: CNPq 141692/2015-4

CAPES

AFIP

Title: A quest for the neurobiological underpinnings of PTSD-like symptoms in traumatic stress susceptible rats

Authors: *M. B. L. CAREAGA[1], C. E. N. GIRARDI[2], D. SUCHECKI[1]
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Abstract: Exposure to highly stressful situations may lead, in some individuals, to long-lasting behavioral and neurobiological changes, characterizing Posttraumatic Stress Disorder (PTSD). Since not all people exposed to traumatic events develop PTSD, individual variability in response to stress is an important aspect that preclinical models should not neglect. An important component of PTSD is fear conditioning, a learning process related to re-experience and avoidance symptoms of this disorder. Thus, an animal model based on fear conditioning enabling

the distinction of behavioral emotional responses may be suitable to study PTSD modifications. Using a traumatic stress protocol in male rats based on contextual fear conditioning (CFC) the aim of the present study was to investigate long-term phenotypical and neurobiological changes in stress-exposed animals. During the traumatic stress session, stress exposed animals (N = 30) were allowed to explore the context for 2 min and then 1 foot shock (2 mA; 1 s duration) was delivered. Freezing response was assessed 15 days later and this response allowed for the separation of animals in stress-susceptible (scores ≥ 65%; N = 8) and stress-resilient (scores ≤ 21.67%; N = 9) groups. Animals exposed only to the context (N = 15) or to the foot shock, without context exploration (N = 15), were used as control groups. Higher context fear response in stress-susceptible rats lasted for fifty days after the stressful event. This group also displayed a greater fear reaction to an unknown and potentially threatening stimulus (i.e. a loud sound), suggesting a sensitization of fear response. Moreover, susceptible animals exhibited higher immobility time and reduced ambulation in the closed arms of the elevated plus maze, indicating impairment of exploratory behavior. Stress-resilient animals, on the contrary, did not show any remarkable behavioral differences from control groups. The behavioral data suggest that the traumatic stress protocol induced a set of behavioral modifications that resemble important features of PTSD, in vulnerable animals. Interestingly, a preliminary analysis of Fos expression in the hippocampus, amygdala and paraventricular nucleus of the thalamus after the first exposure to the context did not reveal any difference among the groups. Ongoing analysis of Fos expression in fear expression-related brain areas, such as medial pre-frontal cortex and periaqueductal gray, 15, 29 and 50 days after the exposure to traumatic stress may provide the neurobiological underpinnings for these behavioral alterations.

Disclosures: **M.B.L. Careaga:** None. **C.E.N. Girardi:** None. **D. Suchecki:** None.

Poster

247. Animal Models of Trauma, Stress, and Anxiety II

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 247.07/PP22

Topic: G.06. Post-traumatic Stress Disorder

Support: Veterans Association Merit Review Award

Title: Open hardware/open source acoustic startle device

Authors: *M. L. JACOBSON[1], D. MCKINNON[3,2], B. ROSATI[2]
[1]Psychology and Integrative Neurosci., [2]Neurobio. and Behavior, Stony Brook Univ., Stony Brook, NY; [3]Veterans Affairs Med. Ctr., Northport, NY

Abstract: We have developed a low cost open hardware acoustic startle device complemented by open source software. Acoustic startle response, pre-pulse inhibition, startle habituation and

sensitization are robust, reproducible and easy to administer measures of psychological and physiological function. The acoustic startle response is a defensive reflex consisting of a rapid sequence of flexor motor movements elicited by presentation of an abrupt intense acoustic stimulus. The startle response is a popular measure of fear and anxiety, and is translatable across many species, including rats and mice. Although startle equipment is commercially available, the relatively high cost of the apparatus and software can limit the number of animals that can be tested in parallel. The long test times (typically 20-30 minutes) make it time consuming to test large numbers of animals and introduces problems of circadian variation. This open source device eliminates this problem as well as having the advantage of being very flexible, allowing easy modification to accommodate novel experimental paradigms.

Construction of the device uses techniques popularized by the Maker Movement. In particular, the device uses a high performance low-cost microcontroller linked to an audio board to output the startle stimulus and record behavioral responses. The same software, a modified C^{++} environment, that is used to program Arduino boards is used to program this device. A small custom circuit board is used for signal conditioning. Design files for this board are available and it can be fabricated inexpensively using on-line suppliers. Another trope of the Maker movement is the repurposing of commonly available objects. A low cost cabinet from IKEA was used to house the apparatus and several readily available items were repurposed to construct the test apparatus. The complete device can be built using a small number of tools that can be found in any university workshop.

Software for the control of multiple devices was written in Python. This software, which is available for download, can be used to calibrate the device, run different experimental protocols, and analyze the resultant data. Different test protocols can be easily modified and managed. Data is represented graphically in real time, is accessible for quick view summary directly following test cessation, and can be exported in a format compatible with Excel. Offline batch processing of data files is also possible.

The apparatus and software, which have been tested over several years, matches or exceeds the performance of equivalent commercial products, while retaining key advantages of open source software and hardware.

Disclosures: **M.L. Jacobson:** None. **D. McKinnon:** None. **B. Rosati:** None.

Poster

247. Animal Models of Trauma, Stress, and Anxiety II

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 247.08/PP23

Topic: G.06. Post-traumatic Stress Disorder

Support: NIMH RO1MH62122

NIDA DA005010

NIMH F31MH185207-02

Title: Chronic opiate administration produces a long-term potentiation of fear and anxiety in a model of post-traumatic stress disorder

Authors: *Z. T. PENNINGTON[1], K. D. LI[1], C. J. EVANS[2], W. M. WALWYN[2], M. S. FANSELOW[1,2]
[1]Psychology, [2]Psychiatry & Biobehavioral Sci., UCLA, Los Angeles, CA

Abstract: Fear and anxiety disorders are highly comorbid with substance use disorders. Although traditional views on this relationship have proposed that substance use ensues in an effort to reduce fear and anxiety (i.e. self-medication), little research has examined the influence chronic drug use has on fear and anxiety. We assessed the impact of a chronic escalating regimen of morphine and withdrawal on fear in a mouse model of post-traumatic stress disorder: stress-enhanced fear learning (SEFL). Mice that received morphine exposure and withdrawal 1 week prior to a 10-shock trauma session displayed heightened freezing during the trauma session, without displaying differences in shock reactivity. When subsequently given a mild aversive stimulus, morphine treated animals showed a robust sensitization of the enhanced fear learning that is typically seen in traumatized animals. However, fear was not elevated in animals given morphine that had not experienced trauma. These results suggest that the potentiation of stress systems by trauma is exacerbated by prior opiate exposure. In a separate experiment, we showed that when morphine is given after the traumatic stressor, it also has the ability to augment fear responses, indicating that opiate exposure isn't merely augmenting trauma sensitivity. Lastly, morphine treated animals expressed increased anxiety in an elevated plus maze (a test that does not involve a painful stimulus), and did not show altered reactivity to a range of shock amplitudes, negating the possibility that the previous effects on fear behaviors were the consequence of heightened pain sensitivity. To our knowledge, this is the first demonstration in which chronic drug exposure is able to produce a lasting enhancement of fear systems, and may be of relevance to the comorbidity between fear and substance use disorders.

Disclosures: Z.T. Pennington: None. **K.D. Li:** None. **C.J. Evans:** None. **W.M. Walwyn:** None. **M.S. Fanselow:** 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.; Neurovation Labs, Inc., Teva Pharmaceuticals.

Poster

247. Animal Models of Trauma, Stress, and Anxiety II

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 247.09/PP24

Topic: G.06. Post-traumatic Stress Disorder

Support: NIH Grant F32NS098694 (AH)

NIH Grant R01MH062122 (MSF)

NIH Grant R01MH062122 (DH, CG)

Depression Grant Challenge Fellowship Fund (MSF, AH)

UCLA Brain Injury Research Center

UCLA Easton Labs for Brain Injury

UCLA Steve Tisch BrainSPORT

Title: Traumatic brain injury leads to long term enhanced auditory fear learning and stimulus generalization

Authors: *A. N. HOFFMAN[1,2], E. HSIEH[1], N. CHAVDA[1], J. LAM[1], D. A. HOVDA[2], C. C. GIZA[2], M. S. FANSELOW[1]
[1]Psychology, [2]Neurosurg., UCLA, Los Angeles, CA

Abstract: Cognitive impairments and emotional liability are common long-term consequences of Traumatic Brain Injury (TBI). Increasing prevalence of comorbid TBI and Post-Traumatic Stress Disorder (PTSD) emphasizes an urgency for a better understanding of how injury affects interactions between sensory, cognitive, and emotional systems that may underlie maladaptive responding. We have previously shown changes in auditory-emotional network activity and enhanced contextual fear learning following white noise fear conditioning early after TBI, prior to the resolution of typical physical symptoms. In the current study, we asked whether TBI would have chronic effects on auditory fear learning and responses to novel stimuli. Four weeks following either mild-moderate lateral fluid percussion injury (FPI) or sham surgery, adult male rats were fear conditioned to either white noise or unsignaled shocks. All groups were tested for contextual fear memory and context extinction then subsequently tested for fear responses to either pure tones or white noise auditory stimulus trials in a new context. While FPI did not impact freezing across acquisition trials, FPI led to increased shock reactivity if white noise preceded the shock. As expected, unsignaled conditioned groups had greater contextual fear relative to noise-shock groups. However, FPI noise-shock animals froze more to the context than respective shams, consistent with our previous findings. During white noise cue testing, FPI noise-shock rats had increased freezing on the first trial of white noise cue testing compared to respective shams. Interestingly, when presented with novel pure tones FPI noise-shock animals displayed robust fear to the novel, untrained auditory stimulus compared to noise-shock shams. These data indicate an injury-induced increase in auditory stimulus generalization, and a unique phenotype chronically following diffuse TBI. This novel finding illustrates both a cognitive impairment and increased fear in the chronic phase after TBI, where stimulus generalization may underlie maladaptive fear and hyperarousal common to comorbid TBI-PTSD.

Disclosures: **A.N. Hoffman:** None. **E. Hsieh:** None. **N. Chavda:** None. **J. Lam:** None. **D.A. Hovda:** None. **C.C. Giza:** None. **M.S. Fanselow:** None.

Poster

247. Animal Models of Trauma, Stress, and Anxiety II

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 247.10/PP25

Topic: G.06. Post-traumatic Stress Disorder

Support: F32 MH107212-01A1

R01 GM118801

R01 MH062122

R21NS102761

Depression Grand Challenge Fellowship Fund

NSF GRFP

Title: Acute traumatic stress in a rodent model of PTSD (SEFL) produces fear sensitization, increased anxiety and a long-lasting increase in GLUA1 protein levels in the basolateral amygdala

Authors: *A. K. RAJBHANDARI[1], S. T. GONZALEZ[1], J. PERUSINI[3], V. MAKHIJANI[4], Y. HUANG[5], A. N. HOFFMAN[1], J. WASCHEK[2], M. S. FANSELOW[1]
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Abstract: Post-traumatic stress disorder (PTSD) involves inappropriate expression of fear after exposure to life-threatening traumatic experiences. Our lab has developed a model of non-associative fear sensitization in rats that examines how acute exposure to a “traumatic” stressor can affect future fear learning and we have termed this stress-enhanced fear learning (SEFL). Here we further explore the SEFL phenomenon in rats and also generalize the work to mice. The traumatic stress procedure involves placing a rodent in a conditioning chamber and giving it unsignaled shocks (15 in rats, 10 in mice) randomly distributed over a single session (90 min in rats, 60 min in mice). On day 2, the rodents are placed in a novel conditioning context where they receive a single shock. Subsequently, on day 3 they are placed back in the same context as in day 2 and tested for changes in levels of freezing. Animals that previously received the stress display enhanced levels of freezing on the test day compared to animals that received no shocks

on the first day, as well as increased anxiety-related but not depression-related behaviors (mice). We also show that the stress procedure produces a long-lasting enhancement in the level of AMPA receptor subunit, GLUA1 in the basolateral portion (BLA) of the amygdala in the rats. Mice show a similar enhancement in GLUA1 level after stress that is specific to the BLA but not hippocampus. These findings suggest that alterations in GLUA1 signaling could be a potential underlying neural mechanism of the SEFL phenotype. Hence, GluA1 containing AMPA receptors may be a potential novel target for developing therapeutics for anxiety-related disorders such as PTSD.

Disclosures: A.K. Rajbhandari: None. **S.T. Gonzalez:** None. **J. Perusini:** Other; Neurovation Labs. **V. Makhijani:** None. **Y. Huang:** None. **A.N. Hoffman:** None. **J. Waschek:** None. **M.S. Fanselow:** Other; Neurovation Labs, Teva Pharmaceuticals.

Poster

247. Animal Models of Trauma, Stress, and Anxiety II

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 247.11/PP26

Topic: G.06. Post-traumatic Stress Disorder

Support: NIH Grant MH101729.

University of Cincinnati NIH-awarded Training Program Neuroendocrinology of Homeostasis T32 DK059803

Title: Chronic stress during adolescence evokes a resilient phenotype after single prolonged stress: Implications for PTSD study

Authors: *E. M. COTELLA, P. LEMEN, N. BEDEL, J. HERMAN
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Abstract: Posttraumatic stress disorder (PTSD) is a psychiatric condition that can develop after an individual is exposed to traumatic experience. While the probability of facing a trauma during life is 75% in the USA, the prevalence of PTSD is about 6.8 %, suggesting that mechanisms exist to confer resilience to some individuals, whereas others are susceptible to developing the condition. We hypothesized that chronic stress during adolescent life may modulate risk. In these studies, we used chronic variable stress (CVS) during adolescence to model early life adversity in the rat. Rats of both sexes were subjected to CVS for 2-weeks starting at PND44. Stressors were presented randomly twice daily (cage vibration, cold water swim, warm water swim, cold room, hypoxia, or restraint) and every 2-3 days they had overnight stressors (single housing or overcrowding). Control animals were only handled for cage cleaning and body weight measurement. At 85 days of age, we exposed half of the animals to single-prolonged stress (SPS)

(restraint for 2 hours, followed by 20 minutes of swim, followed by exposure to ether until loss of consciousness), a regimen that is commonly used to generate PTSD-like symptoms in rats. Performance in an auditory-cued fear conditioning paradigm was tested one week following SPS. There were no differences in acquisition of freezing in response to the pairing of the shock to the auditory tone in any group or sex. During extinction, SPS males increased freezing behavior during all extinction sessions ($p<0.05$), which was prevented by the previous exposure to stress during adolescence ($p<0.05$). In females, the first day of extinction, all the stressed groups had higher retrieval of the behavior ($p<0.05$). During recall, CVS and SPS males showed higher incidence of freezing ($p<0.05$), whereas males exposed to both CVS and SPS were similar to controls. Both males and females SPS ($p<0.05$) rats had increased freezing during the reinstatement session, and this was prevented by previous exposure to CVS ($p<0.05$ respectively). In summary, previous history of stress makes the animals resilient to the effects of SPS later in life, suggesting that some of the physiological adaptations during adolescent stress could prevent the effects of PTSD in adulthood. The differences between sexes in the effects of adolescent CVS preventing SPS effects would be suggest that the mechanisms for adaptations to stress during development are different in males and females.

Disclosures: E.M. Cotella: None. **P. Lemen:** None. **N. Bedel:** None. **J. Herman:** None.

Poster

247. Animal Models of Trauma, Stress, and Anxiety II

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 247.12/PP27

Topic: G.06. Post-traumatic Stress Disorder

Support: Supported by grant W81XWH-16-1-0016 from US Army MOMRP

Title: Progression of changes in anxiety and gene expression in locus coeruleus in rat PTSD model

Authors: *L. I. SEROVA, N. MOLINA, E. L. SABBAN
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Abstract: Following exposure to traumatic stress, PTSD is diagnosed when symptoms are sustained for a considerable time even get progressively worse. The locus coeruleus (LC) the major noradrenergic (NE) nucleus in the brain is rapidly activated by stress providing adaptive responses for survival from life-threatening situations. Dysregulation of the central noradrenergic system including norepinephrine transporter (NET) is a core feature of PTSD. In the rat model of PTSD, seven days after exposure to single prolonged stress (SPS) stressors we found, among other impairments, sustained dysregulation in LC/NE system (Sabban et al., JNC, 2015, 135:975-986). Here we analyzed progression of SPS-elicited anxiety behavior and changes in

gene expression in the LC/NE system of male SD rats at various times 1, 2 and 4 weeks after exposure to SPS stressors. Several characteristics of anxiety behavior tested on the elevated plus maze were significantly higher two weeks compared to one week following the SPS exposure. For example, 61% of rats (27/44) did not enter the open arms after two weeks compared to 25% (12/47) one week after the SPS stressors. While shortly after the SPS, in LC/NE system tyrosine hydroxylase and dopamine β-hydroxylase mRNA levels were elevated (Serova et. al., Neuroscience, 2013, 236:278-312) with longer time there were no changes in their gene expression. However, divergent changes in NET mRNA levels (about fourfold increase or twofold decrease) were detected at 2 and 4 weeks. Corticotrophin releasing factor receptor one (CRFR1) mRNA levels in SPS group were above unstressed controls at all times examined. Significant time-dependent changes were observed in the LC/neuropeptide Y (NPY) system. While unchanged earlier, NPY mRNA levels had declined about 40% at 2 and 4 weeks. Elevation of mRNA for Y1 receptor was evident only at 2 weeks. At 4 weeks Y1 mRNA was back to basal and Y5 mRNA, not previously change, displayed robust 5-fold increase. Y2 receptor mRNA was significantly decreased during the entire time period. The results revealed that with longer time after SPS without treatment, there is progressively increase of anxiety. In the LC, although there were no long-term changes in mRNA for NE-biosynthetic enzymes, NET mRNA levels were altered. There were sustained elevation of CRFR1 and reduction in Y2 mRNA levels. With longer time, new impairments in gene expression of NPY and Y1 and Y5 receptors appeared. These multiple maladaptive changes in the LC gene expression might relate to impairments in arousal, memory acquisition, attention, vigilance and reactions to stress which characterize PTSD patients.

Disclosures: L.I. Serova: None. **N. Molina:** None. **E.L. Sabban:** None.

Poster

247. Animal Models of Trauma, Stress, and Anxiety II

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 247.13/PP28

Topic: G.06. Post-traumatic Stress Disorder

Support: W81XWH-16-1-0016 from US Army MOMRP

Title: Cardiovascular responses to intranasal neuropeptide Y in SPS rodent PTSD model

Authors: *E. L. SABBAN[1], R. CAMP[1], C. STIER[2], L. SEROVA[1], J. MCCLOSKEY[1], J. EDWARDS[3]
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Abstract: Neuropeptide Y (NPY) is associated with resilience to stress triggered neuropsychiatric diseases, such as PTSD. We previously demonstrated that non-invasive delivery

of NPY to the brain by single intranasal infusion shortly before or right after traumatic stress in the single prolonged stress (SPS) rodent PTSD model prevented development of a broad range of behavioral, neuroendocrine, and molecular impairments. However, it is unclear how intranasal NPY might have affected cardiovascular responses to the stress. In the periphery NPY, co-released with norepinephrine during sympathetic excitation, enhances vasoconstriction. When centrally administered, there are conflicting reports on its cardiovascular effects while few studies have included response to stress. Here, we assessed effects of intranasal delivery of NPY to brain in the presence and absence of SPS. Telemetric probes (TA11PA-C40, Data Sciences) were implanted in male Sprague Dawley rats. After recovery from surgery, when basal parameters were established, animals were subjected to SPS stressors and given intranasal infusion of either 150 µg NPY (n=6) or vehicle (n=5). Rats were returned to receivers and data measured every 2 min for 2 hrs and every 10 min for 6 days afterwards. SPS stressors triggered rapid rise in mean arterial pressure (MAP) and heart rate (HR), which remained near maximal for 1 hr afterwards. MAP reached peak increases of 30 and 29 mmHg over baseline in NPY- and vehicle-treated animals respectively. NPY significantly mitigated the increase in HR relative to vehicle. MAP returned to control levels within 2 hrs, but HR remained elevated for 6 hrs in both groups. In subsequent days following SPS stressors, MAP was near basal levels, as was HR in the light phase. However, during the dark (normally active) phase, HR and locomotor activity were reduced in both groups and had not returned to basal values on the 6th night after the SPS stressors. When given in the absence of SPS infusions of vehicle or NPY under light isoflurane anesthesia led to similar HR and MAP responses. Echocardiography assessed effects of intranasal NPY on HR, stroke volume (*S*V), and cardiac output (Q) in unstressed controls as well as in animals exposed to SPS. While SPS reduced SV and Q, there were no differences between groups given intranasal NPY or vehicle under any of these conditions. Overall, the finding that intranasal NPY did not have a major impact on cardiovascular functions is encouraging from a translational point of view. It indicates that administration of intranasal NPY shortly after trauma would not further increase the stress-elicited elevation in MAP and HR and might actually mitigate the initial rise in HR.

Disclosures: E.L. Sabban: None. **R. Camp:** None. **C. Stier:** None. **L. Serova:** None. **J. Mccloskey:** None. **J. Edwards:** None.

Poster

247. Animal Models of Trauma, Stress, and Anxiety II

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 247.14/PP29

Topic: G.06. Post-traumatic Stress Disorder

Support: “MOST 105-2410-H-007-026 -” (Taiwan)

Title: Pre-extinction activation of the orbitofrontal cortex impairs fear extinction learning in rats

Authors: *Y.-H. CHANG, C.-H. CHANG
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Abstract: Anxiety disorders, such as post-traumatic stress disorder (PTSD), panic disorder, phobia, and obsessive-compulsive disorder (OCD), are noxious disorders that seriously lower the qualities of patients' life. Comorbidity among these anxiety disorders has been reported in several clinical researches. Numerous studies have revealed the high possibility of comorbid development of PTSD and OCD. To extend the knowledge regarding this relationship, we sought to establish the fundamental neural circuitry underlying this. As hyper-activation of the orbitofrontal cortex (OFC) is a common trait seen among OCD patients, we hypothesized that activation of the OFC would interfere with extinction of fear memories, which is widely accepted that failure of extinction may lead to PTSD. Behaving rats were trained with Pavlovian fear conditioning and extinction paradigm. Animals were conditioned with 5 tone-footshock pairings during conditioning on Day 1, then extinguished and tested with 45 tones on Day 2 and Day 3, respectively. The OFC was activated with N-Methyl-D-aspartic acid (NMDA) or vehicle (VEH) before the animals underwent the extinction (EXT) or exposure (NoEXT) procedure on Day 2. The results suggested that pre-extinction activation of the OFC not only abolished the expression of learned fear, it also impaired the acquisition of extinction memories, winding up with deficit to suppress fear responses in general. The resulting behavior is consistent with our previously reported electrophysiological data showing that there is an inhibitory modulation from the activated OFC on the mPFC-amygdala pathway. We are currently working on exploring whether the behavioral effect is also amygdala-dependent.

Disclosures: Y. Chang: None. **C. Chang:** None.

Poster

247. Animal Models of Trauma, Stress, and Anxiety II

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 247.15/QQ1

Topic: G.06. Post-traumatic Stress Disorder

Support: NIH/NIMH Grant MH084888 (AKD)

Title: A novel orally active triple reuptake inhibitor for the treatment of post-traumatic stress disorder (PTSD): D-578 attenuates abnormal fear behavior in a rodent model of traumatic stress

Authors: *M. J. LISIESKI[1], A. HARUTYUNYAN[2], B. DAS[3], I. LIBERZON[5], F. P. BYMASTER[6], M. E. REITH[7], S. A. PERRINE[4], A. K. DUTTA, Dr[4]
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Pharmaceut. Sci., Wayne State Univ., Detroit, MI; [3]Wayne State Univ., Department of Pharmaceutical Sciences, MI; [4]Wayne State Univ., Detroit, MI; [5]Psychiatry, Univ. of Michigan Hlth. Syst., Ann Arbor, MI; [6]Euthymics Biosci. Inc, Cambridge, MA; [7]Psychiatry, New York Univ. Sch. of Med., New York, NY

Abstract: Post-traumatic stress disorder (PTSD) is a common disorder which often results in marked functional impairment. Currently, the only approved drugs for the pharmacotherapy of PTSD are two serotonin selective reuptake inhibitors (SSRIs), paroxetine and sertraline. These drugs are only moderately effective and have significant adverse events. Clinical research and animal models of traumatic stress exposure have shown that, in addition to serotonin (5-HT), norepinephrine (NE) and dopamine (DA) systems are dysfunctional in PTSD, suggesting that multi-modal modulation of these monoamines could result in improved pharmacotherapy of PTSD. Therefore, we have investigated the effects of a novel triple reuptake inhibitor (TRI) D-578 in a rodent model of traumatic stress. D-578 inhibits NE, 5-HT, and DA transporters with Ki values of 6, 21, and 30 nM, respectively, and exhibits little to no affinity for other CNS receptors. The effects of D-578 and paroxetine were evaluated in a rat model for traumatic stress exposure - the single prolonged stress (SPS) model - which has been shown to have construct, predictive, and behavioral validity for PTSD. Adult male Sprague-Dawley rats were exposed to SPS, which is the serial application of three stressors (restraint, forced swim, ether). On the 8th day after sham treatment or SPS, rats began a cued fear conditioning procedure, which consisted of acquisition (day 8), extinction (day 9), and extinction retention (day 10) sessions. Rats treated with vehicle, paroxetine, (5 mg/kg), or D-578 (10 mg/kg) 90 min prior to each session. SPS had no effect on the acquisition of conditioned fear or extinction behavior compared to sham treatment, but impaired the retention of extinction learning. D-578, but not paroxetine, attenuated the extinction-retention deficit induced by SPS. Neither drug altered acquisition or extinction learning. These findings suggest that the D-578 has greater efficacy in normalizing traumatic-stress induced extinction-retention learning in a model for PTSD compared to paroxetine. Further supporting the efficacy of D-578 in pharmacotherapy of PTSD, D-578, like classical antidepressants used in PTSD, was highly efficacious in the rat forced swim test and did not have motor stimulant properties. Overall these results suggest that D-578 may attenuate maladaptive retention of fearful memories and support further testing of this agent for the pharmacotherapy of PTSD.

Disclosures: **M.J. Lisieski:** None. **A. Harutyunyan:** None. **B. Das:** None. **I. Liberzon:** None. **F.P. Bymaster:** Other; Chief Scientific Officer, TRImaran Pharma. **M.E. Reith:** None. **S.A. Perrine:** None. **A.K. Dutta:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent for experimental compound. Other; Head of Scientific Advisory Board, TRImaran Pharma.

Poster

247. Animal Models of Trauma, Stress, and Anxiety II

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 247.16/QQ2

Topic: G.06. Post-traumatic Stress Disorder

Support: NIH Grant R15HL132322

Title: Propranolol is ineffective at blocking the cardiovascular consequences of a predator-based psychosocial stress model of PTSD

Authors: *B. A. KOHLS[1], R. M. ROSE[1], T. S. STOOPS[2], M. E. HEIKKILA[1], B. J. HERTENSTEIN[1], K. L. ROBINSON[1], K. E. MUCHER[1], M. R. HUNTLEY[1], P. A. D'ALESSIO[1], P. R. ZOLADZ[1], B. R. RORABAUGH[2]
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Abstract: Individuals with PTSD are at increased risk for cardiovascular disease. We previously reported that a predator-based psychosocial stress model of PTSD led to greater myocardial sensitivity to ischemic injury. Here, we examined whether chronic administration of the β-receptor antagonist propranolol would prevent such effects. Male Sprague-Dawley rats were exposed to psychosocial stress or control conditions for 31 days. Stressed rats were given two cat exposures, separated by 10 days, and subjected to daily social instability throughout the paradigm. Control rats were handled daily. Beginning on Day 2, half of the stressed rats and half of the controls rats were given 0.5 g/l propranolol in their drinking water, which continued until the end of the experiment. Rats were tested for anxiety-like behavior on the elevated plus maze (EPM) on Day 32, and on Day 33, rat hearts were isolated and subjected to 20 min ischemia and 2 hr reperfusion on a Langendorff isolated heart system. Stressed rats, regardless of treatment condition, exhibited heightened anxiety on the EPM, as well as larger myocardial infarcts following ischemia. These findings suggest that the increased myocardial sensitivity to ischemic injury observed in psychosocially stressed rats is not dependent on β-receptor activity.

Disclosures: B.A. Kohls: None. **R.M. Rose:** None. **T.S. Stoops:** None. **M.E. Heikkila:** None. **B.J. Hertenstein:** None. **K.L. Robinson:** None. **K.E. Mucher:** None. **M.R. Huntley:** None. **P.A. D'Alessio:** None. **P.R. Zoladz:** None. **B.R. Rorabaugh:** None.

Poster

247. Animal Models of Trauma, Stress, and Anxiety II

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 247.17/QQ3

Topic: G.06. Post-traumatic Stress Disorder

Support: Mindlin Foundation

Title: Active vs. passive coping across paradigms: Sex differences in trait-like behaviors and neural markers

Authors: J. COLOM-LAPETINA[1], A. LI[1], W. KUWAMOTO[1], *R. SHANSKY[2]
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Abstract: Selection of active or passive responses to threatening stimuli or aversive situations is crucial to survival. We recently characterized a novel, escape-like, active fear response known as “darting” that occurs primarily in a subpopulation of females during fear conditioning trials and has been shown to facilitate extinction of learned fear. These findings suggest that darting may represent an adaptive response that confers resilience during threatening situations. In addition, darting may reflect a “trait” in animals that are generally more likely to select active, rather than passive response strategies. However, the notion that selection of active responses during fear learning has predictive validity for responses during other paradigms of inescapable stress has yet to be established. In this study, a classic model of Pavlovian fear was combined with the forced swim test (FST) to test the hypothesis that active responding during fear conditioning predicts active responding during subsequent exposure to alternate models of inescapable stress. Here, 48 male and female Sprague-Dawley rats underwent cued fear conditioning testing in groups of four via exposure to five 30s tone (CS) presentations, followed by seven tone presentations that co-terminated with a mild foot shock (CS-US). On Day 2, fear learning was assessed via 2 CS presentation test. On Day 14, a single 15 minute FST session was conducted by placing subjects in large, plexiglass cylinders full of water. Ethovision software was used to score freezing and changes in velocity during the tone in fear conditioning trials, as well as to analyze forced swim sessions for active and passive behaviors, including immobility, swimming, climbing, and diving. Head-shaking behavior was scored manually. We observed that female rats engaged in darting during fear conditioning in greater proportions than males. Additionally, female rats spent greater time engaging in active FST behaviors such as climbing and diving, and displayed a shortened latency to perform these behaviors in comparison to males. Subjects were euthanized immediately following forced swim exposure and brains were collected in order to perform immunogenetic analysis of markers of synaptic plasticity in brain regions that likely drive these alternate behaviors.

Disclosures: **J. Colom-Lapetina:** None. **A. Li:** None. **W. Kuwamoto:** None. **R. Shansky:** None.

Poster

247. Animal Models of Trauma, Stress, and Anxiety II

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 247.18/QQ4

Topic: G.06. Post-traumatic Stress Disorder

Support: Department of Biotechnology, Government of India, Grant number- BT/MB-CNDS/2013

Title: Strategies for post-stress intervention against the delayed effects of stress on the amygdala

Authors: *P. CHAKRABORTY[1], S. CHATTARJI[2]
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Abstract: A single, traumatic exposure to stress can lead to a delayed emergence of effects, as in Post-Traumatic Stress Disorder. Using an acute stress model in rats, we found that exposure to a single bout (2 hours) of immobilisation stress causes an increase in anxiety (*Anxiety Index*, Control: 0.51 ± 0.02, Acute Stress: 0.62 ± 0.03) and dendritic spines in basolateral amygdala neurons (Control: 85.6 ± 2.7, Acute Stress: 102.4 ± 4.5) 10 days later, but not 1 day later (Mitra et al, 2005). This suggests that the effects develop over time, hence prompting the question if these delayed effects could be prevented by intervening after stress exposure. Indeed, intervention with the anxiolytic diazepam (DZP) 1 hour after acute stress prevented both increase in spines (Control + DZP: 61.8 ± 4.1, Acute Stress + DZP: 58.2 ± 2.7) as well as increase in anxiety (*Anxiety Index*, Control + DZP: 0.49 ± 0.04, Acute Stress + DZP: 0.46 ± 0.03) 10 days after stress. Interestingly, intervention up to 1 day after stress was also sufficient in preventing the delayed effects (*Dendritic Spines*, Control + DZP: 60.4 ± 4.2, Acute Stress + DZP: 52.7 ± 3.7; *Anxiety Index*, Control + DZP: 0.51 ± 0.05, Acute Stress + DZP: 0.52 ± 0.04). Moreover, we also found that intervention with vehicle (VEH) after stress, both 1 hour and 1 day later, was sufficient by itself in preventing the delayed increase in dendritic spines and anxiety (1 Hour: *Dendritic Spines*, Control + VEH: 72.4 ± 2.7 , Acute Stress + VEH: 65.6 ± 3.8; *Anxiety Index*, Control + VEH: 0.54 ± 0.04, Acute Stress + VEH: 0.52 ± 0.02; 1 Day: *Dendritic Spines*, Control + VEH: 70.1 ± 4.2, Acute Stress + VEH: 64.8 ± 3.4; *Anxiety Index*, Control + VEH: 0.52 ± 0.04, Acute Stress + VEH: 0.52 ± 0.04). The mechanism of this vehicle-mediated prevention is currently being examined to better understand the possible approaches that could eventually translate to therapeutic intervention strategies.

Disclosures: **P. Chakraborty:** None. **S. Chattarji:** None.

Poster

247. Animal Models of Trauma, Stress, and Anxiety II

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 247.19/QQ5

Topic: G.06. Post-traumatic Stress Disorder

Support: VA Merit Award (Sah;2I01BX001075-04)

NIH Grant T32DK059803

Title: Modulation of fear behavior and neurocircuitry by interoceptive threat: relevance to comorbid panic and PTSD

Authors: *K. M. MCMURRAY[1], J. SCHURDAK[2], R. SAH[3]
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Abstract: Post-Traumatic Stress Disorder (**PTSD**) and Panic Disorder (**PD**) are prevalent and debilitating psychiatric disorders. PD and PTSD are highly comorbid and this comorbidity is associated with worse patient outcomes. Despite a high prevalence and debilitating effects, the neurobiology of these disorders is still largely unknown. Preclinical studies are required for improved mechanistic understanding of panic-PTSD comorbidity. Consistent with the negative valence construct within research domain criteria (RDoC) initiative of NIMH, our lab uses CO_2 inhalation to simulate an acute, interoceptive threat producing defensive behaviors representative of fear. This is relevant to spontaneous panic attacks, a cardinal feature of PD. Importantly, low dose CO_2 inhalation consistently induces panic attacks in PD subjects compared to healthy controls. A recent study showed prior sensitivity to CO_2 predicted PTSD symptom severity, suggesting CO_2 inhalation may be useful in elucidating mechanisms underlying PD and PTSD. The current study investigated the emergence of PTSD-relevant behaviors (fear conditioning, acoustic startle) following conjunct exposure of CO_2 inhalation and single prolonged stress (SPS); as well as potential circuits that may contribute to these behaviors. We hypothesized enhanced fear and startle behaviors in CO_2-exposed mice as well as exaggerated responses in mice exposed to both stress and CO_2 inhalation. Male BALB/C mice were exposed to SPS or were undisturbed. The next day, all mice were exposed to air or 5% CO_2 and freezing behavior was scored. After one week of recovery, acoustic startle and context fear conditioning were assessed. Tissue was collected from mice the day after fear conditioning reinstatement, and ΔFosB expression (marker of neural plasticity) was analyzed by IHC. In an additional study, mice first underwent air or 5% CO_2 exposure and then SPS the next day, followed by acoustic startle and context fear conditioning one week later. Consistent with our hypothesis, prior CO_2 exposure sensitized conditioned fear, delayed extinction and exaggerated acoustic startle responses. Additionally, CO_2-evoked freezing correlated with shock-evoked freezing (context

fear conditioning) one week later suggesting CO_2 sensitivity may predict fear outcomes. Ongoing neurochemical studies will reveal potential circuits that may contribute to enhanced fear and startle behaviors. In conclusion, consistent with clinical observations, we report enhancement of traumatic stress evoked fear and startle by interoceptive threat, CO_2. This novel paradigm will facilitate the mechanistic understanding of comorbid PTSD and panic disorder.

Disclosures: K.M. McMurray: None. **J. Schurdak:** None. **R. Sah:** None.

Poster

248. Cortical Circuits and Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 248.01/QQ6

Topic: H.01. Animal Cognition and Behavior

Support: NIH Pioneer award

Title: Brain states and behavior: Insights from dorsolateral prefrontal cortex of freely moving monkeys

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Abstract: Neural activity in a particular brain region results from the integration of bottom-up sensory inputs with top-down, internally-generated signals. The behavioral state of the animal is a prominent global variable involved in shaping neuronal activity in all cortical regions. In this study, we sought to better characterize the neuronal activity associated with resting and locomotor states in the dorsolateral prefrontal cortex of freely moving rhesus macaques. We recorded from populations between 29 and 50 single neurons, in addition to 96 channels of local field potential recordings. All recordings were made in a freely-moving, naturalistic experimental setting. Single unit spike waveforms were characterized by their peak-to-trough width and classified as broad-spiking and narrow-spiking neurons. Neuronal firing rates, population synchrony and local field potential spectra were computed in order to investigate the relationship between neuronal activity and behavioral states. In all behavioral states analyzed, we determined that the population of narrow-spiking neurons has a higher firing rate and is more synchronous than the broad-spiking population. Additionally, we found a strong decrease in firing rates and an associated increase in population synchrony and LFP power ratio (0.5 - 10Hz : 20 - 59Hz) in rest as compared to wakefulness. We further investigated the influence of behavior on these measures by quantifying the monkeys' body movement using computer vision algorithms. Firing rates were significantly correlated with movement, and population synchrony

was significantly anti-correlated with movement, which motivated us to further subdivide the wake state into active and quiet wakefulness. Active wakefulness resulted in a significant increase in firing rates and a decrease in population synchrony as compared to quiet wakefulness. These findings strongly imply the presence of global cognitive variables that shape neuronal activity and are associated with behavioral states in nonhuman primates.

Disclosures: R. Milton: None. **N. Shahidi:** None. **V. Dragoi:** None.

Poster

248. Cortical Circuits and Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 248.02/QQ7

Topic: H.01. Animal Cognition and Behavior

Support: NIH R01MH085666

NIH R21MH110678-01

Title: The role of prefrontal cortex in social behaviors

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Abstract: The PFC is of pivotal importance for multiple social behaviors, including social interaction and social memory . Specific subregions may have different contribution to these social behaviors. Social memory, one of the fundamental bases of social organization, is the ability to identify and recognize individuals of their own species. Although the PFC controls multiple memory processing, its role in social memory remains unclear. To explore this, we combined the use of fosTRAP mice with social recognition test, and immunostaining of c-fos and tdTomato expression. We found that free interaction in the mice homecage significantly increased the interaction time, but not the strength of social recognition memory. We also observed that social training resulted in widespread neuronal activations exhibited with increase of tdTomation expression in the neocortex, including the medial prefrontal cortex (mPFC), anterior cingulate cortex (ACC), and ventrolateral orbital cortex (VLO). Interestingly, there were laminar differences in Layer 2/3 versus Layer 5 in the mPFC and ACC. At the time of memory retrieval, a significantly more cells were activated with c-fos expression (compared to tdTomoto) in the mPFC and ACC, but not in the VLO. Ongoing study is to use electrophysiology to compare the laminar differences and the functionality of the memory-activated cells. Our current study aims to identify the dynamic changes during social memory processing and to provide new

insights for a better understanding of how the PFC is involved in the social behaviors.
Supported by NIH R01MH085666 and NIH R21MH110678-01 to W. J. Gao.

Disclosures: **Y. Zhang:** None. **B. Xing:** None. **C. Yan:** None. **W. Gao:** None.

Poster

248. Cortical Circuits and Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 248.03/QQ8

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant R01AA024845

Whitehall Foundation Grant 2014-12-68

NIH Grant T32NS063391

NIH Grant T32GM008181

Title: Functional modulation of frontal and parietal cortices by claustrum

Authors: *M. G. WHITE, C. MU, B. N. MATHUR
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Abstract: The claustrum projects widely across cortex but the functional implications of this direct glutamatergic input remain unclear. Anatomical studies indicate that the claustrum innervates executive and association cortices to a greater degree than primary and secondary sensorimotor cortices. Moreover, the density of claustrocortical input varies across cortical layers and this pattern of layer-specific innervation differs between cortical areas. However, it is not known onto which cell types in which cortical regions the claustrum projects in order to exert control over cortical function. In this study, we optogenetically interrogate claustral innervation of two cortical areas, the anterior cingulate cortex (ACC) and the parietal association cortex (PtA), in a layer- and cell-specific manner using whole-cell patch clamp electrophysiology. Our preliminary findings suggest monosynaptic claustrocortical synapses onto pyramidal neurons exist across cortical layers and exhibit a high release probability. While the behavioral impact of claustrum control of cortex requires examination, the present results suggest a previously underappreciated role for the claustrum in powerfully influencing cortical activation.

Disclosures: **M.G. White:** None. **C. Mu:** None. **B.N. Mathur:** None.

Poster

248. Cortical Circuits and Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 248.04/QQ9

Topic: H.01. Animal Cognition and Behavior

Title: Changes in macaque V4 during visual task learning

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Abstract: The neuronal changes behind perceptual learning remain a mystery, which has led to the formation of different hypotheses in an attempt to explain what neuronal changes may underlie performance improvement. We investigate the encoding/decoding hypothesis, which suggests that perceptual learning is either a result of (1) increased information transmission by upstream neurons (i.e. improved encoding) or (2) increased understanding of such transmitted information by downstream neurons (i.e. improved decoding). We specifically address (1) by characterizing how information transmitted by V4 neurons changes during learning. Additionally, we quantify how broad synchronization in V4 fluctuates over the time course of learning. Both will be steps in developing a model of visual task learning. Monkeys were shown a natural scene on-screen followed either by a rotated version or the same scene, and were required to respond whether the two stimuli are the same or different. This was a supervised learning task, as a juice incentive was provided when correct. Analysis of local field potentials (LFPs) and spike timings revealed heightened local synchronization between V4 neurons during learning, suggestive of a change in population encoding. Inspired by other past work, our initial analysis will first focus on noise correlations between neurons, determining how correlations are altered over the time course of learning. Analysis will be extended to signal correlations by treating the different rotations of imagery as different stimuli. Both correlation analyses will allow us to conclude how information encoded by neurons changes over the time course of learning. We will also investigate broader synchronization during visual task learning via pairwise LFP analysis between channels of different probes that were inserted into macaque V4. Initially we will use coherence to measure linear interactions, but then will also utilize mutual information in frequency, a recently formalized technique, to measure nonlinear interactions and cross-frequency coupling. The results from these diverse analyses will culminate with the generation of a data-driven model of visual skill learning in macaque V4. Ultimately we will test our model in vivo by stimulating V4 neurons to create the observed phenomena while they perform a visual task. Our stimulation technique will result in a faster perceptual learning rate, and help learning disabilities.

Disclosures: **J.D. Young:** None. **V. Dragoi:** None. **B. Aazhang:** None.

Poster

248. Cortical Circuits and Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 248.05/QQ10

Topic: H.01. Animal Cognition and Behavior

Support: NFS IOS1258111

VA I01BX001978

Title: Molecular mechanisms of tone detection learning in primary auditory cortex

Authors: *A. I. VAZDARJANOVA[1], W. GUO[2], D. TALLEY[2], D. T. BLAKE[3]
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Abstract: Plasticity in primary auditory cortex (A1) is necessary for learning to associate an auditory stimulus with reinforcement, or tone detection learning. Although it has been known that responses to the target tone (target responses) increase after weeks of training, we have previously demonstrated that the initial phases of learning: days 1-3 of tone detection of a 5kHz tone; are marked by a small decrease of target responses in the target responsive low frequency part of A1 (LF) and a simultaneous and very striking increase of responses in the non-target high frequency part of A1 (HF). We have further demonstrated that tone detection as well as plasticity in both the LF and HF regions are blocked by suppressing the levels of a plasticity-associated immediate-early gene, Arc, which is emerging as a master regulator of plasticity. In cell cultures, Arc is known to be necessary for both long-term depression through interacting with the endocytocic machinery to decrease surface AMPA-receptor levels, and for long-term potentiation by affecting the cytoskeleton. We hypothesized that both of these processes are needed for plasticity in A1 during the early stages of perceptual learning, but they occur differentially in the LF and HF regions. To test this hypothesis, we infused Tat-GluR23Y peptide, latrunculin or jasplakinolide in either the entire A1, LF, or HF regions before the 3rd day of tone detection and assessed performance for the next two days. Consistent with our hypothesis we found that latrunculin/Tat-GluR23Y disrupted tone detection only when infused in the LF region, while jasplakinolide was most effective when infused in the HF region. The fact that the effects were smaller than those obtained with *Arc* antisense infusions, suggests that, in A1, Arc simultaneously and bi-directionally regulates plasticity in a sub-region-specific manner. We are currently testing the hypothesis that it is the relative abundance of Arc's molecular partners in these sub-regions that drives the differential engagement of Arc in sub-regions of A1 to shape overall plasticity necessary for auditory perceptual learning.

Disclosures: **A.I. Vazdarjanova:** None. **W. Guo:** None. **D. Talley:** None. **D.T. Blake:** None.

Poster

248. Cortical Circuits and Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 248.06/QQ11

Topic: G.07. Other Psychiatric Disorders

Support: NARSAD YI 25242

Title: Hippocampal CA3 hyperactivity may contribute to psychosis-like behaviors in mice

Authors: *D. SCOTT, C. TAN, C. A. TAMMINGA
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Abstract: Although psychosis is the defining and the most recognizable symptom domain in schizophrenia, the biological mechanism underlying psychosis remains unknown. Analysis of post-mortem human hippocampal tissue and in vivo human imaging studies in schizophrenia have detected abnormalities within hippocampal subfields: decreased GluN1 within the dentate gyrus (DG), increased synaptic plasticity markers in CA3, and increased basal activity within CA3 which correlate with psychosis severity. However, a causal link between this hippocampal dysfunction and psychosis has yet to be determined. Therefore, we sought mouse model systems where we could manipulate subfield activity independently, selectively, and dynamically. We infused mice with AAVs containing designer receptors exclusively activated by designer drgus (DREADDs) to specifically activate CA3, allowing manipulation of activity with spatial, temporal, and cell-type specificity. Following surgery, we treated mice, either acutely or chronically, with vehicle or clozopine-N-oxide, and performed behavioral analysis, utilizing paradigms associated with a psychosis-like phenotype in mice: prepulse inhibition, fear conditioning, and social memory. Acute activation of ventral, but not dorsal CA3 is sufficient to enhance contextual fear conditioning. Acute activation of the dorsal CA3 can impair social memory. Behavioral analysis after chronic activation of CA3 in dorsal and ventral regions is currently underway and will be contrasted. This combination of phenotypes resembles those in a reverse translational mouse model system of schizophrenic psychosis, where GluN1 is selectively knocked out within DG, inducing homeostatic upregulation of cellular excitability within CA3, as well as pharmacological model systems of psychosis. Results suggest that different aspects of this psychosis-like phenotype are affected by acute activity along the longitudinal axis of CA3, possibly modeling the psychosis process and suggesting novel therapeutic targets based upon symptomatology. These experiments have led us to suggest that alterations in excitatory signaling within the hippocampus may lead to aberrant signaling in afferent regions, possibly underlying the biological model of psychosis.

Disclosures: **D. Scott:** None. **C. Tan:** None. **C.A. Tamminga:** None.

Poster

248. Cortical Circuits and Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 248.07/QQ12

Topic: H.01. Animal Cognition and Behavior

Support: R21 MH107001

NSF 1533623

Title: Modulation of neural activity in anterior cingulate cortex by the locus coeruleus

Authors: *S. JOSHI, J. LEVINE, J. I. GOLD
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Abstract: Changes in physiological arousal, assessed via changes in pupil diameter and other measures, can affect perception, learning, memory, attention, and other aspects of higher brain function. These effects are mediated partly by arousal-linked modulation of brain activity via the locus coeruleus (LC)-norepinephrine (NE) system. We recently showed that fluctuations in pupil diameter are related to neuronal activity in not just LC but also, with a slight delay, several other cortical and subcortical brain regions that receive direct LC projections. These results suggest that arousal-linked changes in LC activation may transiently modulate coordinated patterns of neuronal activity throughout the rest of the brain. To test this idea, we made paired recordings in LC and anterior cingulate cortex (ACC) of awake, behaving monkeys while also measuring physiological arousal via pupil diameter (PD) and electroencephalography (EEG). We targeted the ACC because it both projects to and receives projections from the LC.
We recorded simultaneously from single, well-isolated LC neurons and groups of 2–19 well-isolated ACC neurons. Recordings were made while the monkey maintained stable fixation for 1–5 s. On a randomly selected subset of trials, a startling sound was played (beep trials). These approaches allowed us to assess how both spontaneous and evoked changes in LC activation and arousal affect ACC activity patterns. We quantified these effects by computing spike-count and spike-time variability of individual ACC neurons (Fano factor and coefficient of variation) and coordinated spiking of pairs of ACC neurons (pairwise spike count correlations, PWC). Preliminary results indicate that each of these measures varies considerably as a function of time relative to simultaneously measured LC spikes. Further, these measures show striking differences when measured under conditions of low versus high LC activity. Together, these results suggest a substantial role for the LC-NE system in modulating ACC activity.
In separate blocks of trials, we delivered electrical microstimulation in the LC while measuring population activity in ACC and evaluated the same metrics. Consistent with previous reports,

microstimulation caused a transient suppression in ACC neuron spiking. Further, it caused an increase in ACC PWC and a reduction in spike count variability. Our measurements provide a direct link between changes in activity in the monkey LC-NE system and modulation of cortical population dynamics.

Disclosures: S. Joshi: None. **J. Levine:** None. **J.I. Gold:** None.

Poster

248. Cortical Circuits and Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 248.08/QQ13

Topic: H.01. Animal Cognition and Behavior

Support: NIDA Grant R01 DA033123

Department of Psychological Science, University of Vermont

Title: Inactivation of the prelimbic and infralimbic cortices differentially affects minimally and extensively trained actions

Authors: *M. L. SHIPMAN[1], S. TRASK[3], M. E. BOUTON[4], J. T. GREEN[2]
[1]Neurosci. Grad. Program, [2]Dept. of Psychological Sci., Univ. of Vermont, Burlington, VT; [3]Dept. of Psychological Sci., The Univ. of Vermont, Colchester, VT; [4]Univ. Vermont, Burlington, VT

Abstract: Several studies have examined a role for the prelimbic cortex (PL) and infralimbic cortex (IL) in free operant behavior. A typical result is that a PL lesion affects goal-directed behavior (sensitive to reward devaluation) but not habitual behavior (insensitive to reward devaluation). PL lesions render a goal-oriented response habitual, but leave an extensively trained habit intact. The opposite effect is seen with IL lesions; habitual responding is affected while goal-directed responding is not. To further examine the involvement of these regions in the expression of goal directed and habitual behavior, we used a within-subject design to examine both an extensively and a minimally trained operant response. In Experiment 1, rats were implanted with bilateral guide cannulae into their PL. Following recovery, rats performed two responses to produce a food reinforcer, R1 and R2, each in its own context. R1 received extensive training and R2 received minimal training. Rats then received lithium chloride injections either paired or unpaired with the sucrose pellet reinforcer in both contexts until paired rats rejected all pellets. On test day, rats received either an infusion of saline or baclofen/muscimol into the PL and were tested (in extinction) on both their R1 and R2 responses. No habit was demonstrated on either the extensively or minimally trained response, but rats with an inactivated PL showed a selective decrement in responding on the minimally

trained response. This may suggest a role for the PL in expression of response-outcome associations early in learning. Because of the role of the IL in habits, we then hypothesized that the IL would play a role in expression of an extensively trained response. For Experiment 2, we utilized the same paradigm as Experiment 1 but with IL inactivation. Our preliminary results suggest that extensively trained responding that is still sensitive to reward devaluation may be dependent on the IL.

Disclosures: M.L. Shipman: None. **S. Trask:** None. **M.E. Bouton:** None. **J.T. Green:** None.

Poster

248. Cortical Circuits and Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 248.09/QQ14

Topic: H.01. Animal Cognition and Behavior

Title: Cognitive tasking capability in the siamang (Symphalangus syndactylus; Hylobatidae)

Authors: G. M. VAIRA, *P. M. NEALEN
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Abstract: Historically, the cognitive evaluation of non-human primates has focused on the Old World monkey (Cercopithecoidea, including macaques) and Great Ape (Hominidae, including chimpanzees and gorillas) lineages. This research effort has bypassed the Hylobatidae ("lesser apes", gibbons), phylogenetically situated between the Cercopithecoidea and the Hominidae, from which they diverged ca. 20 mya and 15 mya, respectively. Extant gibbons exhibit anatomical and behavioral traits with similarity to both monkey and great ape lineages.
To assess the effects of these evolutionary divergences on primate cognition, we have performed cognitive testing of siamangs (*Symphalangus syndactylus*, the largest hylobatid). This evaluation will fill-in a glaring void in our understanding of primate cognition, as well as inform efforts to house/rehabilitate captive animals, known to benefit from environmental enrichment.
Testing of zoologically-housed siamangs is conducted using touch-screen hardware and software (CANTAB, Lafayette Instruments) that evaluates a range of cognitive capabilities. After training on the use of the touch-screen, over 600 cognitive trials were completed with the first subject (nulliparous female, age 7) over 10 testing sessions (~50 trials/session). Five cognitive tests were used: Delayed Matching/Non Matching (DM/NM), Conditional Visual Discrimination (CVD), Spatial Working Memory (SWM), Paired Associated Learning (PAL) and Concurrent Discrimination (CD).
SWM performance ranged from 100 - 38% correct, and was strongly, and negatively, correlated with the number of test stimuli (ranging from 3-6; Pearson $r = -0.82$, $n = 8$ trial blocks; $p < 0.01$). Cumulative performance on DM/NM (mean = 45% correct, $n = 2$ sessions) and CVD (47%, $n = 2$ sessions) was lower than that of CD (82%, $n = 4$ sessions; ANOVA: $F(2,5) = 23.67$, $p < 0.003$).

The addition of distractors to CD trials caused a 1-session drop in performance that was subsequently recovered. Cumulative performance of PAL (47% n=2 sessions) mirrors that of DM/NM.
Siamangs are highly competent using touch-screens, with response latencies during CVD (3.24 sec) consistently longer than those of DM (1.55 sec) and CD (1.69 sec; ANOVA: $F(2,5) = 12.39$, $p = 0.012$).
These data suggest that hylobatids are as cognitively capable as rhesus macaques (*Macaca mulatta*) and may possess cognitive abilities approaching some great ape species. This study provides pioneering data demonstrating the poorly-studied cognitive abilities of hylobatids, and also provides critical comparative information for evolutionary evaluation of the primate brain.

Disclosures: G.M. Vaira: None. **P.M. Nealen:** None.

Poster

248. Cortical Circuits and Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 248.10/QQ15

Topic: H.01. Animal Cognition and Behavior

Support: NIH Intramural Funding ZIA DA000587

Title: Orbitofrontal cortex neurons signal associations underlying model-based inference

Authors: *B. F. SADACCA, H. WIED, Y. MARRERO-GARCIA, J. CONROY, N. LOPATINA, D. NEMIROVSKY, G. SCHOENBAUM
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Abstract: Using knowledge of the structure of the world to infer is at the heart of ‘model-based reasoning’. This ability relies on several structures, including the orbitofrontal cortex (OFC): with an intact OFC rats and primates can use information gathered in the absence of anything overtly good or bad to infer the value of elements of the environment on-the-fly, with OFC inactivated or lesioned, they cannot. How might the OFC support this calculation? Prominent theories focus on the ability of OFC neurons to encode the value of reward-predictive cues. In some, OFC inactivation should eliminate the signaling of value for use in guiding choice. However, inactivation or lesions of OFC typically only disrupt behaviors dependent on “model-based” value. For this reason, others suggest that neurons of the OFC encode associations among cues or states, which can be used as a framework or cognitive map to simulate the value of predictive cues based on known associations. Here, OFC inactivation eliminates these associative links, thereby affecting behavior based on inferred value. A clear distinction can be made in the predictions of these accounts in situations where there are associations learned among valueless cues. The former account would predict little or no representation of these

neutral associations, whereas the latter would predict that these relationships should be prominently represented in the firing of OFC neurons. To test between these models, we recorded neurons in the OFC of rats during a sensory preconditioning task. In this task, rats are exposed to pairs of neutral cues, later learn that an element of one pair leads to reward, and, in a final test, infer a relationship between the other element of the pair and reward. We recorded 294 neurons in the OFC in the initial preconditioning phase. These neurons developed firing patterns that represented the neutral cue pairs as the rats were exposed to them. The correlates changed with reward pairing, but they were present in preconditioning prior to reward, and developed with training as if representing the learned associations. This result indicates that, as predicted by an associative view of orbitofrontal function, this region represents information about the causal structure of the world even when it is not directly relevant to obtaining reward.

Disclosures: B.F. Sadacca: None. **H. Wied:** None. **Y. Marrero-Garcia:** None. **J. Conroy:** None. **N. Lopatina:** None. **D. Nemirovsky:** None. **G. Schoenbaum:** None.

Poster

248. Cortical Circuits and Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 248.11/QQ16

Topic: H.01. Animal Cognition and Behavior

Support: NSF GRFP

NIH Grant R01 GM111293

NIH Grant NINDS 1U01NS094375-01

A. Alfred Taubman Medical Research Institute

Title: Nitrous oxide reduces corticortical information transfer at sub-anesthetic doses without loss of consciousness

Authors: *C. S. NU[1], K. E. SCHROEDER[2], S. R. NASON[1], E. J. WELLE[1], P. G. PATIL[4], G. A. MASHOUR[3], C. A. CHESTEK[2]
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Abstract: Nitrous oxide (N_2O) and ketamine are unique among clinically-relevant anesthetic drugs because, unlike their GABAergic counterparts (e.g. propofol), they tend to increase regional brain metabolism (Reinstrup *et al.*, 2008, *Brit J Anaesth*) and enhance higher-frequency electroencephalographic activity (Lee *et al.*, 2013, *Anesthesiology*). Previous work from our group has shown in the non-human primate brain that thalamocortical transfer of somatosensory

information to primary sensory cortex (S1) is preserved during ketamine anesthesia but corticocortical information transfer from S1 to primary motor cortex (M1) is disrupted (Schroeder *et al.*, 2016, *NeuroImage*). This is consistent with findings in humans using surrogate measures of information transfer derived from electroencephalography during ketamine anesthesia (Lee *et al.*, 2013, *Anesthesiology*). In the current study we are examining the hypothesis that corticocortical information transfer would also be reduced during N_2O exposure in a dose-dependent manner, with somatosensory-related activity in M1 used as a surrogate for corticocortical information transfer based on our past study (Schroeder *et al.*, 2016, *NeuroImage*). One male Rhesus macaque monkey was implanted with a 96-channel Utah microelectrode array (Blackrock Microsystems) in M1 and S1. We randomly stimulated the monkey's fingers (thumb, index, and little) using 2Hz strokes with cotton swabs in 5 second trials under awake, 40% N_2O, and 70% N_2O conditions. Intracranial spiking data were high-pass filtered at 250Hz and at a threshold of -4.5 RMS. We then used a naïve Bayes classifier with 10-fold cross validation to perform offline 1-of-3 decoding on which finger had been stimulated (the primary outcome of interest), and analyzed network information transfer by means of high order transfer entropy (HOTE) (Ito *et al.*, 2011, *PLoS One*) within M1. Similar to ketamine, our preliminary data show that 70% N_2O resulted in reduced average decode performance from 66% correct to 35% correct and significantly reduced local directed connectivity as measured by HOTE ($p < 0.001$), while 40% N_2O exhibited a decode performance drop from 55% to 45% and a non-significant reduction ($p = 0.11$) in HOTE. These data support the hypothesis that N_2O causes a dose-dependent reduction in corticocortical information transfer in the primate brain.

Disclosures: C.S. Nu: None. **K.E. Schroeder:** None. **S.R. Nason:** None. **E.J. Welle:** None. **P.G. Patil:** None. **G.A. Mashour:** None. **C.A. Chestek:** None.

Poster

248. Cortical Circuits and Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 248.12/QQ17

Topic: H.01. Animal Cognition and Behavior

Support: Special Funding for Research Stimulation, Vice-rectory of Research, Univeristy of Costa Rica

Title: Habituation and spatial memory in the context of emotional regulation: Behavioral and genetic mechanism underlying context information-processing and de-arousal grooming

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Abstract: Habituation is the ability to passively reduce a response after repeated or prolonged exposures to a particular stimulus. From a cognitive perspective, habituation is a basic, information-gating process that contributes to filter out irrelevant information in order to focus cognitive sources on a specific goal. In higher order capabilities as in spatial memory, a similar process takes place with the purpose of facilitate navigation towards the target place. In rodents, some forms of physical and social stimulation, like environmental enrichment (EE), potentiate both habituation and spatial memory. Here, we examined whether habituation capacity predicts spatial memory in the Barnes maze test (BMT). Male Wistar rats were kept for 30 days either on EE or on standard housing. During that time, half of the animals within each group were tested weekly in a 15-min open-field test (OFT) with the aim to explore long-term habituation. After the housing period, all rats were tested during four consecutive days in the OFT to assess short-term habituation. Afterwards, a three-day BMT protocol was used to evaluate several spatial and non-spatial memory parameters. To assess some brain mechanisms related with memory formation and brain plasticity, the hippocampal mRNA levels of BDNF, CREB, and p250GAP genes were evaluated. Evidence about the effects of EE on short-term and long-term OFT habituation and on BMT will be provided. We will show the likely contribution of OFT behaviors, including certain types of grooming behavior, as predictors of spatial memory. Also, the association between gene expression and behavioral parameters will be presented. Because non-associative memory is observed in a plethora of species as a first-level mechanism of information processing, elucidating its functions could shed some light to better understand the complex interplay of cognitive systems.

Disclosures: M. Rojas: None. **O.A. Rodríguez-Villagra:** None. **A. Sequeira-Cordero:** None. **J.F.C. Fornaguera:** None. **J.C. Brenes:** None.

Poster

248. Cortical Circuits and Behavior

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 248.13/QQ18

Topic: A.02. Postnatal Neurogenesis

Support: Funding provided by Abbott Nutrition through the Center for Nutrition, Learning and Memory at the University of Illinois, Urbana-Champaign

NIH grant P51OD011092

Title: Development of functional connectivity of macaque cerebral cortical networks: Comparison of infants fed breast milk or formulas with low or high carotenoid content and synthetic or natural α-tocopherol

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Abstract: BACKGROUND/OBJECTIVE: While it has been shown that lutein, the predominant carotenoid in primate brain, and α-tocopherol are correlated with measures of cognition and visual perception, little is known about roles of these nutrients in brain development. This study used resting-state functional connectivity MRI (rs-fcMRI) to characterize cortical organization in monkey infants as a function of carotenoid intake and α-tocopherol source.
DESIGN: From birth, rhesus macaques were breastfed (BF, n=8), or fed either a commercial formula supplemented with lutein, zeaxanthin, β-carotene and lycopene plus natural **α**-tocopherol (SF, N=8), or an identical control formula, but with low levels of these carotenoids and with synthetic **α**-tocopherol (CF, N=7). Functional connectivity was characterized at 2, 4 and 6 mo of age. Cortex was parcellated into 82 regions of interest (ROIs) as defined for rhesus macaque by Bezgin et al. (2012), and each ROI was assigned to a unique functional network (Grayson et al. (2016)). A repeated measures ANOVA was used to identify longitudinal changes in functional connectivity within and between functional networks, where the functional connectivity from each ROI (82x82 connectivity matrix) was grouped according to diet, functional network, and time.
RESULTS: We found significant differences among networks, diet groups, ages, and for all interactions ($p<0.05$, corrected for multiple comparisons and lack of sphericity). Connectivity between and within each functional network followed distinct maturational patterns. For some network pairs, the formula groups showed a divergent pattern of maturation compared with BF. The group fed the low carotenoid control formula diverged the most, as clearly seen in the interconnections between the default and sensory-motor, default and dorsal attention, and visual and somatosensory networks. In some cases, despite strong initial differences between formula-fed and BF infants, their patterns of brain connectivity converged, as shown within the default mode network.
CONCLUSION: This study provides the first examination of developmental changes in rs-fcMRI in macaque cerebral cortex. Patterns of functional connectivity in infants receiving formula with supplemental carotenoids and natural **α**-tocopherol more closely resembled breastfed infants than did those in infants fed a formula without supplemental carotenoids and with synthetic α-tocopherol.

Disclosures: O. Miranda Dominguez: None. **S.D. Carpenter:** None. **E. Feczko:** None. **L. Renner:** None. **J.W. Erdman:** 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.; Abbott

Nutrition through the Center for Nutrition, Learning, and Memory at the University of Illinois. **M.J. Kuchan:** A. Employment/Salary (full or part-time):; Abbott Nutrition. **M. Neuringer:** 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.; Abbott Nutrition through the Center for Nutrition, Learning, and Memory at the University of Illinois. **D.A. Fair:** 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.; Abbott Nutrition through the Center for Nutrition, Learning, and Memory at the University of Illinois.

Poster

249. Prefrontal Cortex: Physiology of Decision Making

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 249.01/QQ19

Topic: H.01. Animal Cognition and Behavior

Support: NIH RO1 NS086104

Title: Modeling of preference reversal in a temptation task

Authors: *T. RAHIMI-MOGHADDAM, J. HWANG, E. E. EMERIC, V. STUPHORN
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Abstract: There has been a debate about the neural basis of intertemporal decision-making. Two main types of models have been proposed: Single and Dual System models. Single System models suggest that agents make their choice by directly comparing the value of options, using the output of a single evaluation system based on the magnitude of reward and length of delay, without an additional cognitive process such as self-control. On the other hand, Dual System models suggest that two different systems evaluate the value of options. One operates over a short time horizon, while the other operates over a long time horizon. In this case, delay of gratification depends on the ability of the far-sighted evaluation system to suppress the short-sighted system. This form of self-regulation is called self-control. To investigate this question, we designed an experiment that dissociates the possible effect of self-control from reward magnitude and delay. This allowed us to examine how changes in the level of self-control affect choice behavior, as well as to identify neural activity that is correlated with changing levels of self-control. In this experiment, monkeys had to choose between a smaller-sooner and a larger-later reward option. Normally, they received the chosen reward after the indicated delay. However, in a minority of ‘temptation’ trials, after making the decision, the alternative option remained available and monkeys had the chance to change their choice. Results in two monkeys showed a significant preference shift toward sooner rewards in temptation trials. These findings

indicate that monkeys often do not maintain their initial preference for larger, but more delayed reward in the presence of smaller, but more immediate reward. Statistical analysis indicated a significant difference in chosen delay between initial and final decisions. We also tested, if a Single System model can explain our behavioral findings. We fitted a hyperbolic discounting model to the initial choices and used it to predict the subsequent final choices on temptation trials. The model could not predict the observed proportion, direction and timing of switching behavior. Since a simple uniform hyperbolic evaluation model could not explain this switching behavior, it seems necessary to include self-control as an effective factor in decision-making.

Disclosures: T. Rahimi-Moghaddam: None. **J. Hwang:** None. **E.E. Emeric:** None. **V. Stuphorn:** None.

Poster

249. Prefrontal Cortex: Physiology of Decision Making

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 249.02/QQ20

Topic: H.01. Animal Cognition and Behavior

Support: RO1 DA040990

Title: Neural mechanism underlying multi-attribute decision making in primates

Authors: *Y.-P. YANG[1], K. JUSTUS[1], E. NIEBUR[2], V. STUPHORN[3]
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Abstract: Normative models of rational behavior predict that the relative choice ratio between specific option pairs should remain constant. However, humans and other animals often show preference reversal, i.e. they change their choice ratio between the original options when irrelevant alternatives are added to the choice menu. It indicates that preferences are constructed at the time of elicitation and are therefore dependent on the decision context, which violates the axiom of “independence of irrelevant alternatives” in normative theories.
To investigate the neuronal mechanism underlying the dynamic preference formation, we are recording the neuronal activity in monkey orbitofrontal cortex performing a multi-attribute decision-making task. In this task, we present two options each with two attributes: reward amount and probability. The reward amount and reward probability are parametrically indicated by visual stimuli. These stimuli are displayed in spatially separate locations. A boundary cue indicates that they belong to the same option. Each attribute cue is coved by a colored mask (yellow for amount; blue for probability), which is only removed when the monkey fixates the cue. Monkeys are allowed to inspect the two options freely with their eyes, before indicating their choice by moving a joystick. The resulting eye trajectory provides temporal and spatial information about the monkey’s focus of attention during the value computation and decision

process.
In preliminary human behavioral data, we found that subjects usually made decisions efficiently with only 4-5 fixations of attribute cues. Most subjects inspected information about probability first, implying that probability may be the more important attribute for these subjects. The subjects showed two markedly different information sampling strategies. One group used a within-option sampling strategy (i.e., they first inspected the two attributes within one option, then inspected the two attributes of the other option). The other group used a within-attribute sampling strategy (i.e., they first compared a specific attribute across options, then compared the other attribute across options). The subjects showed a large range of different risk attitudes. These behavioral findings provide us clues about computational models that explain how separate decision-variables (i.e. attributes) are integrated to compute the overall subjective value (SV) of choice options, how the SV for each options are compared to make the final decision, and how attention influences the value computation of choice options.

Disclosures: **Y. Yang:** None. **K. Justus:** None. **E. Niebur:** None. **V. Stuphorn:** None.

Poster

249. Prefrontal Cortex: Physiology of Decision Making

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 249.03/QQ21

Topic: H.01. Animal Cognition and Behavior

Support: NIH R01MH085666

NARSAD Independent Award 2015

Title: Conditional GSK3β KO in GABAergic parvalbumin interneurons differentially affects behaviors in adult male and female mice

Authors: *S. MONACO, A. J. MATAMOROS, G. HAN, E. M. BLACK, R. A. ESPAÑA, W.-J. GAO
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Abstract: The ability to perceive, filter, prioritize, update and ultimately respond appropriately to incoming stimuli requires efficient prefrontal cortex (PFC)-dependent processing, with both N-methyl-D-aspartate receptors (NMDARs) and GABAergic interneurons playing a major role. What remains to be known is how NMDARs on GABAergic interneurons are regulated and how this affects cognitive function. We hypothesize that GSK3β is a common factor linking NMDARs, GABAergic signaling, and PFC-dependent cognition. To elucidate the role GSK3β plays in GABAergic parvalbumin interneurons, we have developed a novel animal model using three transgenic lines: GSK3β flox, Parvalbumin-cre, and cre-dependent Td-Tomato.

Parvalbumin (PV)-specific GSK3β KO male and female adult mice show no differences in PV florescence expression, particularly in the PFC, and demonstrate normal locomotion and anxiety compared to control littermates. However, following amphetamine administration, male PV-GSK3β KO mice demonstrate resistance to amphetamine-induced hyperlocomotion, whereas female mice of both genotypes show resistance to amphetamine-induced hyperlocomotion. MK-801 treatment induced hyperlocomotion in male mice, but no differences in females were observed. Male and female PV-GSK3β KO mice exhibited comparable learning and working memory to control. Whereas, male PV-GSK3β KO mice exhibit fewer total errors and random errors on a cognitive flexibility task. Both male and female KO mice exhibited an increased acoustic startle response, with baselines also higher compared to control mice. *This proposal aims to identify whether GSK3β affects NMDAR subunit expression in PFC PV interneurons and the effects on behavior and neurophysiology*. Gaining a better grasp on this signaling cascade will help provide an essential framework for understanding how GSK3β regulates NMDA receptors in the PFC, specifically within PV interneurons**.**

Disclosures: S. Monaco: None. **A.J. Matamoros:** None. **G. Han:** None. **E.M. Black:** None. **R.A. España:** None. **W. Gao:** None.

Poster

249. Prefrontal Cortex: Physiology of Decision Making

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 249.04/QQ22

Topic: H.01. Animal Cognition and Behavior

Support: CAS 100 talents

Title: Role of the superior colliculus in value-base decisions during a saccade foraging task

Authors: *B. ZHANG[1], J. Y. KAN[2], M. DORRIS[1]
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Abstract: Value-based decision-making requires choosing the option with the highest value. Although much progress has made in understanding its neural basis, how values are represented, compared and the final choice made are not fully understood. Here we asked whether premotor brain regions are involved in value-based decision-making or they simply enact the preselected motor response. Specifically, we ask whether the midbrain superior colliculus (SC) is involved in choosing value-based saccadic eye movements. To investigate this question, we either recorded the activity of single SC neurons, or artificially activated a population of SC neurons, in two rhesus macaques during a saccade foraging task. On each trial, a grid of colored dots was presented. The physical attributes of the dots were identical except that each was one of three

colors. Monkeys harvested water reward from the targets by fixating them for a pre-specified amount of time. All targets of the same color shared the same value [value = reward magnitude/required fixation time]. Each target yielded only one reward per trial and, importantly, trials ended before all of the items could be harvested. In accordance with foraging theory, monkeys maximized their intake of reward by selecting targets in descending order of their value rank.Recording results showed that, during a new fixation, activity was initially strongly correlated to the value of the target in the neuron's response field. However, just before a target was harvested, this activity reached a constant 'threshold' level if the response field target was chosen. Interestingly, if the response field target was not chosen, the value of that target was still reflected in SC activity. To test the causal role of SC in the value-based decisions, we used electrical microstimulation to perturb activity on the SC map and observed whether this biased choices. Subthreshold stimulation biased choices towards the stimulation site especially if occupied by high-valued targets.Lastly, we examined how patterns of activity across the SC map were updated as high valued targets were harvested and the 2nd (or 3rd) ranked targets became the most valuable. Both our recording and stimulation results indicate that SC value representations are dynamically updated as the value rankings change within the target array. Together, our results suggest that the SC dynamically represents the value of potential targets and is actively involved in the choosing value-based saccades.

Disclosures: B. Zhang: None. **J.Y. Kan:** None. **M. Dorris:** None.

Poster

249. Prefrontal Cortex: Physiology of Decision Making

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 249.05/RR1

Topic: H.01. Animal Cognition and Behavior

Support: SC and TN supported by Peter Morgane Research Fellowships from UNE College of Osteopathic Medicine

Title: Effects of estrogen on attention and monoamines in the prefrontal cortex of the female rat

Authors: *D. J. MOKLER[1], S. C. CHEN[2], S. KOLANGARA[2], T. NEWELL[2], J. A. MCGAUGHY[3]
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Abstract: The prefrontal cortex is involved in executive functions including attention. Evidence of a role of estrogen in affecting the working of the prefrontal cortex (PFC) has been found in human and animal studies. The monoaminergic neurotransmitter system involving norepinephrine (NE), dopamine (DA) and serotonin (5HT) are considered to be primary systems

involved in executive functions in the PFC. We have reported in previous studies using the attentional set shifting task (ASST) that noradrenergic systems in the PFC are important (Mokler et al., 2017; Newman et al., 2017). Low levels of NE innervation are associated with poor performance on reversals in the ASST. In the current experiment we examined three groups of female Long-Evans rats. In one group we performed a sham surgery for ovariectomy (SHAM). In a second group we preformed ovariectomies followed by regular injections of estradiol (OVX+E). A third group had ovariectomies following by vehicle injections (OVX). Following recovery from surgery, animals were assessed for attention in an attentional set-shifting task (ASST)(Bradshaw et al., 2016). Animals were then implanted with guide cannulae into the left and right prefrontal cortices for *in vivo* microdialysis. Probes were placed into medial prefrontal cortices and basal levels of NE, DA and 5-HT were determined over a 1 hour period. Atomoxetine was then injected i.p. at a dose of a 0.1 mg/kg. Samples were collected over another three hour period. Results: In the ASST, all groups performed similarly, except in the total reversals. In total reversals, the OVX group had significantly fewer trials to criteria than either the SHAM or the OVX+E groups. Assessment of the medial PFC showed that the OVX+E group had a significant increase in basal extracellular NE in the left mPFC. No significant changes were seen in extracellular DA or 5-HT. These data suggest a role for estrogen in the levels of NE in the prefrontal cortex, although the link to attention is not clear.

Disclosures: D.J. Mokler: None. **S.C. Chen:** None. **S. Kolangara:** None. **T. Newell:** None. **J.A. McGaughy:** None.

Poster

249. Prefrontal Cortex: Physiology of Decision Making

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 249.06/RR2

Topic: H.01. Animal Cognition and Behavior

Title: Effects of a "junk-food" diet and a high fat diet on working memory and prefrontal cortex protein expression in Sprague Dawley rats

Authors: D. OBIRI-YEBOAH, C. L. WINGROVE, *P. J. VOLLBRECHT
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Abstract: Along with a number of physiological conditions such as type II diabetes and cardiovascular disease, emerging evidence suggests that obesity has negative neurological implications. A number of brain regions have been shown to be affected by obesity, including the prefrontal cortex (PFC), which is known to play an important role in “executive” functions such as inhibitory control, working memory, and decision-making. In fact, a number of studies have demonstrated decreased PFC function associated with obesity. In an effort to tease apart differing roles of diet and obesity-development in observed PFC deficits we explored the effects

of both a junk-food diet and a high fat diet on PFC mediated behaviors and PFC protein expression. Rats were fed either a junk-food diet (19.6% fat) calorically matched to standard chow and intended to mimic a typical Western diet, a high fat diet (60% kcal from fat), or a standard chow diet. Behavioral testing was conducted following a 4-week diet manipulation during which only animals fed the high fat diet gained significant weight compared to their control counterparts. Behavioral tests suggest deficits in PFC function arise in response to a high-fat diet and concurrent obesity-development, but not following consumption of a highly palatable "junk-food" diet. Protein expression differences in the PFC following diet exposure were then examined. Specifically, studies examined proteins involved in synaptic plasticity and astrocyte function. BDNF is a neuropeptide that aids in neurogenesis and synaptic plasticity, and has been demonstrated to play an important role in working memory and other PFC functions. Alterations in GLT-1 expression and activity have previously been linked to changes in PFC structure and function. In addition, inflammation and gliosis are hallmark characteristics of obesity, however few studies have explored their role in obesity development. Exploring the effects of a highly palatable diet compared to a high fat diet will improve our understanding of cognitive deficits associated with obesity.

Disclosures: D. Obiri-Yeboah: None. **C.L. Wingrove:** None. **P.J. Vollbrecht:** None.

Poster

249. Prefrontal Cortex: Physiology of Decision Making

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 249.07/RR3

Topic: H.01. Animal Cognition and Behavior

Support: NSF IIS-1350990

ZIA MH002928-01

Title: Unsupervised nonlinear dimensionality reduction of large-scale neural recordings in prefrontal cortex

Authors: *M. R. WHITEWAY[1], R. BARTOLO[4], B. B. AVERBECK[4], D. A. BUTTS[2,3]
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Abstract: Decisions rely on the collective action of large numbers of neurons. While experimental technology is able to deliver simultaneous recordings from increasingly large populations of neurons, new analysis techniques are required to understand these high-dimensional datasets. Dimensionality reduction (also called latent variable modeling) is a popular approach because it allows for the analysis of population activity in a much lower

dimensional space (the latent space). However, idenfying the latent space relevant for a particular task is challenging, especially when many variables of interest are not under experimental control, and might have nonlinear relationships with other variables. Here we apply the Rectified Latent Variable Model (RLVM; Whiteway and Butts 2017), an unsupervised dimensionality-reduction technique with a nonlinear extension, to simultaneous recordings from 8 microelectrode arrays implanted bilaterally in the prefrontal cortex (PFC) of macaque monkeys. Single and multi-unit activity was recorded while the monkeys performed an oculomotor saccade task, in which the saccade was directed to a target presented either to the left or right of a fixation point. First, we find that the nonlinear version of the RLVM is able to more accurately reconstruct the population activity using the same number of latent variables than the linear version. Second, we demonstrate the ability to decode the monkey's behavior (saccade right vs. saccade left) at near perfect accuracy in the latent space, despite the fact that this information was not used to determine the latent variables. Though decoding accuracy is equivalent between the linear and nonlinear spaces, the trajectories have a much larger separation in the nonlinear latent space. Finally, we demonstrate the ability to predict the reaction time on a trial-by-trial basis using the latent space, and show that this prediction ability is lost when using a related supervised dimensionality reduction technique. Taken together, these results illustrate the utility of unsupervised dimensionality reduction in attempting to understand the information represented in the activity of large populations of neurons.

Disclosures: M.R. Whiteway: None. **R. Bartolo:** None. **B.B. Averbeck:** None. **D.A. Butts:** None.

Poster

249. Prefrontal Cortex: Physiology of Decision Making

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 249.08/RR4

Topic: H.01. Animal Cognition and Behavior

Title: Dimensionality reduction and dynamic encoding in PFC during context-dependent decision making

Authors: *M. C. AOI[1], V. MANTE[2], J. PILLOW[1]
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Abstract: Recent work in mice, rats, and monkeys has indicated an important role for prefrontal cortex (PFC) in perceptual decision-making. Underlying this role is dynamic interactions among PFC neurons. The goal of the present study is to characterize these interactions using a new dimensionality reduction method. In this study, we examine high-dimensional population responses in monkey PFC during a context-specific decision making task (Mante et al., Nature,

2013). We approach the analysis of these data from the perspective that neuronal responses can be represented as low-dimensional trajectories through a linear subspace. While a number of dimensionality reduction methods have been proposed in recent years, methods aimed at distinguishing between the effects of different task variables are becoming increasingly important to distinguishing between the effects of different experimental inputs and outputs. In particular, existing methods have not been developed to perform inference on the dimensionality of the data. We introduce a new method of dimensionality reduction that identifies the primary axes of population activity responsible for the representation of different task variables during sensory integration, allowing us to examine how information about task context, stimulus, and choice is encoded over time. With our method, based on a probabilistic generative model of the data, we infer the optimal dimensionality of the low-dimensional subspaces required to faithfully describe population activity. Our method reveals time-dependent encoding of task variables in PFC represented as trajectories of latent variables through multi-dimensional encoding subspaces. We show that the best 1-dimensional linear encoding subspace is not constant in time; giving the appearance of transient encoding if latent variables are erroneously viewed in only one dimension. The trajectories of latent variables display a distinct "early" phase where activity lies on a 1-dimensional linear axis, followed by a "rotational" phase, where the activity is pseudo-periodic. This spatiotemporal partitioning of the activity closely resembles distinct phases of "preparatory" and "movement" activity previously reported in premotor cortex (Kaufman et al., Nat. Neuro. 2014) despite all actions in the present study being covert in the trial epoch examined. We speculate that the transition between "early" and "rotational" dynamics is a correlate of decision commitment.

Disclosures: **M.C. Aoi:** None. **V. Mante:** None. **J. Pillow:** None.

Poster

249. Prefrontal Cortex: Physiology of Decision Making

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 249.09/RR5

Topic: H.01. Animal Cognition and Behavior

Support: KAKENHI (no. 16H01289)

Title: Instability of neural trajectories in medial frontal cortex predicts individual differences in perceptual decision making

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Abstract: Decision behaviors of different subjects obey common neural mechanisms. However, decision behavior also varies significantly across individual subjects under uncertainty. Little is known about the neural characteristics of individual differences. Although a few studies have investigated the relation between functional connectivity across multiple cortical areas and individual differences in cognitive performance, no study has analyzed how neural activities within a local cognitive area influences individual differences in decision behavior. Here, we explore such characteristics in neural population dynamics recorded from the medial frontal cortex (mFC) of rats and elucidate the underlying mechanism in building a recurrent network model. In this experiment, rats performed a sensory-guided alternative choice task. The rats were trained to make a LEFT or a RIGHT choice in response to two auditory cues. After the training, when rats were exposed to the unfamiliar (unlearned) stimuli, choice responses varied significantly across individual rats: some rats responded differently to different stimuli (sensitive rats), while others responded similarly to them (insensitive rats). What kind of mechanism in neural dynamics underlies this individual difference? To this end, we constructed a reservoir network model and trained it to associate two stimuli with two choices. After training, we applied unfamiliar stimuli to the reservoir and analyzed its neural dynamics. The network replicated neural trajectories and individual difference that are observed in the rats. To understand property of neural dynamics, we applied the perturbations to a particular neural state along a neural trajectory and computed its disturbance called as susceptibility. We found that the susceptibility predicts behavioral traits: a network with higher susceptibility shows more sensitive behavior, while that with lower susceptibility shows less sensitive behavior. In addition, the susceptibility was correlated with the trial-by-trial variability of neural trajectories and then, the variability explains individual difference in response behavior. We found that trial-by-trial variability in neural trajectories in mFC can predict the difference across individual rats. A trajectory with higher susceptibility to perturbation implies shallower landscape around the trajectory, while that with lower susceptibility implies deeper landscape. Our study suggests that the different land scape of neural dynamics in mFC regulates individual differences in responding behavior.

Disclosures: **T. Kurikawa:** None. **T. Handa:** None. **T. Fukai:** None.

Poster

249. Prefrontal Cortex: Physiology of Decision Making

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 249.10/RR6

Topic: H.01. Animal Cognition and Behavior

Support: CIHR Grant MOP-93784

CIHR Grant MOP-84319

Title: How much do changes in movement or spatial location impact anterior cingulate cortex (ACC) neurons?

Authors: *A. HARATIKIA[1], A. LINDSAY[2], N. J. POWELL[3], J. SEAMANS[2]
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Abstract: Although the putative cognitive functions of the anterior cingulate cortex (ACC) receive considerable attention, there is a growing body of evidence to suggest that these neurons also encode information about movement, spatial location and/or body position. Disambiguating these signals from each other and from the encoding of other behaviourally or task relevant factors is an important challenge. In the present study, bundles of implanted tetrodes recorded the activity of ACC neurons as rats freely roamed an experimental enclosure. Simultaneously, using two CCD cameras and custom tracking software, we captured the xyz coordinates of the center of mass and 9 points on the rat's body every 200ms throughout the session. This yielded a matrix of 18 xyz coordinates that were precisely aligned to the neuronal firing data. Single neuron responses were analyzed using a Generalized Linear Model and ensemble decoding was achieved by use of regression and classification of movements and positions using Artificial Neural Networks and Random Forests. The firing of 61.98% of individual ACC neurons were found to be significantly related to either spatial location or one of the limb movement factors, yet overall these factors only accounted for 1.85% of the total firing rate variance. However, the distribution was highly skewed such that these factors accounted for a reasonable portion of the firing rate variance in a few neurons and very little in the rest. In addition, most neurons were responsive to more than one factor. While the vast majority of individual neurons were generally quite poor at tracking movements or locations, ensembles were much better. When trained and tested on different portions of a session, ensemble accuracy in predicting limb movements was as high as 53.36% while average accuracy at predicting spatial location (correct position out of 32 possibilities) was 52.12%. In sessions where we inserted Pavlovian tone (5s)-shock(1s) or tone(5s)-food(1 pellet) pairings, the proportion of firing rate variance related to the tones was significantly higher than the proportion related to movements or changes in spatial location. Somewhat surprisingly however, limb movement or spatial location decoding accuracy did not change appreciably during the tone periods. Taken together, these results imply that limb movement and spatial location are encoded by many ACC neurons but have very little relative influence over the firing patterns of most neurons.

Disclosures: A. Haratikia: None. **A. Lindsay:** None. **N.J. Powell:** None. **J. Seamans:** None.

Poster

249. Prefrontal Cortex: Physiology of Decision Making

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 249.11/RR7

Topic: H.01. Animal Cognition and Behavior

Support: Brain & Behavior Research Foundation Young Investigator Award to YY

the Penn State Hershey Neuroscience Institute to RBM

the Parkinson's Disease Gift Fund of the Penn State University to RBM

Title: The medial prefrontal cortex modulates spatial working memory in the T-maze through strategic neuronal encoding

Authors: *Y. YANG, R. B. MAILMAN
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Abstract: The medial prefrontal cortex (mPFC) is critical for spatial working memory (sWM). We examined how its strategic neuronal encoding correlated with T-maze behavior of rats. Neurons increased their firing rate around choice, and this increase was largely before choice as a prospective encode of behavior. Moreover, it could be classified as sensitive to spatial information or sensitive to choice outcome. The sensitivity to spatial choice was defined by neuronal firing rate before left or right choice; there were no differences in the number of left- or right-choice-sensitive neurons. There was, however, location-related neuronal activity in which neurons fired at distinct rates when rats were in left or right location after choice. More neurons were sensitive to left location, and the majority of these were recorded from rats who preferred the right location. The sensitivity to outcome was defined by if a neuron fired at the correct or at the error choice. Significantly more neurons were sensitive to error outcome, and among these, more preferred to encode prospectively, increasing firing in advance of an error outcome. Similar to single neuronal activity, the mPFC enhanced its neuronal network as measured by the oscillation of local field potential. The maximum power of oscillation was around choice, and occurred slightly earlier before error versus correct outcome. Taken together, our results suggest that the mPFC modulates sWM, including not only spatial information, but also outcome-related strategy. Additionally, neuronal ensembles monitor behavioral outcome to make strategic adjustments to ensure successful task performance.

Disclosures: Y. Yang: None. **R.B. Mailman:** None.

Poster

249. Prefrontal Cortex: Physiology of Decision Making

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 249.12/RR8

Topic: H.01. Animal Cognition and Behavior

Title: Prefrontal cortex GIRK channel function in cognitive deficits associated with chronic stress and depression

Authors: *S. LOKE[1], D. GOMEZ[2], E. MARRON FERNANDEZ DE VELASCO[4], K. WICKMAN[4], M. C. HEARING[3]
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Abstract: Functionality of the medial prefrontal cortex (mPFC) relies on precisely coordinated activity of principal glutamatergic pyramidal neurons. Functional imbalances in excitatory and inhibitory signaling that result in increased (disorganized) activity of pyramidal neurons in the mPFC are believe to significantly contribute to impaired working memory, social withdrawal, and anxiety-like behavior in stress-related psychiatric disorders. GIRK channels are potent regulators of mPFC pyramidal neuron excitability and effectors for inhibitory metabotropic receptors, including perisomatic $GABA_BRs$ - a target of local GABA neurons that regulate firing of pyramidal cells. The present study sought to evaluate whether functional integrity of PFC-dependent cognition relies on pyramidal neuron GIRK channel function, and if reductions in GIRK signaling represent an underlying factor in stress-induced cognitive and negative symptoms associated with neuropsychiatric disorders. We used a neuron and brain-region specific approach to target the GIRK1 subunit by infusing an adeno-associated virus (AAV8-CaMKII-Cre) into the mPFC of mice harboring a 'floxed" version of the *Girk1* gene (*Girk1*$^{flox/flox}$). Behavioral testing involved assessment of working memory, behavioral flexibility and anxiety-like behavior. Whole-cell recordings in acute brain slices showed that AAV-expression increased intrinsic excitability and spike firing, and diminished GABAB- and GIRK1-mediated signaling in Layer 5/6 pyramidal neurons. *Girk1*$^{flox/flox}$ infused with AAV-Cre exhibited increased anxiety-like behavior and significantly reduced accuracy in a T-maze delayed alternation test of working memory -- the former of which can be rescued with a systemic injection of the GIRK-selective agonist, ML-297. In an operant model of set-shifting, reductions in mPFC pyramidal cell GIRK signaling did not alter initial lever training, but impaired performance in the visual-cue training. Unexpectedly, these mice performed slightly better during subsequent visual-cue to response set-shift, compared to controls. We also examined the impact of chronic unpredictable stress (CUS) on mPFC pyramidal neuron $GABA_B$-GIRK signaling. 5-10 d following CUS, mice displayed deficits in working memory that were paralleled by a reduction in baclofen-induced currents as well as increased excitability and spike firing in Layer 5/6 pyramidal neurons. Current studies are underway to examine the temporal and projection-specific nature of these adaptations, and whether up-regulation pharmacological or genetic approaches that upregulate GIRK signaling rescue stress-induced behavioral deficits.

Disclosures: S. Loke: None. **D. Gomez:** None. **E. Marron Fernandez de Velasco:** None. **K. Wickman:** None. **M.C. Hearing:** None.

Poster

249. Prefrontal Cortex: Physiology of Decision Making

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 249.13/RR9

Topic: H.01. Animal Cognition and Behavior

Support: MH104716

Title: Noradrenergic modulation of premotor cortex during decision execution

Authors: *E. M. RODBERG, C. R. DEN HARTOG, M. A. KELBERMAN, E. M. VAZEY
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Abstract: Rodent premotor cortex (M2) integrates information from sensory and cognitive networks for motor planning and movement initiation. M2 function is regulated by cortical inputs and ascending neuromodulators, including norepinephrine (NE) from the locus coeruleus (LC). To probe the role of NE on M2 function and cognitive performance, we used α1 and β adrenergic antagonists with extracellular electrophysiology in awake behaving animals during a two-alternative forced choice (2AFC) task.

Adult Long-Evans rats (both sexes) were implanted with 32-channel microelectrode arrays in M2. Rats were trained on a two-alternative forced choice task (2AFC) in which they learned to press the correct lever indicated by cue lights to obtain a sucrose reward. Rats self-initiated trials by nosepoking an IR beam for a variable hold until receiving one of two cues with 50% probability on each trial. Rats could perform up to 250 trials per 40 minute session. After rats could reliably perform the task (~3 weeks, > 70% accuracy), they were tested with various adrenergic compounds, including the β antagonist ((S)-(-)-propranolol 10mg/kg), its less active enantiomer ((R)-(+)-propranolol 10mg/kg), the α1 antagonist (prazosin 1mg/kg), or vehicle. Behavioral performance in this task was measured by performance accuracy, number of trials initiated, omissions, and reaction time from cue onset to lever choice.

Manipulations of NE signaling show that systemic propranolol decreased accuracy and increased omitted trials whereas prazosin only increased total number of trials initiated. Comparisons between sexes show that in females, all compounds decreased reaction time though only propranolol increased omitted trials. Analysis of recordings is ongoing with over 90 single units from M2. We expect to see an increase in firing rate preceding a behavioral response during a trial and a disruption of neuronal activity by propranolol that will correlate with changes in behavioral accuracy. Results from this study indicate that propranolol can impair focused decision-making by lowering β noradrenergic signaling and that there may be sex-specific interactions in noradrenergic influence over cognition.

Disclosures: E.M. Rodberg: None. **C.R. den Hartog:** None. **M.A. Kelberman:** None. **E.M. Vazey:** None.

Poster

249. Prefrontal Cortex: Physiology of Decision Making

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 249.14/RR10

Topic: H.01. Animal Cognition and Behavior

Title: Npas4-deficient mice lack cellular resilience against mild stress in adolescence and show impaired cognitive flexibility in adulthood

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Abstract: The prefrontal cortex (PFC) relies on a balance of excitatory and inhibitory neurotransmission to integrate perceptions, memories, and emotions toward guiding goal-directed behavior. This excitatory/inhibitory (E/I) balance is largely established during early postnatal and adolescent development and depends on activity-dependent maturation of the GABAergic system. Genetic and/or environmental factors during adolescence can disrupt E/I balance and maturation and lead to cognitive and emotional dysfunction in adulthood. The present study examined in mice the interaction between chronic mild stress (CMS) during adolescence [postnatal day - PND - 28-42] and deficiency of Npas4, an activity-dependent, brain-specific transcription factor that regulates the formation and maintenance of inhibitory synapses. Npas4 wild type (WT) and heterozygous (HET) mice were tested and brains were collected in adulthood [PND 63-68]. Anxiety behaviors were measured in the elevated plus maze and open field test, and PFC-dependent cognitive function was measured using the attentional set shifting task (ASST). Behaviorally, adolescent CMS lead to increased anxiety in adulthood, an effect that was not mediated by Npas4. Only the Npas4 HET mice trended toward impaired cognitive flexibility in adulthood following adolescent stress, as observed by poor performance on the extradimensional set shift trial of the ASST. At the cellular level, adolescent stress increased the percentage of PV cells that were surrounded by perineuronal nets (PNNs) in WTs. HET mice, on the other hand, did not show this increase in PNNs. Preliminary data also show that adolescent stress may increase expression of inducible nitric oxide synthase (iNOS), a producer of nitric oxide and thereby a marker of oxidative stress. PNNs protect PV cells from oxidative damage, and decreases in PNNs and PV expression have been observed in the brains of schizophrenia patients. Further analyses will investigate whether a stress-induced increase in iNOS, together with a lack of PNN upregulation in HETs, impacts the PV cells of HET mice. These results suggest that WT mice are capable of exerting homeostatic compensatory changes in response to adolescent stress, such as increasing PNN coverage of PV cells, which protect against cognitive impairment in adulthood: an ability that Npas4 HET mice lack. This

demonstrates a novel gene by environment interaction that influences E/I balance and resilience vs. vulnerability to stress, with implications for adolescent onset disorders like schizophrenia.

Disclosures: C. Page: None. **J. Alexander:** None. **L. Coutellier:** None.

Poster

249. Prefrontal Cortex: Physiology of Decision Making

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 249.15/RR11

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant R01MH104251

NIH Grant 1R01DA038063-01

Title: Adapting choice behavior and neural value coding in monkey orbitofrontal cortex

Authors: *J. ZIMMERMANN[1,2], P. W. GLIMCHER[2], K. LOUIE[2]
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Abstract: Behaving organisms face constantly changing environments, requiring nervous systems to encode broad ranges of information efficiently within finite coding constraints. In sensory systems, this problem is widely believed to be addressed by adaptive coding mechanisms like temporal adaptation and spatial normalization. Recent work has demonstrated that temporal adaptation occurs in reward-processing and decision-related brain areas, but the computational mechanisms and behavioral consequences of this temporal adaptation is largely unknown. Here, we present data from a saccadic choice task in which trained monkeys chose between two options differing in reward magnitude and juice type. Blocks of trials were composed of a mixture of “adaptor trials” and “measurement trials”. In measurement trials (identical across blocks), monkeys chose between an unvarying reference reward and one of 5 variable rewards. These trials quantify the monkey’s probability of choosing the reference reward as a function of the magnitude of the variable reward; a *choice curve*. Across blocks, we systematically varied the structure of the adaptor trials to induce narrow or wide background reward environments. While monkeys performed this task, we recorded single-unit activity from orbitofrontal cortex (OFC; area 13). We found that adaptor variability had a significant effect on both choice at the behavioral level and neural value coding in OFC. Consistent with an adapting decision mechanism, monkeys exhibited steeper measurement trial choice curves in narrow vs. wide background reward environments. Out of 121 OFC neurons, 48 exhibited a significant ($p<0.05$) modulation by value in the measurement trials (cue or reward period). Consistent with neural adaptation, the slope of value coding was steeper in narrow vs. wide blocks. We then tested if the extent of this coding difference (narrow vs. wide) correlated with the behavioral difference in the

choice curve slopes (narrow vs wide) across sessions. In both the cue and reward intervals, cells that exhibited a significant modulation by value exhibited a correlation between neural and behavioral adaptation (cue interval: rho=0.74, p=0.02; reward interval: rho=0.63, p=0.005). These results suggest a neurometric-psychometric link between choice performance and value coding in OFC neurons, suggesting a neural mechanism for adaptive decision-making. Ongoing work will examine whether adapting choice behavior and OFC responses correspond to predictions of dynamic divisive normalization-based models of history-dependent decision making.

Disclosures: J. Zimmermann: None. **P.W. Glimcher:** None. **K. Louie:** None.

Poster

249. Prefrontal Cortex: Physiology of Decision Making

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 249.16/RR12

Topic: H.01. Animal Cognition and Behavior

Support: R01-DA032758

Title: Neuronal activity in orbitofrontal cortex during economic decisions under sequential offers

Authors: *S. N. BALLESTA, C. PADOA-SCHIOPPA
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Abstract: Evidence from lesion studies and neurophysiology links economic decisions to the orbitofrontal cortex (OFC). In particular, experiments in which non-human primates chose between different types of juice identified in this brain area three populations of neurons reflecting the input and the output of the decision process. Offer value cells encode the value of one of the two juices, while chosen juice and chosen value cells encode the identity and the value of the chosen juice, respectively. This observation and corroborating results suggest that good-based decisions may be generated in a neural circuit within the OFC. However, our current understanding suffers from an important limitation: the vast majority of studies to date examined choices between goods offered simultaneously. Yet, in many real-life decisions, options available for choice appear sequentially. Thus the present study was designed to assess whether/how current notions generalize to decisions under sequential offers. In the experiments, one adult male monkey (*Macaca mulatta*) chose between two juices offered in variable amounts (i.e., 1 drop of apple juice vs. 3 drops of tea). In each trial, the animal maintained center fixation while two offers were presented centrally and sequentially. Terms "offer1" and "offer2" refer to the first and second offer, independently of the juice type and amount. After a delay following offer2, two saccade targets appeared on the two sides of the fixation point, and the monkey

indicated its choice with a saccade. For each pair of juice quantities, the sequential order varied pseudo-randomly. Importantly, the two offers were such that in most trials the animal had to wait for offer2 before making a decision. We recorded and analyzed the activity of 550 cells. Firing rates were examined in several time windows and regressed against a large number of variables potentially encoded in the OFC. The task design afforded the representation of goods and values in multiple frames of reference. Thus the analysis included both juice-based and order-based variables. The neuronal representation in OFC was overall diverse. Many neurons encoded the identity or value of individual juices (as observed with simultaneous offers), but a sizable population of cells also reflected juice value and identity in an order-based reference frame. Other cells encoded the chosen value, independently of the juice type or sequential order. Remarkably, many neurons presented specific patterns of responses across time windows. These patterns might reflect the organization of a neural decision circuit.

Disclosures: S.N. Ballesta: None. **C. Padoa-Schioppa:** None.

Poster

249. Prefrontal Cortex: Physiology of Decision Making

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 249.17/RR13

Topic: H.01. Animal Cognition and Behavior

Support: NIMH Grant MH097061

Title: Confidence representations across sensory modalities in orbitofrontal cortex

Authors: *T. OTT[1], P. MASSET[1,2], J. HIROKAWA[1], A. KEPECS[1]
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Abstract: Evidence informing the confidence we have in our decisions can come from many sources, including different sensory modalities. Neurons in orbitofrontal cortex (OFC) signal confidence in olfactory discriminations and OFC inactivation impairs the ability of rats to report their confidence. However, it is unclear if confidence computations in OFC depend on the sensory modality used to make a choice. Here we tested the hypothesis that confidence representations in OFC generalize across modalities by recording single neuron activity during olfactory and auditory decisions. Rats were trained to make a choice based on either olfactory or auditory stimuli, interleaved pseudo-randomly, by entering one of two choice ports. The difficulty of olfactory decisions was controlled by varying the odor-mixture ratio, while for auditory decisions we varied the balance of left/right rates in binaural streams of random clicks. Reward delivery was delayed so we could measure the willingness of rats to wait for reward at the choice port, providing a post-decision temporal wager as a report of decision confidence.

This task allows us to compare the responses of individual neurons in a single session to sensory stimuli from two modalities. We record 350 well-isolated single units from 3 rats. First, we found neurons in OFC represented decision confidence for both sensory modalities. Consistent with these representations neurons (n = 41) predicted the outcome of a trial (correct/error) during the waiting time period after the rats entered the choice port across both modalities. Outcome selectivity was strongly correlated between the two modalities at the beginning of the waiting time period and just before rats left the choice port. We also found that the activity of many single neurons in OFC was correlated trial-to-trial with the waiting time report, predicting the duration rats were willing to wait for a reward several seconds in advance of leaving. Our results suggest that single neurons in OFC represent decision confidence irrespective of the sensory modality used to make the decision. Thus, OFC might compute a metacognitive confidence signal providing a general estimate that the choice taken was correct.

Disclosures: **T. Ott:** None. **P. Masset:** None. **J. Hirokawa:** None. **A. Kepecs:** None.

Poster

249. Prefrontal Cortex: Physiology of Decision Making

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 249.18/RR14

Topic: H.01. Animal Cognition and Behavior

Support: CAS Hundreds of Talents Program

Title: Top-down attention modulates activity of value-encoding orbitofrontal neurons

Authors: *Z. ZHANG, Y. XIE, T. YANG
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Abstract: Attention has been suggested to play an important role in value-based decision making. Previously we showed that OFC neurons encoded the value of the attended stimulus through a bottom-up attention mechanism even when monkeys were only passively viewing the stimuli. In the current study, we looked at how top-down attention may modulate prefrontal cortex activity. We first trained a monkey with a passive viewing task to learn the association between five shapes and their respective reward: 0, 1, 2, 4, 8 drops of juice. The monkey had to maintain fixation for 4.5 seconds when a shape was presented and received its associated reward after the fixation period expired. After the monkey learned the stimulus-reward association, we then trained it to perform a visual detection task. The monkeys had to look at a center fixation point when two shapes, randomly selected from the five previously learned shapes, were presented on both the left and the right sides of the fixation point. After a random period, one of the shapes was dimmed (go cue), and the monkey had to report this visual change by saccading to a target 6 degrees above the fixation point within 400 ms after the go-cue onset. A square

frame was presented transiently for 400 ms at 200 ms before the shapes appeared and served as a location cue to indicate which shape would be dimmed. In 85% of the trials (valid cue), the frame was on the opposite side of the dimmed shape. For the rest 15% trials (invalid cue), the frame was on the same side as the dimmed shape. The monkey was rewarded if it performed the detection correctly. Importantly, the reward was randomly selected between the two shapes. Thus, the value of attended shape was dissociated from the value that the monkeys expected to receive. We found that the monkey's reaction time was negatively correlated with the value of the shape that served as the go cue. Most importantly, the animal responded significantly faster in the valid-cue trials than in the invalid-cue trials, suggesting that the monkey paid more attention to the cued shape. We then recorded single unit activity in the OFC and the dorsolateral prefrontal cortex (DLPFC). We found that the OFC neurons encoded the value of the attended shape, which was on the opposite side of the cue. They did not encode the spatial location of either the attention or the cue (left vs. right). In contrast, DLPFC neurons encoded both the value and the spatial location of the attended shape. These results suggest that the top-down attention modulates the OFC activity similarly to the bottom-up attention and the DLPFC plays a different role from the OFC in the processing of value information.

Disclosures: Z. Zhang: None. **Y. Xie:** None. **T. Yang:** None.

Poster

249. Prefrontal Cortex: Physiology of Decision Making

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 249.19/RR15

Topic: H.01. Animal Cognition and Behavior

Support: Pew Charitable Trusts

Swiss National Science Foundation

Title: Functional assessment of large scale cortical networks during multi-sensory decision-making

Authors: *S. MUSALL, S. GLUF, A. K. CHURCHLAND
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Abstract: The transformation of sensory inputs into an appropriate behavioral response is a key brain function for decision-making. A number of cortical areas have been implicated in this transformation, especially for the accumulation of sensory evidence over time. However, they are mostly studied in isolation and it remains unclear if other areas may be part of a larger cortical decision-making circuit. Moreover, inhibition of parietal cortex can impair animal performance with visual but not auditory stimulation, indicating that some areas may be modality

specific.
To gain a more complete picture of cortical decision-making, we trained head-fixed mice in a two-alternative forced choice paradigm for discrimination of bilaterally presented stimulus sequences. Each sequence consisted of randomly timed sensory events and mice were trained to report the side where more events were presented. Events were either visual flashes, auditory clicks or both modalities combined. Mice achieved performance above 90% in the easiest condition and psychophysical reverse correlation confirmed that animals' decisions were affected by events during the whole 1-s stimulus duration. We then used a tandem lens macroscope to measure large-scale cortical activity patterns through the cleared skull of task-performing mice. Mice were triple-transgenic (Emx1-Cre;LSL-tTA;Ai93D) and expressed the calcium indicator GCaMP6f in cortical pyramidal neurons. Retinotopic mapping of trained mice revealed the location of up to eight higher visual areas, enabling a precise localization of decision signals during behavior. To identify decision signals, we used a linear support vector machine (SVM) classifier. The SVM was trained and cross-validated on imaging data at independent times during the trial to predict the animal's subsequent choice. Classifier performance continuously increased over the course of the stimulus presentation and was close to optimal just before the decision period onset. During stimulus presentation, the SVM mainly relied on activity in multiple visual areas, such as V1, AM, PM and MMA. Moreover, we identified multiple areas in frontal cortex that were most informative of animal choice during the decision period.
Our results demonstrate that wide-field calcium imaging is an effective method to image large-scale cortical activity in mice trained to make perceptual decisions. The combination of this approach with a complex behavioral task in mice allowed us to identify a number of candidate areas that may support decision-making. Further investigation is needed to identify the functional role of these candidate areas and causally verify their importance for behavior.

Disclosures: **S. Musall:** None. **S. Gluf:** None. **A.K. Churchland:** None.

Poster

249. Prefrontal Cortex: Physiology of Decision Making

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 249.20/RR16

Topic: H.01. Animal Cognition and Behavior

Support: COGNITO grant, Danish Research Council

Title: Prefrontal nicotinic- and NMDA-receptor activity is necessary for performance in a task of cognitive flexibility in rats

Authors: *D. PHENIS[1], V. VALENTINI[1,2], J. P. BRUNO[1]
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Abstract: Executive functions such as cognitive flexibility require the integrity of the PFC. Deficits in cognitive flexibility appear in many psychiatric disorders characterized by PFC pathophysiology. Examinations of the neurochemical basis of cognitive flexibility utilizing an attentional set-shifting task (ASST) have previously revealed performance deficits following systemic antagonism of either glutamatergic or cholinergic neurotransmission. What is less established is the impact of local antagonism of specific subtypes of glutamatergic or cholinergic receptors in the PFC and whether performance in particular stages of the task is selectively linked to either class of receptors. In this study male adult rats were implanted with infusion cannula bilaterally into the prelimbic region of the medial PFC. Animals were infused bilaterally with an aCSF vehicle, MK-801(6.0 μg/hemisphere), a N-methyl-D-aspartate receptor (NMDAR) antagonist, or mecamylamine (10 μg/hemisphere), a non-selective nicotinic receptor antagonist. Local administration of these drugs resulted in decreased performance (in the two-choice ASST digging task), relative to vehicle-infused controls, during the first reversal stage (trials to criterion, vehicle = 16 ± 3; MK801 = 23 ± 5; mecamylamine = 24 ± 2) as well during the extradimensional shift (EDS) stage (vehicle = 15 ± 4; MK-801 = 21 ± 6; mecamylamine = 24 ± 3) despite no difference in the intradimensional shift (IDS) stage (trials to criterion 7-10 across the 3 groups). These data further support the role of prefrontal cholinergic (nicotinic) and glutamatergic (NMDA) transmission in cognitive flexibility. Ongoing studies, to be presented, seek to validate these results using a rodent touchscreen version of the traditional ASST. The touchscreen task is part of a battery designed to improve the face and construct validity of cognitive tasks used in translational research. Continued research into the drug conditions that produce deficits in reversal and extra dimensional shifting may further justify the focus on specific novel targets for cognition enhancement in psychiatric disorders.

Disclosures: D. Phenis: None. **V. Valentini:** None. **J.P. Bruno:** None.

Poster

249. Prefrontal Cortex: Physiology of Decision Making

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 249.21/RR17

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant EY017921

NIH Grant EY017292

Title: Fine patterns of prefrontal connections mapped by electrical microstimulation and fMRI in the macaque

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Abstract: Lateral prefrontal cortex (LPFC) plays an important role in cognitive control. Recent evidence suggests subregions of LPFC may contribute differentially to various components of a cognitive task, e.g., the ventral prearcuate (VPA) region for feature-based visual attention (Bichot et al., 2015). Fine delineation of connections of LFPC can provide invaluable constraints for understanding its functional architecture. Although previous anatomical tracing studies have looked at connections of LPFC, it is difficult to reach a clear and fine map of connectivity due to the sparseness of injection sites and individual differences across animals. Moreover, the tracing results usually lack same-subject comparisons with neurophysiological observations in behaving animals. Here we mapped the fine patterns of LPFC connections *in vivo* using combined electrical microstimulation and fMRI (EM-fMRI) in the macaque.
A male macaque monkey (8 kg) was scanned in a 3T Siemens Trio magnet under propofol anesthesia (0.1-0.4 mg/kg/min) with his eyes covered. We delivered 500 μA, 333 Hz charge-balanced bipolar current pulses for 210 ms every second in 30-sec blocks. The locations of stimulations sites were confirmed with T1- and T2-weighted structural images during each session. At each site, we collected four runs (34 mins) of MION signals using an EPI sequence (2 mm isotropic), to balance between maximizing SNR and minimizing scanning time. We also collected diffusion-weighted images from the same subject in a 3T Siemens Prisma magnet using a multi-shell sequence (0.8 mm isotropic; b=1000/2000/3000; 160 directions/shell). The same sequences were run for both AP and PA phase encoding directions.
We stimulated 66 LPFC sites close to the junction between the arcuate and principal sulci, including the frontal eye field (FEF), VPA, area 46, and dorsolateral prefrontal cortex. The EM-fMRI connectivity patterns were robust across sessions and in general consistent with monosynaptic connections reported in previous tracing studies. Most interestingly, we found systematic shifts in patterns of connections as we moved the site of stimulation along certain trajectories within LPFC. For example, from dorsal to ventral FEF to VPA, the preference of connections shifted from mid- to high-level visual areas. Diffusion-based analysis captured some coarse difference between LPFC subregions defined by EM-fMRI, but its sensitivity and specificity was not comparable to the latter. The results suggest that EM-fMRI is a powerful tool for mapping fine-grained patterns of connectivity and potentially targeting inter-connected areas for recording and manipulation on an individual basis.

Disclosures: R. Xu: None. **N.P. Bichot:** None. **P.K. Weigand:** None. **A. Takahashi:** None. **R. Desimone:** None.

Poster

249. Prefrontal Cortex: Physiology of Decision Making

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 249.22/RR18

Topic: H.01. Animal Cognition and Behavior

Support: R01DA042038

F30MH110084

Klingenstein-Simons Foundation

MQ Fellowship

NARSAD

Whitehall Foundation

Sir Henry Wellcome Postdoctoral Fellowship

Title: Action-outcome encoding in dorsomedial prefrontal cortex

Authors: B. A. BARI, C. D. GROSSMAN, R. K. NIYOGI, *J. Y. COHEN
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Abstract: In an unstable world, the brain relies on recent experience to generate behavior. The dorsomedial prefrontal cortex (dmPFC) is among the areas involved in generating flexible behavior, but how it does so is unknown. To determine how dmPFC encodes rewards and choices dynamically, we developed a foraging task in thirsty, head-restrained mice, adapted from one in monkeys (Sugrue LP, Corrado GS, Newsome WT, Science 304, 1782, 2004; Lau B, Glimcher PW, J Exp Anal Behav 84, 555, 2005). On each trial, an olfactory "go" cue signaled to the mouse to make a choice (or a rare "no-go" cue signaled to wait for the next trial). Mice chose freely between two "lick ports," one on the left of the tongue, one on the right. Each lick port delivered reward probabilistically, and these probabilities changed over time. Thus, to maximize reward, mice needed to use recent reward outcomes to choose actions flexibly. Consistent with this, logistic regression revealed that mice used reward history on the past 3-5 trials to determine choices on a trial-by-trial basis. Value- and policy-based model-free reinforcement-learning models predicted choice behavior similarly, suggesting that multiple algorithms could mimic behavior. To determine how dmPFC neurons encoded behavioral variables, we first reversibly inactivated it, using the $GABA_A$ receptor agonist muscimol. This prevented mice from updating choices appropriately. Next, we recorded action potentials from 2130 dmPFC neurons in six mice across 132 sessions of the foraging task. The majority of neurons were task responsive and

encoded information that could be used to generate an action-outcome contingency table. Populations of neurons encoded the mouse's choice (26%), reward (23%), and the interaction between choice and reward (53%). A subset of neurons encoded the upcoming choice, even before the go cue (7%). Another subset tracked the local history of rewards received (6%). These data are consistent with the hypothesis that dmPFC encodes basic variables needed to make actions on the basis of past outcomes and is necessary for adaptive outcome-based behavior.

Disclosures: B.A. Bari: None. **C.D. Grossman:** None. **R.K. Niyogi:** None. **J.Y. Cohen:** None.

Poster

249. Prefrontal Cortex: Physiology of Decision Making

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 249.23/RR19

Topic: H.01. Animal Cognition and Behavior

Support: Center for Sensorimotor Neural Engineering, NSF EEC-1028725

NIH Grant NS078127

The Sloan Foundation

The Klingenstein Foundation

The Simons Foundation

The McGovern Institute

Rubicon Grant (2015/446-14-008) from the Netherlands Scientific Organization

Title: Neural signature of Bayesian interval timing in dorsomedial frontal cortex

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Abstract: In an uncertain environment, monkeys and humans integrate sensory measurements with prior experiences, consistent with Bayesian integration. However, neural representation of the prior knowledge and neural computations supporting the Bayesian integration are not understood. To tackle this question, we recorded from dorsomedial frontal cortex (DMFC) of monkeys performing a novel time-interval reproduction task. Animals had to measure a sample interval (t_s) demarcated by two visual cues ("Ready" and "Set"), and reproduce it ("Go") afterwards as accurately as possible. In this task, when the t_s is randomly drawn from a prior distribution across trials, responses exhibit a robust bias toward the mean of the prior, as

predicted by Bayes-optimal integration. To investigate how the prior and measured t_s are integrated, we designed a variant of the Ready-Set-Go task with two "prior contexts". In the "Short" context, t_s was drawn from a uniform distribution between 480 and 800 ms, and in the "Long" context, between 800 and 1200 ms. On each trial, the context was cued by the color of the fixation point and switched unpredictably after 5-25 trials. Animals were able to perform the task and demonstrated prior-dependent biases in both contexts.
DMFC responses were strongly modulated by both elapsed time and prior context throughout the trial. However, single-neuron responses were highly heterogeneous and did not reveal the logic of integration. In contrast, analysis of responses across the population revealed a highly structured representation with context-dependent rotational dynamics temporally tuned to the range of the prior. Therefore, we hypothesized that the prior-dependent biases result from the evolution of noisy neural trajectories constrained by the rotational dynamics. Analysis of the a linear dynamical system fitted to each prior context revealed fixed points in the vicinity of the rotational dynamics. This suggests that the prior might exert its influence via the action of fixed points that shape the latent dynamics. Accordingly, we found that the fixed points were stable and capable of biasing noisy trajectories in a prior-dependent manner. To further evaluate the role of fixed points in generating prior-dependent biases, we analyzed the latent dynamics of a Bayesian recurrent neural network (RNN) model trained to perform the same task. Analysis of the trained RNN revealed similar rotational dynamics mediated by prior-dependent fixed points. These results suggest that prior experience establishes fixed points in the neural state space, which can exert a biasing force on noisy neural trajectories, consistent with Bayesian integration.

Disclosures: H. Sohn: None. **D. Narain:** None. **M. Jazayeri:** None.

Poster

249. Prefrontal Cortex: Physiology of Decision Making

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 249.24/RR20

Topic: H.01. Animal Cognition and Behavior

Support: CIHR Grant MOP-93784

CIHR Grant MOP-84319

Title: Neonatal Ventral Hippocampal Lesioned (NVHL) rats show attentional deficits on a delayed alternation task

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Abstract: Neonatal Ventral Hippocampal Lesioned (NVHL) rats have been used as a model of the cognitive deficits in schizophrenia for many years. As a result of inappropriate connectivity during adolescence, lesioned animals show signs of a disinhibited prefrontal cortex in adulthood. Previous studies have found that these lesions produce deficits in executive functions including working memory and set shifting, similar to those reported in patients with schizophrenia. We analyzed in detail the behavior of a set of NVHL rats and a set of sham control rats (both Male, Long Evans) on a delayed alternation lever press task in an operant environment. On each trial of the task, the animals made a lever press and if it was correct, received a reward. They then had to wait out a delay period until a cue light turned on, at which point they would execute a nose poke in order to extend the levers on the other side of the box. They would then cross the box and press the lever opposite to the one they just pressed on the previous trial to receive a reward. We imposed delays of 3, 5, 10, 20 and 30 seconds quasi-randomly. Both lesioned and sham-lesioned animals were highly accurate at this task when delays were less than 10 seconds, and both were correct around 50% of the time (chance) at delays longer than 20 seconds. However, the NVHL animals were much less accurate at intermediate delays of 10-20 seconds. A trajectory analysis revealed that sham-lesioned animals spent most of their time either at the nose poke or lever locations or on direct paths between them, while lesioned animal spent more time in other regions of the box, especially for longer imposed delays, indicating that they had more difficulty maintaining their attention on the task. As a result they missed some nose poke cues, and experienced more unnecessarily long delays than sham lesioned animals, which partially explains their poorer overall task performance. In addition, NVHL animals had a higher propensity to disengage from the task by sitting in one location especially later in the sessions. We recorded multiple unit activity from these animals with tetrodes implanted in the Anterior Cingulate Cortex (ACC) during task behavior. Units recorded from the NVHL animals showed signs of disinhibition and over-dispersion, indicative of the typical changes in a disinhibited cortex. These changes may account for the attentional deficits, as well as some remaining working memory deficits we observed.

Disclosures: **N.J. Powell:** None. **J.K. Seamans:** None.

Poster

250. Prefrontal Cortex and Reward

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 250.01/RR21

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant AA019967

NIH Grant AA022701

NIH Grant 4T32AA007474-29

Title: Adolescent binge-like ethanol exposure differentially affects probabilistic reversal learning in Long-Evans versus Sprague-Dawley rats

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Abstract: Recent evidence from both human and animal studies indicates that the prefrontal cortex (PFC) is especially vulnerable to repeated episodes of binge alcohol exposure. Studies in animals have reported that binge-like exposure to alcohol during adolescence is associated with cognitive dysfunction when tested in adulthood. In the present study, we examined the effect of adolescent intermittent ethanol (AIE) exposure by vapor inhalation on performance of a probabilistic reversal learning (PRL) task in adult Long-Evans (LE) rats. This task requires rats to complete serial reversals within an operant learning session using probabilistic reward reinforcement. Compared to controls, AIE-exposed rats were moderately impaired on the first discrimination of the first day of PRL testing, indicating that AIE is associated with mild deficits in probabilistic reinforcement learning. However, we did not observe any effects of AIE on reversal learning. This finding was unexpected in light of previous studies using various non-operant procedures that reported deficits in reversal learning. To determine whether the lack of effect we observed on PRL in the present study could be a strain-specific effect of AIE, we repeated the examination of the effect of AIE on performance of the PRL task using Sprague-Dawley (SD) rats. These follow-up studies revealed that SD rats subjected to AIE-exposure displayed retarded acquisition of the PRL task, indexed by the number of reversals completed over 16 days of training, when compared to control rats. In addition, AIE treatment also caused a trend ($p = 0.06$) towards reduced win-stay/lose-shift behavior, suggestive of impairments in sensitivity to both rewards and negative feedback. Interestingly, this same impairment of win-stay/lose-shift behavior has been demonstrated following inactivation of the medial orbitofrontal cortex, which contributes in part to decision-making involving reward uncertainty. Taken together, these results are consistent with previous studies showing that AIE exposure alters prefrontal function in adulthood and that some of these impairments may be mediated by perturbed orbitofrontal functioning. Furthermore, these findings identify potential strain differences in the impact of AIE on cognitive function.

Disclosures: S.C. Garr: None. **J.T. Gass:** None. **S.B. Floresco:** None. **L. Chandler:** None.

Poster

250. Prefrontal Cortex and Reward

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 250.02/RR22

Topic: H.01. Animal Cognition and Behavior

Title: Local-field oscillatory activity in the medial prefrontal cortex responds to the execution of effortful behavior but not to the anticipation of effort or reward

Authors: *L. CROWN[1], D. A. NITZ[3], S. L. COWEN[2]
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Abstract: The initiation and maintenance of effortful behavior requires the coordinated activity of neural ensembles in cortical and subcortical regions. Neural activity in the anterior cingulate subregion of the medial prefrontal cortex has been implicated in effort-guided decision-making and in sustaining ongoing effortful behaviors. Furthermore, interactions between the frontal cortex and subcortical regions, such as the nucleus accumbens and ventral tegmental area, may also contribute to effort-guided behaviors. Low frequency (4 Hz) oscillatory activity has been suggested to coordinate activity between these regions (Fujisawa and Buzsáki, 2011). We investigated the possibility that low-frequency oscillations in the medial prefrontal cortex increase during the anticipation or execution of effortful behaviors. In this study, rats (n = 4, 32 sessions) were trained to perform an effort- and reward-guided reversal task in which the selected path indicated either the level of effort or reward (Cowen et al., 2012). Effort was presented in the form of an obstacle that was climbed to obtain reward. In this study, we examine local field potential activity in the rat medial prefrontal cortex as animals performed this task. Although no difference in local-field oscillatory activity was observed during periods of effort or reward anticipation, an increase in delta (1 - 4 Hz) power was observed during periods when rats scaled the barrier ($p < 0.025$, nonparametric permutation test). These data bolster the idea that oscillatory activity in the medial prefrontal cortex supports the execution and maintenance of effortful behavior.

Disclosures: **L. Crown:** None. **D.A. Nitz:** None. **S.L. Cowen:** None.

Poster

250. Prefrontal Cortex and Reward

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 250.03/RR23

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant MH110822

Brain and Behavior Foundation NARSAD

Intramural NIMH

Icahn School of Medicine

Philippe Foundation

Title: Amygdala input differentially influences prefrontal local field potential and single neuron encoding of reward-based decisions

Authors: *F. M. STOLL[1], C. P. MOSHER[1], S. TAMANG[1], E. A. MURRAY[2], P. H. RUDEBECK[1]
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Abstract: Reward-guided behaviors require functional interaction between amygdala, orbital (OFC), and medial (MFC) divisions of prefrontal cortex, but the neural mechanisms underlying these interactions are unclear. Here, we used a decoding approach to analyze local field potentials (LFPs) and single neurons recorded from OFC and MFC of three male monkeys (*macaca mulatta*) engaged in a stimulus-choice task, before and after excitotoxic amygdala lesions.
Whereas LFP responses in the OFC were strongly modulated by the amount of reward associated with each stimulus, MFC responses best represented which stimulus subjects decided to choose. This was counter to what we observed in the level of single neurons where their activity was closely associated with the value of the stimuli presented on each trial. After lesions of the amygdala, stimulus-reward value and choice encoding were reduced in OFC and MFC, respectively. However, while the lesion-induced decrease in OFC LFP encoding of stimulus-reward value mirrored changes in single neuron activity, reduced choice encoding in MFC LFPs was distinct from changes in single neuron activity.
Our results indicate that LFPs and single neurons represent different information required for decision-making in OFC and MFC. At the circuit-level, amygdala input to these two areas play a distinct role in stimulus-reward encoding in OFC and choice encoding in MFC.

Disclosures: F.M. Stoll: None. **C.P. Mosher:** None. **S. Tamang:** None. **E.A. Murray:** None. **P.H. Rudebeck:** None.

Poster

250. Prefrontal Cortex and Reward

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 250.04/RR24

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant EY014924

Title: Representation of reward risk by primate frontal eye field neurons

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Abstract: Given the stochastic nature of the environment, humans and other animals need to make decisions under varying degrees of uncertainty. Despite the importance of risky decisions for behavior, little is known about risk or reward uncertainty representations in the brain. The primate Frontal eye field (FEF) is an area within prefrontal cortex that is causally involved in visual stimulus selection. We have begun investigating a possible role of the FEF in risky decisions during a dynamic foraging task. In this foraging task, monkeys choose between a 'sure' option, which yields 0.2 ml of juice on every trial, and a 'risky' option, which yields either no reward or a high reward of 0.8 ml of juice. The high reward probabilities of 'risky' options are 0.25, 0.5, or 0.75, and are varied randomly between blocks. Within a given experimental session, the average expected value of the 'risky' option always matches the expected value of the 'sure' option; however, it can be larger, equal, or smaller than the expected value of the 'sure' option in a given block. In each block, one 'risky' option and the 'sure' option are randomly assigned to one of two stimulus locations. The visual features of the two stimuli are identical. On each trial, the monkey indicates its choice by making a saccadic eye movement to one of the two stimuli. To optimize its choices and maximize the total amount of juice, the monkey must identify the 'risky' option and estimate its reward probabilities based on choice and reward histories. While the monkey performs the task, we record simultaneously from multiple FEF neurons using multichannel (≥24) linear array electrodes. Our results thus far show that the animal exhibits stable risk-seeking behavior during the dynamic foraging task, consistent with previous studies. In addition, thus far we observe that in addition to various components of the risky decision, such as chosen target location and choice probability, the activity of FEF neurons can reflect reward uncertainty.

Disclosures: X. Chen: None. **M. Zirnsak:** None. **T. Moore:** None.

Poster

250. Prefrontal Cortex and Reward

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 250.05/RR25

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant F31-MH107111

NIH Grant R01-DA032758

Title: Neurons in orbitofrontal cortex adapt differently to changes in maximum and minimum value

Authors: *K. CONEN[1], C. PADOA-SCHIOPPA[2]
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Abstract: Neuronal adaptation was recently observed in neurons in the orbitofrontal cortex (OFC) encoding the values of offered and chosen goods. These neurons encode values in a linear way, and the slope of encoding is inversely related to the maximum possible value. However it is not clear whether changes in the minimum value have a comparable effect on encoding. In this study, we tested the possibility that both the maximum and the minimum of the value distribution provide reference points for the tuning functions of value-coding cells.
In this task, rhesus monkeys chose between two juices offered in variable amounts. Each session consisted of 2-3 blocks of ~250 trials. Within each block, the range of values remained constant while the quantities offered varied pseudo-randomly from trial to trial. Between blocks, the range of values for each juice changed in one of the following ways: 1) the maximum increased or decreased while the minimum remained constant; 2) the minimum increased or decreased while the maximum remained constant; or 3) the maximum and minimum shifted concurrently while the difference between them was unchanged.
We recorded the activity of ~900 neurons from OFC while animals performed the task. We analyzed the data in seven 500 ms time windows during and after offer onset, focusing on responses that encoded the offer value or the chosen value. For each response, we regressed firing rate onto value independently for each block. We compared the tuning slope, y-intercept, and activity range across conditions. Adaptation was defined as a systematic change in the tuning slope or y-intercept of a response with a particular change in condition. We considered adaptation “complete” if a neuron’s activity range was the same across conditions - i.e. if the minimum and maximum responses in one condition were the same as the minimum and maximum responses in the other.
Tuning functions were close to linear in all conditions, and we did not observe changes in curvature across ranges. However, tuning functions varied systematically across blocks. In blocks with a narrow value range, neuronal responses were more sensitive to changes in value (steeper tuning slope). Interestingly, the degree of adaptation depended on the type of change that occurred in a session. When both the maximum and minimum values changed, responses showed near-complete adaptation to both parameters. Complete adaptation also occurred in sessions where only the maximum value changed. In contrast, when only the minimum value changed, we measured little to no adaptation. This observation raises the possibility that triggering neuronal adaptation requires a salient change in the distribution of possible values.

Disclosures: K. Conen: None. **C. Padoa-Schioppa:** None.

Poster

250. Prefrontal Cortex and Reward

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 250.06/RR26

Topic: H.01. Animal Cognition and Behavior

Support: NIH NIDA R21/DA041791

Title: Reinforcement learning drives overrepresentation of subjective value in frontostriatal brain networks

Authors: *E. B. KNUDSEN, J. D. WALLIS
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Abstract: Intrinsic valuation of extrinsic environmental stimuli is a ubiquitous feature of animal behavior. Positive and negative outcomes experienced in the course of ongoing behavior drive learning processes in corticostriatal networks. These processes in turn drive subsequent behaviors towards maximizing positive outcomes while mitigating negative outcomes. However, when these networks become maladaptive, such as in response to repeated exposure to traumatic stimuli, this ability to optimize behavior diminishes. These maladaptations can culminate in symptoms associated with neuropsychiatric disorders. As a step towards novel systems-based therapies, it is critical to identify the neural substrates underlying behavioral optimization during normal learning behavior.

To this end, we investigated how neurons within primate orbitofrontal cortex (OFC), a frontal region critical for value-based decisions, respond during a behavioral task in which non-human primates learn dynamically-changing probabilistic stimulus-outcome (SO) associations in order to maximize reward. In this task, subjects chose between two of three available stimuli. Once optimal choices were established, reward probabilities drifted towards new stable points. Using multisite linear array electrodes in one subject, we recorded 466 OFC and 451 striatal neurons in 14 sessions.

We found that when SO associations were stable and the optimal decision policy does not change, value-related encoding in OFC neurons was generally retrospective, suggesting an ongoing monitoring of contingencies without needing to update representations to guide exploratory behavior. Conversely, when SO associations randomly drifted towards new values, variability in neuronal firing was well explained by subjective value at several time points throughout the trial, and peaked as the animals' behavior began to reflect the changed contingencies, with a nearly 100% increase in explained variance compared to periods of stable value. Our results support the notion that prefrontal cortex is critical in situations requiring flexibility in response to changing circumstances.

Disclosures: E.B. Knudsen: None. **J.D. Wallis:** None.

Poster

250. Prefrontal Cortex and Reward

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 250.07/RR27

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant MH051383

Title: Value-based decision making in the nematode *Caenorhabditis elegans*

Authors: *S. R. LOCKERY[1], A. KATZEN[1], P. W. GLIMCHER[2], W. HARBAUGH[1]
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Abstract: Value-based decision making - choices driven by subjective assessments of utility - is a central function of the brain and the focus of intensive study in mammals. Until now, evidence that nematodes are capable of value-based decision making has mainly been suggestive. However, economists have developed formal procedures for determining whether a consumer's decisions are based on subjective value as opposed to random or capricious impulses. We recently developed microfluidic devices that enable such tests to be performed on nematodes for the first time. The worm is held at the confluence of contiguous streams of high and low quality bacterial food leaving its head free to move. Bacteria concentrations are adjusted by the experimenter to change the relative "prices" of the two foods in terms of number of bacteria consumed per pharyngeal pump. Food concentrations can also be adjusted in tandem to increase or decrease the worm's overall consumption possibilities, i.e. "budget." Consumption is measured by counting pharyngeal pumps recorded electrically.

Worms typically fed in both streams, consuming a mixture of high and low quality food that was unique for each combination of price and budget. We found that worms make globally rational choices in that they obey transitivity. That is, for all sets of food mixtures A, B, and C, if A is preferred to B, and B to C, then A is preferred to C. As transitivity is the necessary and sufficient condition for value maximization, these data provide formal evidence that C. elegans exhibits value-based decision making.

Further, we found that the olfactory neuron AWC, known to be activated by the sudden absence of food, is required for intact food choice behavior. Surprisingly, however, we found that AWC is also activated by the switch from high quality food to low quality food, even when the two foods are at the same concentration (price). Thus, subjective value may be represented at the level of individual olfactory neurons.

Our behavioral and neuronal data are consistent with a model in which olfactory neurons represent the subjective value of the local environment to direct behavior toward preferable mixtures of particular foods. To our knowledge, this is the first formal demonstration of value-based decision making in a genetically tractable model organism with a simple nervous system, opening the door to the discovery of conserved genes and neural circuits for rational decision making.

Disclosures: S.R. Lockery: None. **A. Katzen:** None. **P.W. Glimcher:** None. **W. Harbaugh:** None.

Poster

250. Prefrontal Cortex and Reward

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 250.08/RR28

Topic: H.01. Animal Cognition and Behavior

Support: MEXT KAKENHI 16K18380

Title: Differential routing of reinforcement signals from orbitofrontal cortex to striatum depending on environmental uncertainty

Authors: *J. HIROKAWA[1,2], S.-J. LI[2], A. VAUGHAN[2], J. L. PIE[2], L. DESBAN[2], Y. OSAKO[1], T. OHNUKI[1], H. MANABE[1], Y. SAKURAI[1], A. KEPECS[2]
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Abstract: Neurons in orbitofrontal cortex (OFC) represent a variety of decision variables relevant for valuation. Distinct neuronal populations within OFC project to specific downstream subcortical targets such as ventral striatum (VS) and ventral tegmental area (VTA). Whether these distinct projection neuron types carry distinct decision variables is not known because conventional unit recording is blind to the projection types. Here, we employed the optogenetic tagging method to record neuronal activity from specific projection neuron types such as OFC -VS and OFC -VTA that are entirely distinct. We trained rats in a two alternative binary odor mixture categorization task. By interleaving trials of different odor-mixture ratios we adjusted the uncertainty of individual decisions, and across blocks we also changed the reward value of the two sides. Behavioral responses were in proportion to the strength of sensory evidence but biased toward the higher reward value, suggesting that animals make decisions by optimally integrating sensory evidence and reward value. Furthermore, our model-based analysis suggests that the animals updated the reward value based on the reward prediction error. We labeled either OFC-VS or OFC-VTA projection neurons with channel-rhodopsin 2 and implanted optic fiber-coupled tetrode microdrive in the OFC and used light activation to identify projection neurons. Consistent with our previous studies, we identified various decision variable representations predicted by our model such as decision confidence, reward value and their integrated value. We then mapped how these different decision variable representations fall into the specific projection types. Our preliminary data shows that all of the identified OFC-VS projections neurons (n=10) from one animal exclusively represent negative integrated value whereas OFC-VTA projection neuron (n=1) was matched with reward prediction error. Interestingly, the negative integrated value representation in OFC-VS projection neurons was only evident in the animal who is engaged in adjusting their bias in response to reward manipulations. These preliminary data suggest reserved usage of OFC-VS pathway to convey negative integrated value to drive

switching behavior and OFC plays a role to gate the output of the updated value to striatum depending on environmental uncertainty.

Disclosures: **J. Hirokawa:** None. **S. Li:** None. **A. Vaughan:** None. **J.L. Pie:** None. **L. Desban:** None. **Y. Osako:** None. **T. Ohnuki:** None. **H. Manabe:** None. **Y. Sakurai:** None. **A. Kepecs:** None.

Poster

250. Prefrontal Cortex and Reward

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 250.09/RR29

Topic: H.01. Animal Cognition and Behavior

Support: SDI-STEM Diversity Institute Grant # S1111000000063

Title: Differential effects of dorsal and ventral mPFC inactivation are driven by reward availability

Authors: *J. P. CABALLERO[1], D. E. MOORMAN[2]
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Abstract: In general it is thought that rodent dorsal medial prefrontal cortex (mPFC; typically prelimbic) promotes the expression of drug-seeking, and ventral mPFC (typically infralimbic) promotes response inhibition. However, both ventral and dorsal mPFC are necessary for reward seeking and extinction and these established roles may not apply to all forms of motivated behavior. This model also neglects potential mPFC hemispheric differences. To better understand the roles of dorsal and ventral mPFC in motivated behavior we pharmacologically inactivated these areas during operant reward seeking, extinction and reinstatement. Male Long-Evans rats learned a fixed ratio 1 (FR1) sucrose seeking task where each nose poke resulted in a tone and delivery of 0.1 ml 15% sucrose. Responding was then extinguished and followed by cue-induced reinstatement. During each phase, rats received unilateral or bilateral dorsal mPFC or ventral mPFC infusions of baclofen/muscimol (.3 ul) or vehicle. A separate group of rats underwent the same paradigm, but were only bilaterally infused during reinstatement testing. These rats were then bilaterally inactivated during a progressive ratio sucrose seeking task. During FR1, both the total number and rate of nosepokes and well-entries increased following bilateral, and to a lesser degree, right-hemisphere dorsal mPFC inactivation ($p<0.05$). In contrast, bilateral ventral mPFC inactivation increased the rate, but not total number of responses. Unilateral ventral mPFC inactivation increased well entries. There was no effect of dorsal or ventral inactivation on extinction or reinstatement behavior, but ventral mPFC inactivation appeared to decrease reinstatement. Since testing after multiple infusions may have decreased the

effect of baclofen/muscimol, we ran a second cohort of bilateral inactivation during reinstatement only. In this group, there was no effect of dorsal mPFC inactivation, but a significant reduction in nose poking and increase in (non-rewarded) well-entries. Preliminary results also suggest that ventral mPFC inactivation decreases reward seeking in progressive ratio. Our data reveal that the previously established roles of going vs stopping are not applicable to all motivated behaviors. Dorsal, and to a lesser extent, ventral mPFC inactivation increased reward seeking when reward was available, whereas ventral, but not dorsal mPFC inactivation decreased reinstatement. These results, which run counter to the go-stop model of dorsal-ventral mPFC, may align better with other models or may require the development of a new framework for understanding differences in mPFC subregion function.

Disclosures: J.P. Caballero: None. **D.E. Moorman:** None.

Poster

250. Prefrontal Cortex and Reward

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 250.10/RR30

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant MH108643

Title: Neural circuits for working memory and reinforcement learning in primate prefrontal and parietal cortex

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Abstract: The process of learning desirable actions through experience in an uncertain environment can be parsimoniously described by reinforcement learning (RL) theory, in which estimates of long-term reward from alternative actions are iteratively updated and actions are chosen so as to maximize expected reward. Previous studies have shown that neurons in multiple cortical regions, including the dorsolateral prefrontal cortex (DLPFC) and lateral intra-parietal cortex (LIP), contribute to RL by encoding the signals related to animal's choice and reward histories. Moreover, neurons in the same cortical regions often display directionally-tuned persistent activity during memory saccade tasks, believed to be the neural substrate of spatial working memory. Here, we tested whether the same neural circuitry in the DLPFC and LIP contributes to both RL and working memory. Specifically, we compared activity of individual neurons in DLPFC and LIP recorded during a computer-simulated matching pennies (MP) task and a memory saccade (MS) task. During the MP task, the animal chose one of the two horizontally displaced targets and was rewarded when a computer opponent failed to predict its

choice. During the MS task, the animal was presented with a brief visual cue appearing in one of eight different locations, and was rewarded for shifting its gaze to the remembered location after a one-second delay. Using a set of regression models, we analyzed the activity related to the animal's choices in the current and previous trials as well as the outcome of the animal's previous choice during the MP task, and the activity related to the remembered target location during the delay period of the MS task. We found that the neurons in the DLPFC and LIP maintained consistent directional selectivity for animal's upcoming choice across the two tasks. In addition, neurons in both cortical areas consistently encoded the location of the rewarded target in the previous trial during the MP task and the upcoming choice in the MS task. By contrast, the signals related to the animal's choice in the previous trial in MP were not systematically related to the choice signal in the MS task, suggesting that activity in the DLPFC and LIP can maintain the encoding of multiple independent task-related variables. These results hint at the potential role of mnemonic activity in the same DLPFC and LIP recurrent neural networks in supporting processes of reinforcement learning and working memory.

Disclosures: S.K. Murray: None. **D. Lee:** None. **H. Seo:** None.

Poster

250. Prefrontal Cortex and Reward

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 250.11/RR31

Topic: H.01. Animal Cognition and Behavior

Support: Gruber Foundation

R01MH108629

TL1TR000141

Title: Modeling the dynamic effects of reward and temporal uncertainty in perceptual decision making

Authors: *M. SHINN[1], H. SEO[2], D. EHRLICH[2], D. LEE[3], J. D. MURRAY[2]
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Abstract: During decision making in everyday life, the process of integrating noisy sensory evidence must be often adjusted by other information from multiple sources, such as expected payoffs and temporal regularities in the environment. However, it remains unknown how the brain combines this diverse information to achieve a desired level of speed and accuracy. Here, we tested a set of computational models that combine time-dependent integration of perceptual evidence with alternative mechanisms of choice bias related to the expected payoffs.

These models were tested against reaction-time (RT) data collected from two rhesus monkeys performing a two alternative-forced-choice random-dot color-discrimination task, where payoffs for a correct choice and temporal predictability of discriminanda were systematically manipulated. In each trial, reward magnitude was indicated with a thin or thick square around each target. A central square consisting of green and blue pixels that were dynamically rearranged at 20Hz was presented next. This stimulus initially consisted of equal numbers of green and blue pixels and lasted for 0, 0.4 or 0.8-s, followed by the discriminative stimulus for which the ratio between green and blue pixels varied randomly across trials. Animals were allowed to shift their gaze any time after the onset of the discriminative stimulus and were rewarded only when they chose the target with the same color as the majority of the pixels in the discriminative stimulus. We found that animals' RT and accuracy were significantly influenced by the asymmetric reward and the timing of the discriminative stimulus.
We extended the standard drift-diffusion model (DDM) framework to include time- and reward-dependent mechanisms. We fit models to each monkey's RT distributions using numerical simulation based on Fokker-Planck diffusion, differential evolution for parameter optimization, and model comparison based on likelihood. We tested multiple mechanisms potentially underlying asymmetric reward effects, such as a time-dependent increase in reward bias, offset initial starting point, asymmetric lapse rate, re-mapping toward the high-reward target, and high-reward target selection triggered by stimulus change detection. We found that a simple DDM, with either a reward-dependent starting point or lapse rate, failed to mimic the RT distributions, and that more complex mechanisms improved fitting. Our findings suggest mechanisms underlying the effects of asymmetric reward and temporal uncertainty during perceptual decision making, and make predictions for neuronal activity related to decision making.

Disclosures: **M. Shinn:** None. **H. Seo:** None. **D. Ehrlich:** None. **D. Lee:** None. **J.D. Murray:** F. Consulting Fees (e.g., advisory boards); BlackThorn Therapeutics.

Poster

250. Prefrontal Cortex and Reward

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 250.12/RR32

Topic: E.03. Basal Ganglia

Support: New Energy and Industrial Technology Development Organization (NEDO)

Title: Reinforcement learning of motor sequences on motor primitives acquired in the convolutional network-based neocortical model

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Abstract: A neocortical information processing is hierarchical and the information representations are abstracted with the hierarchy. Recent observations suggest that the hierarchy is mimicked by convolutional neural networks, especially in the visual processing. At the present research, we expand these suggestions to motor behaviors and model the neocortical acquisitions of motor actions using convolutional neural network. Moreover, we model the generations of sequential motor actions on the basis of the reinforcement learning that is realized using the deep auto-encoder. Because accumulations of evidences strongly indicate that the basal ganglia circuit plays a key role in the reinforcement learning, it is considered that the model corresponds to the basal ganglia. We hypothesize that motor behaviors compose of the motor primitives which are the frequently co-occurring sets of the actions and work as the bases spanning the "motor space" where our behaviors are represented as the compositions of the bases. Indeed, physiological researches have shown that the frequently co-occurring sets of the motor actions are represented as the neuronal activities and the representations are abstracted with ascending the hierarchy of motor cortex from primary motor to prefrontal cortex. As in the neocortical visual processing, therefore, we hypothesize that the hierarchical abstraction is acquired using the processes mimicked by the convolutional neural networks. Moreover, sequential motor behaviors consisting of primitive action sets adequately abstracted should be realized by activating the acquired neocortical representations in correct orders. Hence, we modeled the acquisition of the adequately abstract motor representation in the motor cortex using convolutional neural network and the generation of motor behaviors as the sequential activation of the representations with reinforcement learning in basal ganglia using reservoir and auto-encoder neural network. Our computational simulation successfully reproduced the acquisition of motor representations which are observed in the monkey neurophysiological experiments. Moreover, our model could generate the commands for motor sequences in right order and timing using temporal signal occurring in the basal ganglia. At this implementation, the learning was executed on the space of primitive motor representations, which enabled to acquire the correct motions much more rapidly compared from the learning on the native angle space, resembling flexible and rapid acquisitions of the motions in biological brains. Together, our model is suggested to provide the mechanism of biological motor behaviors.

Disclosures: H. Kurashige: None. **T. Yamazaki:** None.

Poster

250. Prefrontal Cortex and Reward

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 250.13/RR33

Topic: H.01. Animal Cognition and Behavior

Support: McKnight Foundation

NEI R01 EY014697-01

NIH EY013933-10

T32 MH011574-35

Title: Neuronal ensembles in monkey dorsolateral prefrontal and inferior parietal cortices track reward predictions and outcomes in a probabilistic non-decision paradigm

Authors: *N. C. FOLEY, N. M. SINGLETARY, J. GOTTLIEB
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Abstract: Predicting rewards in uncertain environments is vital for behavior. However, while reward-based decisions have been extensively investigated, less is known about the role of rewards in cognitive functions such as attention and cognitive control. We examined how reward predictions are encoded by single neurons in the pre-arcuate portion of the dorsolateral prefrontal cortex (dlPFC) and parietal area 7a, two areas that are strongly interconnected and have been implicated in both rewards and attention.
Two monkeys performed a task in which they viewed a visual cue predicting the trial's reward probability (expected value, EV) and, after a delay, made a saccade to reveal the reward. Critically, the monkeys could not make decisions to improve on the signaled outcome, so that the cues had value only in updating predictions but not guiding actions.
The monkeys' anticipatory licking coarsely differentiated between high and low reward probabilities (being higher for cues signaling 0.75/1 vs 0.5/0.25/0 reward likelihoods, but modulating little with EV within each category), suggesting that the monkeys used a simplified categorical representation of the possible levels of EV. In addition, licking was sensitive to reward history, being much higher if the prior trial ended in a reward rather than lack of reward, suggesting that the monkeys predicted rewards using both trial-specific information and automatic (possibly "model-free") tracking of reward history.Simultaneous recording of spiking activity using Utah arrays showed that a significant fraction of cells (10-30%) in both 7a and the dlPFC increased or decreased their firing as a function of the prior trial reward and current trial EV. Encoding of EV was categorical rather than linear, and closely aligned with the licking pattern. Moreover, probabilistic rewards seemed to be encoded as mixtures of two firing patterns that transition between resembling those at 100% or 0% reward probability, with the length and probability of a high reward state scaling weakly as a function of reward probability.
The strongest firing rate modulations were found during the outcome epoch, when a large fraction of cells responded more strongly to reward omission rather than reward delivery, and combined these responses with encoding of prior reward and EV. Strikingly, EV encoding strongly increased, and recruited a new population of cells after outcome delivery relative to earlier task epochs. Although slightly stronger in the dlPFC, all the reward responses were highly robust in both areas, suggesting that the dlPFC and 7a form a distributed representation of the variables required for maintaining and updating reward expectations.

Disclosures: **N.C. Foley:** None. **N.M. Singletary:** None. **J. Gottlieb:** None.

Poster

250. Prefrontal Cortex and Reward

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 250.14/RR34

Topic: H.01. Animal Cognition and Behavior

Support: McKnight Foundation

NEI R01 EY014697-01

NIH EY013933-10

T32 MH011574-35

Title: Robust encoding of reward expectation in low beta band power in monkey dorsolateral prefrontal and inferior parietal lobe

Authors: M. NEJATBAKHSH[1], H. R. NASRABADI[1], V. DAVOODNIA[1], E. ZABEH[1], N. C. FOLEY[2], R. LASHGARI[1], *J. P. GOTTLIEB[3]
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Abstract: Predicting rewards in uncertain environments is vital for behavior but, while reward-based decisions are extensively investigated, less is known about the role of rewards in cognitive functions such as attention and cognitive control. We examined how reward predictions are encoded by single neurons in the pre-arcuate portion of the dorsolateral prefrontal cortex (dlPFC) and parietal area 7a, two interconnected areas that are implicated in reward and attention.
Two monkeys performed a task in which they viewed a visual cue predicting the trial's expected value (EV, produced by a combination of reward magnitude and probability) and, after a delay, made a saccade to reveal the reward. Critically, the monkeys could not make decisions to improve on the signaled outcome, so that the cues served to update predictions but not to guide actions.
The monkeys' anticipatory licking coarsely differentiated between high and low levels of EV but showed scant variation within each category, suggesting that the monkeys used a simplified categorical representation of the possible levels of EV. In addition, licking was sensitive to reward history, being much higher if the prior trial ended in a reward rather than lack of reward, suggesting that the monkeys predicted rewards using both trial-specific information and automatic (possibly "model-free") tracking of reward history.
LFP signals (recorded with 2 48-channel Utah arrays) showed a prominent increase in power in the low beta frequency (10 - 20 Hz) that was sustained during the delay period, was highly

consistent across individual electrodes and sessions, and was equally prominent in 7a and dlPFC. GLM-based analyses showed that beta band power decreased as a function of current trial EV and prior trial reward, in a manner that was highly consistent with the behaviorally measured reward prediction; the extent to which different reward levels were discriminated by the LFP power and anticipatory licking were highly correlated ($r = 0.96$, $p = 4.88e\text{-}24$). Further analysis showed that the encoding of EV in beta band power was due sensitivity to both reward magnitude and probability, and that power was moderately sensitive to uncertainty, with a peak on trials with the highest reward entropy (50% probability). Finally, LFP synchrony between frontal and parietal electrodes (indexed by the debiased Weighted Phase Lag Index, wPLI) showed a peak in the low-beta band that was modulated by EV and prior reward predominantly during the late delay and peri-saccadic epochs. Beta band oscillations seem to mediate a distributed fronto parietal representation for maintaining and updating reward expectations.

Disclosures: **M. Nejatbakhsh:** None. **H.R. Nasrabadi:** None. **V. Davoodnia:** None. **E. Zabeh:** None. **N.C. Foley:** None. **R. Lashgari:** None. **J.P. Gottlieb:** None.

Poster

250. Prefrontal Cortex and Reward

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 250.15/RR35

Topic: E.03. Basal Ganglia

Support: DARPA REPAIR Project N66001-10-C-2008

NIH 1R01NS092894-01

NSF IIS-1527747

NYS SCIRB contracts C30600GG and C030838GG

Title: Dynamics of the reward signal in the primary motor cortex

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Abstract: The ability to predict reward provides the animal an opportunity to modify its behavior such that it increases its probability of attaining the predicted reward. The primary motor cortex (M1) in non-human primates has been shown to modulate differently with respect to the presence or absence of reward[1]. We recently reported that Reward Prediction Signal (RPS) exists in M1[2]. Furthermore, we reported that the RPS in M1 shifted its average peak activity

early in the trial from the reward delivery period towards the reward predicting cue with increased trial experience[2]. Continuing on our work to illuminate the reward representation and RPS dynamics in M1, here, we investigate i) the representation of multiple levels of reward in M1 & ii) the dynamics of the RPS with respect to the increased reward prediction certainty in a trial (i.e. 50 or 75% bias towards rewarding trials in a given session). We show that i) M1 differentially encodes expected value of multiple levels of rewards ii) the differentiability between the M1 activity representing multiple levels of reward increased with trial experience and iii) The differentiability post cue increased in the 75% reward bias experiment type compared to 50%.

References:
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2) Venkata S Aditya Tarigoppula, Brandi T. Marsh, Joseph T. Francis. Dynamics of the reward prediction signal in the primary motor cortex (M1). *Neural Control of Movement* (2017).

Disclosures: A. Tarigoppula: None. **J.P. Hessburg:** None. **D.B. McNiel:** None. **J.S. Choi:** None. **J.T. Francis:** None.

Poster

250. Prefrontal Cortex and Reward

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 250.16/RR36

Topic: H.01. Animal Cognition and Behavior

Support: PHS grant PO1 DA031656

Title: Distinguishing between the contributions of depletion of processing resources and increases in opportunity costs to decline in attentional performance

Authors: *K. B. PHILLIPS[1], M. SARTER[2]
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Abstract: Performance on sustained attention tasks declines over time and, more severely, in response to distractors and other performance challenges. In patients with impaired brain function, attentional performance is generally more vulnerable than in healthy subjects. Traditionally, such performance decline has been interpreted as reflecting depletion of attentional or related cognitive resources. However, resource depletion models cannot explain invigorated performance following task switches or increased incentives to perform. An alternate hypothesis for this decline proposes that performers compute cost/benefit calculations for staying on task

versus engaging in alternative action, termed opportunity costs (Kurzban et al., 2013). Increases in opportunity costs are subjectively experienced as increasing boredom, loss of motivation to perform, and attentional fatigue. Thus, task performance declines and alternative action becomes increasingly attractive. Here we employed behavioral manipulations of attentional performance in rats to test conflicting predictions derived from these two theoretical perspectives. Male and female rats were trained on a sustained attention task (SAT) containing pseudorandomized cued and non-cued trials, requiring the reporting of cues as well as non-cue events via separate levers. In addition, rats performed two modified versions of SAT: SAT with sequences of repeated trial types (blocks during which only cued or non-cued trials are given), or blocks during which the intertrial interval (ITI) is shortened. Importantly, the two competing theoretical perspectives predict opposed outcomes of these task manipulations: Trial repetition should not tax attentional resources, in part because the rat does not need to switch between response rules and levers, but it should elevate opportunity costs, partly because the rat's behavior is restrained to one lever and the monotony of repeated cue (or non-cue) processing. Conversely, shorter ITIs are thought to tax processing resources because of greater trial density but shorter ITIs may be neutral with respect to, or even decrease, opportunity costs, partially due to greater reward density. The outcomes of these manipulations are being determined in rats with relatively poor versus relatively high cholinergic-attentional capacities (sign versus goal trackers, respectively) as the former may more effectively reveal effects of task manipulations. Defining the cognitive and neuronal mechanisms mediating attentional decline is crucial for developing rational treatments of the cognitive instabilities that typify a wide range of neuropsychiatric disorders.

Disclosures: K.B. Phillips: None. **M. Sarter:** None.

Poster

250. Prefrontal Cortex and Reward

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 250.17/SS1

Topic: H.02. Human Cognition and Behavior

Support: DFG SFB 779 TPA14N

Title: Interactions of attentional capture and craving in smokers during a perceptual decision task

Authors: *J. A. HARRIS[1,2], S. E. DONOHUE[1,2], K. LOEWE[2,3], H.-J. HEINZE[1,2], M. G. WOLDORFF[1,2,4], M. A. SCHOENFELD[1,2,5]
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Abstract: How the motivational state of craving affects the attention of substance users has implications for understanding the addiction state, as well as for the successful cessation of use. In smokers, some studies find craving enhances attentional capture by smoking-related stimuli, while others have reported suppressive effects. We attempted to extract behavioral and event-related potential (ERP) indices of attention to smoking-related stimuli, and their interaction with craving, using a perceptual decision task. In one session, smokers abstained from smoking for 3 hours (i.e., 'craving'), and were allowed to smoke prior to another session (i.e., non-craving). Non-smoking controls completed the same tasks in a single session. For the first behavioral task block, subjects completed a staircasing procedure in which five classes of images were presented: faces, smoking-related objects, office-related objects, composite face/smoking objects, and composite face/office objects. Subjects categorized the briefly presented images as one of the three canonical categories. Depending on the subject's response to a composite trial, the relative dominance of each element was adjusted for the next trial of the same type (e.g., responding 'face' would result in more dominant non-face content in the next composite image trial, and vice versa). Attention to non-face elements for the composite images was extracted by determining the relative dominance of face content necessary to achieve 50% face categorization performance. For the second task block, continuous EEG data were recorded while composite and pure images were presented in the same manner, without staircasing, and with the relative dominance of face and non-face elements varying between 40 and 60% for the composite images. For each image class (pure and composites), the face-specific N170 ERP component (latency 170 ms) was extracted and compared across conditions of image type and craving. In the staircasing task, more face content was required for smokers relative to nonsmokers to achieve 50% face categorization for face/smoking composites. In addition, craving in smokers reduced the N170 extracted for smoking-dominant composite images, but not the N170 extracted for equally office-dominant composite images. Our overall results demonstrate the attentional capture by substance-related stimuli in users. In addition, our neural measures leverage what is known about the face-specific N170's relationship with visual attention to provide a novel marker of craving-sensitive attentional capture to a competing substance-related stimulus.

Disclosures: J.A. Harris: None. **S.E. Donohue:** None. **K. Loewe:** None. **H. Heinze:** None. **M.G. Woldorff:** None. **M.A. Schoenfeld:** None.

Poster

251. Prefrontal Cortex and Decision Making

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 251.01/SS2

Topic: H.01. Animal Cognition and Behavior

Support: R01MH095894

R01MH1086827

R37MH109728

grant from Simons Foundation SFARI 304935, MLP

Title: Predicting strategic behavior in a competitive two-player game from gaze patterns and neuronal activity in the superior temporal sulcus

Authors: Y. JIANG[1], *M. L. PLATT[2]
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Abstract: Most social interactions are dynamic and open-ended. Yet most neurobiological studies of social interactions reduce these complex behaviors to a very restricted, often binary action space (e.g. prisoner's dilemma), within which the choices of two participating parties often quickly stabilize. The neural processes mediating dynamic social interactions remain largely unknown. To address this gap, we examined the behavior of both humans and rhesus macaques playing a zero-sum competitive soccer game. In this game, one player (the "shooter") uses a joystick to move a "ball" across the screen to reach the "finish line", while the other player (the "goalie") uses a joystick to block the "ball". Whichever player succeeds wins a point (humans) or a squirt of juice (monkeys). This task thus provides an environment with an infinite array of possible interactions motivated by competition. Humans as well as monkeys developed highly complex, dynamic interactions in this task. Both human and monkey shooters demonstrated great variability in terms of the angle, speed, and end point of ball. There was also significant cross-trial variability in their reaction time and the number of sudden direction changes made per trial. Both human and monkey goalies minimized the moment-to-moment distance between the vertical position of the ball and the goalie bar, and made predictions about ball position based on shooter movements in previous trials. Both human and monkey shooters made gaze shifts to the eventual position on the finish line to which they intended shooting the ball, providing evidence of long-range planning. Pupil diameter measured before trials in both shooters and goalies predicted who would win, suggesting pupil-linked variation in attention or arousal may contribute to performance. In monkeys we also recorded the firing rates of single neurons in the mid superior temporal sulcus (mSTS), a region hypothesized to be homologous to human temporo-parietal junction (TPJ). Surprisingly, a large proportion of mSTS neurons responded to both the expectation and delivery of reward. Some mSTS neurons signaled other facets of this dynamic task including the distinction between a sure win/loss and a close win/loss, a prediction error in regard to the opponent's movement, and changes in strategy both within a trial (e.g. sudden change in movement) and across trials (e.g. shooter aiming above or below the goalie). Finally, a subset of mSTS neurons showed elevated activity when monkeys competed against a live opponent compared with competing against a computer or a replay of previously recorded monkey behavior, a signal that may reflect detection or attribution of agency.

Disclosures: Y. Jiang: None. **M.L. Platt:** None.

Poster

251. Prefrontal Cortex and Decision Making

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 251.02/SS3

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant R01MH095894

NIH Grant R01MH108627

NIH Grant R37MH109728

SFARI Grant 304935 MLP

Title: Neural mechanisms mediating cooperation

Authors: *W. S. ONG[1], M. L. PLATT[2]
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Abstract: We hypothesize that cooperation results from the interaction of neural circuits mediating reward, empathy and theory of mind. fMRI studies in humans have shown that the anterior cingulate cortex (ACC) and temporal parietal junction (TPJ) are activated by vicarious reward and mentalizing respectively. These are two functions that conceivably contribute to cooperation, yet the precise neural processes remain unknown. To address this gap, we developed a new task based on the classic “chicken game”. Two monkeys (M1&M2) face each other across a shared screen showing 2 colored annuli framing dot motion arrays and 4 response targets. On some trials, the larger reward (denoted by visual tokens) lies opposite M1 behind the opponent (M2)’s annulus; smaller rewards lie to the left (see figure). To obtain the larger reward, M1 goes straight, but if M2 also goes straight the annuli collide and neither monkey gets reward. On some trials, a “cooperation bar” allows both monkeys to obtain larger rewards if and only if both choose to go left; if only one yields he receives a smaller reward. Dot motion coherence is randomized on some trials to obscure intention signals. Our 4 trained monkeys maximized juice intake by attending to the reward tokens as well as the choices of their opponent. Monkeys’ strategies depended on their opponent. Dominant monkeys preferentially aggressed and required more incentive to cooperate, while subordinates preferentially yielded. Collisions were more frequent when a computer player replayed prior live monkey trials in the presence of a ‘decoy’ monkey, compared with playing a computer in the absence of a decoy monkey or playing an active monkey. Players quickly initiated cooperation for small rewards with an active player, and distinguished between active players and decoys within 15 trials. To determine the neuronal basis of these behaviors, we recorded the spiking activity of 535 neurons from ACC and 449 from the putative monkey TPJ in the middle STS (mTPJ). Neurons in both areas are sensitive to

cued payoffs, decisions, and explicit signaling of intentions in different opponent conditions. Our key finding is that 53% of neurons in mTPJ differentially respond to the same amount of juice when obtained through a cooperative act compared with obtaining it selfishly. Provocatively, this was true only when monkeys played a live opponent. These findings demonstrate that neurons in mTPJ respond differentially to the presence and behavior of (non-) interactive agents, suggesting it plays a role in the integration of social cues, actions, and outcomes to guide strategic social decisions.

Disclosures: W.S. Ong: None. **M.L. Platt:** None.

Poster

251. Prefrontal Cortex and Decision Making

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 251.03/SS4

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant R01MH095894

Title: modeling behavior of non-human primates in an iterative chicken game

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Abstract: Cooperation depends on effective social communication. We typically act in our own interest and infer another's intention in order to maximize reward utility. Many experiments utilizing game theory have been carried out in humans, but it is unfeasible to have them perform thousands of trials and impossible to obtain high resolution neural data. Thus we turn to non-human primates and build a computational model to study the underlying basis of these decision-making mechanisms.
We developed a new task based on the classic "chicken game." Two monkeys (M1 & M2) face each other across a shared screen showing 2 colored annuli framing dot motion arrays and 4 response targets. The dots within the annuli flow in the direction the monkey is currently holding the joystick, and undergo a color change after the monkey commits to a choice by holding the joystick in one direction for 0.5 secs, thus providing an explicit signal of intentions. On 3/4 of trials, the larger reward lies opposite M1 behind M2's annulus; smaller rewards lie to the side. To obtain the larger reward, M1 goes straight, but if M2 also goes straight the annuli collide and neither monkey is rewarded. On some trials, a "cooperation bar" allows both monkeys to obtain larger rewards only if both choose to swerve. On some trials, dot motion coherence is randomized to obscure intention signals.
We found that monkeys play independently against a computer opponent. By contrast, when

playing a live opponent facing a pure cooperation payoff, their behaviors fit a traditional equilibrium model, while in the “chicken game” payoff , they follow a dynamic valuation process and diverge from the equilibrium prediction. We used a hybrid reinforcement learning model and a generalized logit mixed effect model to analyze the behavior of each monkey in different dyads. We find that relative social hierarchy shapes the monkeys’ choices. Despite some individual differences, the strategy used by monkey subjects not only depended on the history of their own reward realization, but also predictions of their opponent’s behavior and implicit social signals, such as gaze direction and the identity of the opponent, which are often omitted in traditional studies in humans. Strengthening our conclusions, when intention signals were obscured, monkeys looked at their opponents’ faces much more and also collided three times as often. These findings show that non-human primates perform sophisticated opponent analysis when making game decisions, much like people do. Therefore, studying the neural basis of these behaviors in non-human primates will provide valuable mechanistic evidence for understanding the neural basis of human strategic decision making.

Disclosures: **X. Li:** A. Employment/Salary (full or part-time):; Humanity and Social Science, California Institute of Technology. **W.S. Ong:** None. **C. Camerer:** None. **M.L. Platt:** None.

Poster

251. Prefrontal Cortex and Decision Making

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 251.04/SS5

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant K01ES025442

NIH Grant MH109728

Simons Foundation Grant SFARI award #304935

Title: Dorsal prefrontal cortex tracks projected outcomes in a dynamic competitive game

Authors: ***J. M. PEARSON**[1], S. N. IQBAL[2], C. B. DRUCKER[1], J.-F. GARIEPY[2], M. L. PLATT[3]
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Abstract: The ecological niches occupied by most organisms, including humans, are both dynamic and uncertain, requiring that actions be taken in real time and modified in response to changing circumstances. However, most studies of dynamic decision-making to date have explored either repeated trials of the same task under slowly changing circumstances or interactions between agents that take place in a restricted action space. Here, we examine data

from repeated trials of a real-time strategic interaction with continuous freedom of movement. We trained monkeys to play a competitive task in which the goal of one (the “shooter”) was to move a colored dot (the “ball”) from the left to right side of a computer monitor using joystick input. The goal of the second monkey (the “goalie”) was to block the dot by moving a vertical line along the right-hand side of the screen to intercept it. Thus, each player controlled an avatar with at least one continuous degree of freedom, in principle allowing for dynamic coupling between the two in real time.We analyzed these data by modeling the trajectory of each player as the result of a linear control model applied to a latent goal state. This goal represented an onscreen position toward which each player directed his avatar at each moment in time. These goal positions followed a Markov dynamics governed by a kinetic energy (the squared change in goal positions in time) and a potential energy that depended on the current observable state of each player. This characterization allowed us to directly look for correspondences between goals and neural activity, as well as to quantitatively characterize each segment of a trajectory as likely or unlikely relative to a player's previous history.We recorded 353 single units from the lateral and medial dorsal prefrontal cortex of three rhesus macaques (137 DMPFC; 216 DLPFC) during 130 sessions in which the recorded monkey played as the shooter. We also found that in 58% of DMPFC cells (79/137) and 43% of DLPFC cells (92/216) spiking activity modulated following shooter wins, with 20% and 18% of cells differentiating between close and easy wins (defined based on a tercile split of ball-goalie distance at end of trial). In fact, this signal often began to emerge even before trial end, at the moment the outcome of the trial became apparent. Thus, cells in dorsal PFC encoded not only trial outcome, but an additional performance signal necessary for updating strategic behavior in the absence of reward variation. Taken together, these findings suggest that single neurons in dorsal PFC not only encode reflect evaluative signals necessary to update behavioral policies, they do so online as the prospects of winning dynamically evolve.

Disclosures: **J.M. Pearson:** None. **S.N. Iqbal:** None. **C.B. Drucker:** None. **J. Gariepy:** None. **M.L. Platt:** None.

Poster

251. Prefrontal Cortex and Decision Making

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 251.05/SS6

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant DA037229

Title: Pupil size supports a comparison-to-reference choice mechanism in a sequential gambling task

Authors: *T. CASH-PADGETT[1], H. AZAB[1], S. YOO[2], B. Y. HAYDEN[1]
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Abstract: Options in a foraging decision are often framed as foreground vs. background; ostensibly, non-foraging binary economic choices may proceed the same way. Specifically, we may evaluate two sequential options asymmetrically, the first serving as a standard (background) in light of which the second is accepted or rejected (foreground). Dispositive evidence for this hypothesis may come from pupil diameter, which has been shown to fluctuate along dimensions related to foreground/background contrast. We examined pupil size responses in rhesus monkeys performing a token gambling task with sequentially presented options. We find that pupil size (negatively) tracks the value of the first attended option, shifts to reflect the value of the second option when attention does and, at that point, reflects the difference between the value of the attended and remembered options. Choice of the second option (i.e. the foreground option at the time of choice) is faster, favored on difficult (near-value) trials, and predicted by smaller pupil size. Following choice but prior to gamble resolution, the relationship between pupil size and value flips and becomes positive, increasing with the value of the chosen offer. Finally, number of tokens (which rose with performance) was associated with diminished pre-choice pupil size and, when the second option was chosen, increased post-choice pupil size. These results are consistent with a reference-to-comparison choice mechanism, and support the idea that pupil size provides an ongoing index of internal cognitive processes underlying choice.

Disclosures: T. Cash-Padgett: None. **H. Azab:** None. **S. Yoo:** None. **B.Y. Hayden:** None.

Poster

251. Prefrontal Cortex and Decision Making

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 251.06/DP13/SS7 (Dynamic Poster)

Topic: H.01. Animal Cognition and Behavior

Support: NIH R01 DA037229

Title: Using Generative Adversarial Networks to estimate agent goals in a Pac-man-like virtual hunting experiment

Authors: *S. YOO[1], S. IQBAL[3], B. Y. HAYDEN[1,2], J. M. PEARSON[3]
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Abstract: Many primates' decisions in natural settings are dynamic, meaning that they are extended in both time and space. For example, when a predator pursues a prey, the pursuit may last hours and range over kilometers, and may involve a continuously changing trajectory and

even plans. Such decisions may also last fractions of a second and occur over only a few centimeters, but in both cases, predators must both track prey and plan an intercept in real time, even as the prey moves. Such pursuit processes are among the most complex and behaviorally crucial of all decisions. Here, we devised a virtual hunting task in which a non-human primate (the predator) controlled an avatar represented on a computer monitor in an overhead view. The goal of the animal was to intercept a moving target (the prey), for which it was rewarded with a drop of juice. The structure of the task was much like a simple version of Pac-man with no walls and no pellets, only a single moving prey. Monkeys exhibited a rich variety of intercept trajectories, but this richness poses a challenge for behavioral analysis, since no two trials are quite the same. As a result, simple trial averaging is inadequate. We applied a recently developed computational model of dynamic trajectories to these data (Iqbal and Pearson, 2017). The motion of the animal's avatar was described by a simple linear control model applied to a dynamic goal state, which represented the animal's intended position at each moment in time. These goal states evolved according to a Markov dynamics governed by a kinetic energy dependent on the change in goal between time steps and a potential energy function dependent on both the predator and prey positions and velocities. This model not only allowed us to infer goal states and energies for each trial individually, but also to generate novel behavior resembling real trials, an indication that the model captured sufficient complexity to describe real behavior. We found that inferred goal states not only tracked the position of the prey at each time but also accounted for current prey dynamics, leading the prey along its current trajectory. More precisely, the dynamics of inferred goals correlated much more strongly with the trajectory of the prey avatar than the trajectory of the predator's own avatar, as would be expected if monkeys were planning based on prey movement. In addition, goal position correlated strongly with gaze position in the smooth pursuit eye movements used by the monkey to track the prey item onscreen. This account of behavior is generative, separates movement goals from short-term motor plans, and allows subsequent modeling of goals and pursuit decisions in terms of the relative value of multiple prey targets.

Disclosures: **S. Yoo:** None. **S. Iqbal:** None. **B.Y. Hayden:** None. **J.M. Pearson:** None.

Poster

251. Prefrontal Cortex and Decision Making

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 251.07/SS8

Topic: H.01. Animal Cognition and Behavior

Support: NSF CAREER Award (BCS1253576)

R01 Grant NIH (DA038615)

Title: Evidence for a comparison-to-reference mechanism of economic choice in the dorsal anterior cingulate cortex

Authors: *H. AZAB, B. Y. HAYDEN
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Abstract: Value-based choices are often biased by attention. However, how attention influences low-level neural mechanisms of value comparison remains unknown. We hypothesize that value comparison is framed as a choice between a default option and an alternative one, where the alternative is the currently-attended option. We recorded neurons in the dorsal anterior cingulate cortex (dACC) of macaques choosing between two asynchronously-presented gambles. We found that value signals were influenced by the subject's upcoming choice, and more so as the trial proceeded. However, even after both gambles were revealed, their values were represented asymmetrically: while the value of the second offer was represented in an entirely post-decisional format, the value of the first offer was not entirely dependent on the upcoming decision. These findings suggest that attention defines a default/alternative neural framework for value-comparison. We find that this process is instantiated in a single population of neurons, rather than two separate populations. Our results suggest that correlations between value and firing rate may reflect processes more sophisticated than computing and representing value.

Disclosures: H. Azab: None. **B.Y. Hayden:** None.

Poster

251. Prefrontal Cortex and Decision Making

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 251.08/SS9

Topic: H.01. Animal Cognition and Behavior

Support: NSF (BCS1253576)

NIH (DA038615)

Title: A scalar sampling race model predicts risk preference in primates

Authors: *B. R. EISENREICH[1], B. Y. HAYDEN[2]
[1]Brain and Cognitive Sci., [2]Univ. of Rochester, Rochester, NY

Abstract: Examinations of economic choice behavior within variable environments have revealed distinct preferences across taxa for risk aversion or risk seeking. One puzzling finding has been the unique preference of primates to seek out and choose risky options within economic decision making tasks. Here we present a memory-sampling race model that captures the factors that influence risk aversion/seeking across taxa, and provides a clear explanation for risk seeking

in primates. Importantly, this model makes predictions about the conditions under which risk seeking is likely to occur based on the reward statistics of the environment.

Disclosures: B.R. Eisenreich: A. Employment/Salary (full or part-time):; University of Rochester. **B.Y. Hayden:** None.

Poster

251. Prefrontal Cortex and Decision Making

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 251.09/SS10

Topic: H.01. Animal Cognition and Behavior

Title: Strategic value encoding in ventromedial prefrontal cortex guides foraging behavior

Authors: *P. MEHTA, B. Y. HAYDEN
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Abstract: Foraging theory is a framework for understanding decision making processes by framing them in terms of accept-reject value-based choices similar to those that animals naturally face in the wild. However, we know very little about the neural mechanisms underlying foraging theory. Ventromedial prefrontal cortex (vmPFC) has been strongly implicated in the processing of subjective value, but its role in higher-level decision making is less clear. In this study, we seek to uncover the neural basis of reward searching behavior in rhesus macaque (Macaca mulatta) vmPFC. Macaques performed a foraging task in which they used eye gaze to search freely through a display of dispersed icons that revealed reward values hidden behind them upon fixation, terminating their search when they decided to accept the currently fixated reward. We hypothesized that vmPFC neural activity would encode several variables related to value and the search process that inform the macaques' search strategy. The macaques indeed performed the task using a near-optimal threshold-based strategy. They also demonstrated real-time adaptation of their search strategy to environments with different numbers of options. As they performed the task, we collected the firing rates of single neurons in vmPFC. We found significant encoding of reward viewing and reward choice, as well as significant correlations of neuronal activity with the relative value of each reward and the cumulative number of reward options viewed over time. These results support the idea that vmPFC is not merely a region that encodes value; it also encodes richer information useful for performing a high-level reward search task that requires both maintaining a representation of multiple values over time and then comparing those values. Neuronal activity in vmPFC may play a key role in guiding foraging strategy.

Disclosures: P. Mehta: None. **B.Y. Hayden:** None.

Poster

251. Prefrontal Cortex and Decision Making

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 251.10/SS11

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant DA037229

Title: Understanding the common underlying neural principles between neuroeconomic decisions and stopping

Authors: *P. BALASUBRAMANI[1], B. Y. HAYDEN[2]
[1]brain and cognitive sciences, [2]Univ. of Rochester, Rochester, NY

Abstract: The process of response inhibition is central for flexible and adaptive behavioral control. It is popularly studied using stop signal paradigms which test for successful cancellation of inappropriate responses as a function of stop signal delay (SSD). On the other hand, neuroeconomic decisions involve processes such as evaluation of offers, their comparison, and offer selection; A choice selection often accompanies successful suppression of events related to the unchosen ones. The goal of our study is to understand the shared principles of cognitive processes during classic neuroeconomic decision making and *stopping*. We recorded from Orbitofrontal cortex (OFC) in macaques using single unit electrophysiology to study their relative contributions to neuroeconomic decisions and executive processes behind inhibitory control. The task interleaves two types of paradigm—a classic stop signal paradigm (SST) and a neuroeconomic (NE) decision paradigm, and the latter matches in design to the former except for their targets which are associated with variable reward magnitudes. Each task-type composes of two different trial-types—go-trials (no-stop) and stop-trials. The go-trials have square-targets appearing at the periphery of the screen after an initial central fixation dot; the subjects are required to saccade to the target and their reaction times are noted. The stop trials have an additional event of one more square-target appearing at the screen's center after a delay (SSD) from the time of go-target presentation. Successful cancellation of motor and cognitive processes supporting a saccade towards go-target, and holding the gaze at the center stop-target, yields a reward in SST; while in NE paradigm, rewards depend on the magnitudes of offer associated with the chosen target, and they are indicated by target color. The SSD associated with fifty percent successful cancellation in SST is used to compute subject's stop signal reaction time. Some preliminary results show strong tuning in OFC to rewards, trial types and spatial positions across tasks. The distributions of spatial coding index differ across trial types. Interleaving neuroeconomic decisions with classic stop-signal paradigm trials allows us to find interaction as well as sequence effects; we find significant reaction time differences in few cases of sequential interactions between reward magnitudes (in NE) and trial-type (in SST). Our study extends to

compare these results to prior reported signals from Frontal Eye Fields, Supplementary Eye Fields, Anterior Cingulate Cortex, and Supplementary Motor Area for performance monitoring and inhibitory control.

Disclosures: P. Balasubramani: None. **B.Y. Hayden:** None.

Poster

251. Prefrontal Cortex and Decision Making

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 251.11/SS12

Topic: H.01. Animal Cognition and Behavior

Support: DFG Grant GU 227/21-1

Title: The avian prefrontal cortex revisited

Authors: *K. VON EUGEN, S. TABRIK, F. STRÖCKENS, O. GÜNTÜRKÜN
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Abstract: While it was long thought birds did not have one, the avian 'prefrontal cortex' (PFC) is one of the prime areas of interest in contemporary avian neuroscience. Also known as the nidopallium caudolaterale (NCL), it is comparable to the PFC in terms of function, connectivity, and cytoarchitecture. The interest is understandable, since on a behavioral level, there is a bulk of literature demonstrating cognitive capacities of birds equaling, and sometimes even exceeding, those of monkeys and primates. In concordance with the role of the PFC in mammals, the NCL is seen as the seat for this array of executive functions in birds. Across mammals, the PFC can be pinpointed in a similar location, while showing variation in subdivisions and extend of expansion. Size estimates in primates and humans found that it scales allometrically to the neocortex. Remarkably, the NCL has been delineated and mapped in pigeons only, and little is known about its exact position in other avian species. We hypothesized that, in accordance with mammalian data, the location of the NCL would not vary across species, and expected the NCL to follow an allometric scaling rule in relation to the telencephalon within the order (e.g. within songbirds). The main aims of this study were to 1) identify the location-, 2) map the trajectory throughout the brain-, and 3) determine the size of the NCL in different species of bird that are known to vary in their level of complex cognition. We delineated the NCL with an immunohistochemical stain against tyrosine hydroxylase (TH). Similar to what has been found for the PFC in primates, the relative size of the NCL in relation to the telencephalon appears to be comparable across different bird species. This does mean that for example corvids have a larger NCL in absolute terms. In contrast to our expectations, however, the initial results indicate that there is a clade-specific organization of the caudal telencephalon, most noteworthy in the songbirds. This is an important finding, since up until now the location of the NCL in other bird

species has been extrapolated from pigeon neuroanatomy. Our results indicate that this translation should be made with caution, and further studies into the exact make-up of the avian caudal forebrain are of crucial importance for past, current, and future research into the NCL in different bird species.

Disclosures: K. Von Eugen: None. **S. Tabrik:** None. **F. Ströckens:** None. **O. Güntürkün:** None.

Poster

251. Prefrontal Cortex and Decision Making

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 251.12/SS13

Topic: H.01. Animal Cognition and Behavior

Title: Distinct fronto-parietal communication channels for separating targets and distractors in working memory

Authors: *S. N. JACOB[1], D. HÄHNKE[1], A. NIEDER[2]
[1]Technische Univ. München, Munich, Germany; [2]Univ. Tuebingen, Tuebingen, Germany

Abstract: The prefrontal cortex (PFC) and parietal cortex are crucial brain structures for maintaining behaviorally relevant (target) information in working memory and protecting it from interference by distracting stimuli. Very little is known about the cross-regional circuit dynamics that underlie this important cognitive control function. We recorded large-scale single-unit activity and local field potentials (LFPs) from the PFC and the ventral intraparietal area (VIP) of two rhesus monkeys trained to resist distracting stimuli in a delayed-match-to-numerosity task. We found task-specific, oscillatory coherence between PFC and VIP in two frequency bands: during stimulus presentation, synchronous activity was strongest in the beta band, while it peaked in the delta and theta range in the memory delays. This synchronization was directed. The beta band was characterized by dominant parieto-frontal (bottom-up) connectivity, while fronto-parietal (top-down) synchronization was stronger in the delta and theta range. In the first memory delay following the target stimulus, target information could be decoded from PFC and VIP oscillatory activity in both frequency bands. However, in the second memory delay following presentation of the distractor, target information was lost in the beta band and shifted strongly into delta and theta frequencies. In this frequency range, the amount of information about both the target and the distractor carried by PFC spiking was VIP phase-dependent, meaning that VIP LFPs could be used as a reading frame to bias readout of PFC neurons towards either the target or the distractor stimulus. High fronto-parietal synchronization after memory interference and good phase-separation of target and distractor information in the theta range was positively correlated with the animals' behavioral performance and predicted fast and accurate

responses. Our results suggest the presence of distinct fronto-parietal communication channels for separating behaviorally relevant and distracting stimuli in working memory.

Disclosures: S.N. Jacob: None. **D. Hähnke:** None. **A. Nieder:** None.

Poster

251. Prefrontal Cortex and Decision Making

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 251.13/SS14

Topic: H.01. Animal Cognition and Behavior

Support: ASM funded by Medical Research Council UK G0800329

ASM funded by Wellcome Trust WT 110157

ZO funded by Royal Society Newton Fellowship NF 160862

AB funded by MRC intramural program MC-A060-5PQ10

DM funded by MRC intramural program MC-A060-5PQ10

MJB supported by MRC and Wellcome Trust

Title: The mediodorsal thalamus contributes to decision making after abstract rule switches

Authors: *A. S. MITCHELL[1], S. CHAKRABORTY[1], A. BELL[1,2], J. SALLET[1], D. J. MITCHELL[2], S. MASON[1], M. BUCKLEY[1], Z. OUHAZ[1]
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Abstract: Learning and decision-making are key cognitive functions that engage frontal cortex and interconnected neural networks. Recent evidence in animal models indicates that the mediodorsal thalamus (MD) also plays a role in successful learning and adaptive decision-making. However, damage to MD in monkeys does not always cause cognitive deficits in tasks shown to be sensitive to frontal cortex damage (Mitchell and Gaffan, 2008). This study investigated executive control mechanisms in rhesus macaque monkeys using a computerized version of the Wisconsin Card Sorting task. Preoperatively, monkeys were trained to learn colour- and shape- matching rules and displayed cognitive flexibility when switching between these matching rules. However, after selective, circumscribed bilateral neurotoxic (NMDA/ibotenic acid) lesions to the magnocellular subdivision of MD (MDmc), within subject comparisons of these monkeys' pre-operative verses post-operative performance demonstrated impaired cognitive flexibility. Monkeys with MDmc damage were readily able to learn the first rule (match to colour or match to shape) in each daily session. However, after experiencing an

arbitrary switch in the matching rule within the session, monkeys with MDmc damage were impaired at updating their choice behavior to respond appropriately to the new matching rule. Interestingly though, monkeys with MDmc damage did not perseverate with their previously rewarded responses after the abstract rule switch. Instead, they made more switches (win-shift) in their choices, and even sampled all three of the available options more readily than during their preoperative performance. Postoperative performance of monkeys with MDmc damage was also compared to monkeys with selective damage to different subdivisions of the frontal cortex. This causal behavioural evidence shows that the MDmc is important in supporting the cortex to perform optimally during specific aspects of learning and adaptive decision-making processes. In addition, several cortical sites showed significant differences in functional connectivity when preoperative verses postoperative anaesthetized resting state functional magnetic resonance imaging analyses were compared. Furthermore, several cortical areas showed significant structural changes when preoperative verses postoperative structural brain images were compared using deformation-based morphometry analyses. Taken together, this evidence indicates that the MDmc provides a unique and critical contribution, via its interactions with the frontal cortex and beyond, during specific aspects of learning and adaptive decision-making.

Disclosures: **A.S. Mitchell:** None. **S. Chakraborty:** None. **A. Bell:** None. **J. Sallet:** None. **D.J. Mitchell:** None. **S. Mason:** None. **M. Buckley:** None. **Z. Ouhaz:** None.

Poster

251. Prefrontal Cortex and Decision Making

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 251.14/SS15

Topic: H.01. Animal Cognition and Behavior

Title: Anterior cingulate cortex lesions abolish budget effects on demand elasticities in rat consumers

Authors: *T. KALENSCHER, S. SCHÄBLE, M. VAN WINGERDEN, Y. HU
Univ. of Duesseldorf, Duesseldorf, Germany

Abstract: Demand theory can be applied to analyze how animal consumers change their selection of commodities within a certain budget in response to changes in price of those commodities. Previous work by us and others using rats has demonstrated that demand elasticities differed between uncompensated budget conditions in which the budget available to be spent on the commodities was kept constant, and compensated budget conditions in which the budget was adjusted so that consumers could potentially maintain their original consumption pattern prior to the price change. We have recently shown that this budget effect on demand elasticity can be explained by budget-dependent valuation of the commodities above and beyond price-effects on valuation. Here, we hypothesized that rat anterior cingulate cortex (ACC) was

necessary to produce the budget effects on demand elasticities. To test this hypothesis, we applied lesions to ACC, or sham lesions, in 24 rats performing an effort task in which they could spend a budget of 80 nose pokes to obtain chocolate or vanilla milk rewards, priced at 2 nose pokes each. All rats generally preferred chocolate over vanilla milk. When the budget was kept constant, their preference for chocolate milk decreased significantly in response to price increases to four nose pokes, and the consumption of vanilla rose when its price was decreased to one nose poke. Crucially, changes in chocolate demand in response to price changes were less pronounced when the budget was compensated, replicating our previous results of budget-effects on demand elasticities. However, ACC-lesioned animals reduced their price-related chocolate demand equally strongly in the compensated and the uncompensated budget conditions, suggesting that they failed to integrate the budget signal into their cost-benefit value computation. We found no main difference in demand elasticities between sham and lesion groups per se, indicating that the lesion effects on the budget-dependence of the rats' demand elasticity was not due to an impaired sensitivity to price changes, or reduced behavioral flexibility. Our results suggest that ACC integrity is necessary for higher-order cost-benefit calculation. Our study yields important new insights the neural basis of budget effects on subjective value computations.

Disclosures: T. Kalenscher: None. **S. Schäble:** None. **M. van Wingerden:** None. **Y. Hu:** None.

Poster

251. Prefrontal Cortex and Decision Making

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 251.15/SS16

Topic: H.01. Animal Cognition and Behavior

Title: Piglets exhibit different discriminative strategies to choose an object in a novel test method to evaluate inference by exclusion

Authors: *P. PAREDES-RAMOS
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Abstract: Inference by exclusion refers to the ability to make decisions based on the systematic exclusion of alternative options. Different studies have shown that animals are able to apply this strategy when required. Nevertheless, the majority of studies employ a touch-sensitive computer screen, where the animals learn to touch one of two images, in order to obtain food. Herein, we present a new approach that allows animals to explore, smell, touch and choose between tridimensional objects. Pigs *(Sus scrofa domesticus)* are explorative animals with apparently sophisticated cognitive skills, for instance, the capacity to memorize human faces, and to learn to use a mirror in order to find food. We used 2- to 4-month-old Yucatan Miniature piglets to

evaluate inference by exclusion. Animals were trained individually by successive approximation to fetch an object. First, animals received a piece of food when they explored the object, then when they picked it up, and finally when they picked it up and delivered it close to the handler. Once animals mastered this ability, they were trained to discriminate between two objects, of which one was rewarded (S+) and one was unrewarded (S-). Training sessions consisted of 28 trials: S+ and S- remained the same throughout all trials. To ensure that animals had learned to discriminate between S+ and S-, they were required to achieve two criteria. Criterion 1 consisted in avoiding to choose novel objects, and criterion 2 involved choosing correctly at least 90% of the training trials for two consecutive sessions. Once criteria were achieved, 30 sessions of four test trials intermixed within 16 training trials followed. Test trial one consisted of a novel positive stimulus (S+1), while the S- remained. In test trial two, the S- was replaced with a novel unrewarded stimulus (S-1) and presented with the S+ of the training trials. Test trial three offered the novel rewarded stimulus of test trial one (S+1) and a new novel unrewarded stimulus (S-2). Finally, in test trial four, the novel unrewarded stimulus of test trial two (S-1) was presented with a new novel rewarded stimulus (S+2). Inference by exclusion was only considered, when correct stimuli were chosen in all four test trials. Statistical analysis indicated that five of eight piglets exhibited inference by exclusion, while the rest of animals showed different strategies like novelty aversion and one-trial learning. These results indicate that piglets are able to discriminate, pick up and choose an object based on the information or value of the alternative option. Future studies may consider our method to evaluate cognitive abilities in animals and the use of pigs to explore animal and human cognition.

Disclosures: P. Paredes-Ramos: None.

Poster

251. Prefrontal Cortex and Decision Making

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 251.16/SS17

Topic: H.01. Animal Cognition and Behavior

Support: NIH R21-DA042882

Title: Contributions of the lateral orbital area to economic decisions in mice

Authors: *M. KUWABARA, N. KANG, G. BLACK, T. HOLY, C. PADOA-SCHIOPPA
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Abstract: Lesion studies and neurophysiology in non-human primates indicate that economic decisions engage the orbitofrontal cortex (OFC). In particular, studies in which monkeys chose between different juices offered in variable amounts identified three groups of cells intimately related to the decision process: offer value cells encoding the value of individual options; chosen

juice cells encoding the binary choice outcome, and chosen value cells encoding the value of the chosen option. Notably, these groups of cells capture both the input (offer value) and the output (chosen juice, chosen value) of the choice process, suggesting that good-based decisions are formed in a neural circuit within OFC. Results obtained in recent years support this hypothesis, but crucial aspects of this circuit remain poorly understood. For example, it is not known whether different groups of cells correspond to morphologically defined cell types, or whether they reside in different cortical layers. Addressing these questions in primates is technically difficult. However, these questions may in principle be addressed using genetic tools available inmice. In the present study, we took several steps in this direction. First, we developed an economic choice task, in which mice choose between two juices offered in variable amounts. Different juices are associated to different odors, and juice quantities are indicated by the odor concentrations. In each trial, the two offers (odors) are presented simultaneously, and the animal indicates its choice by licking one of two liquid spouts. We trained >30 animals in this task. A typical session lasts ~300 trials and choices exhibit a quality-quantity trade-off reminiscent of that observed in monkey behavior. Second, we developed an optogenetic inactivation task focused on the lateral orbital (LO) area, the presumed homologousof the primate central OFC. In a series of experiments, we found that bilateral inactivation of LO had strong effects: Decisions became much more noisy (i.e., shallower choice patterns), indicating that LO is necessary for economic decision making. Third, in other experiments, we recorded the extracellular activity of ~600 cells while animals performed the task. Echoing results from primates, we found neurons encoding variables offer value, chosen juice and chosen value. In contrast with primate OFC, many LO cells were spatially tuned.

Disclosures: M. kuwabara: None. **N. Kang:** None. **G. Black:** None. **T. Holy:** None. **C. Padoa-Schioppa:** None.

Poster

251. Prefrontal Cortex and Decision Making

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 251.17/SS18

Topic: H.01. Animal Cognition and Behavior

Support: NSF 1121147

Title: What, if anything, is the rodent prefrontal cortex?

Authors: *T. K. SWANSON[1], S. R. WHITE[2], A. T. DEMARCO[4], S. P. WISE[5], M. LAUBACH[3]
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Abstract: Many recent studies have reported findings on the “rodent prefrontal cortex”. However, controversy remains over whether the rodent PFC is a useful model for understanding human brain function. Notably, the relative size and gyrification of the PFC differ dramatically between rodents and primates. Moreover, the underlying callosum and brain case are curved in modern primates but not in rodents or early (extinct) primates, as found in measurements that we have made using publicly available endocasts (DOI: 10.1016/j.jhevol.2016.06.005). These structural factors result in positional differences that make it difficult to compare or interpret data across species. We propose a hypothesis for the role of radial expansion of the frontal cortex and underlying callosum in driving a shift from a rostral-to-caudal axis in the inferred euarchontoglires common ancestor (iECA) (PL-to-AC) to a dorsal-to-ventral axis in modern primates (aMCC-to-pgACC). To test this hypothesis we casted molds from 3D-printed rat brains to make silicone brain models based on a study that showed lissencephalic silicone brains expand and show gyrification when placed under hydrostatic stress (DOI: 10.1038/NPHYS3632). We 3D-printed brain cases of rats and humans to constrain the shape of the brain as it expanded under hydrostatic pressure. While our models expanded and developed gyrii, these changes cannot account for the radial displacement of prefrontal areas from their orientation in the iECA (and rodents) to their locations in modern primates. To examine the role of underlying structures, we measured the curvature of the human corpus callosum (56.4 degrees) using Fourier spectrum analysis of directionality (ImageJ). When applied to volumetric graphical models (Waxholm Space Atlas), there was a rotational shift such that the AC and PL areas shifted from a rostral-to-caudal axis in the original rodent model to a dorsal-to-ventral axis in the expanded model, and the IL area rotated below the genu of the callosum. Understanding these positional differences and their evolutionary basis is crucial for incorporating findings from rodent studies into the wider literature on the prefrontal cortex.

Disclosures: T.K. Swanson: None. **S.R. White:** None. **A.T. DeMarco:** None. **S.P. Wise:** None. **M. Laubach:** None.

Poster

251. Prefrontal Cortex and Decision Making

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 251.18/SS19

Topic: H.01. Animal Cognition and Behavior

Support: SRPBS, AMED

Title: Spatial and temporal distribution of value-related and the visual information in the macaque lateral prefrontal cortex

Authors: *S. TANAKA[1], K. KAWASAKI[2], I. HASEGAWA[3], T. SUZUKI[4], M. KAWATO[5], M. SAKAGAMI[1]

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Abstract: Decision making is a mental process that involves weighing the value of one's options when presented with many different choices. Previous studies have shown that areas in the prefrontal cortex (PFC) play an essential role in value calculation and comparison. The lateral prefrontal cortex (LPFC) is known to receive visual input from the visual cortex and represent choice-value during decision making. It is therefore possible that visual information representing reward is converted to value information in the LPFC. However, few studies have directly examined this hypothesis. Our aim was to test this hypothesis and reveal the spatial and temporal distribution of value-related information in the LPFC using reward-related visual stimulus.
Two monkeys were trained to perform a free-choice task with six juice rewards. Initially two reward cues that indicated a type of juice were presented sequentially with a short interval between cues. Then, the two reward cues were presented simultaneously and the monkeys made a choice between the two rewards to obtain the juice reward. From the choice behaviors between two alternatives, we estimated the values of the rewards. Electrocorticographic (ECoG) electrodes were implanted in the left LPFC and ECoG signals were recorded during the free choice task.
We first tried to decode the values of the juice rewards using the ECoG signals during presentation of the first reward cue. We used wavelet power and phase in five frequency domains (δ, θ, α, β, γ) as features and decoded the values of the rewards using the Sparse Linear Regression (SLiR) algorithm. The decoded values were highly correlated with the behaviorally estimated values and the R^2 score was biased to be larger than 0 and indicated a good decoding performance. Additionally, the shuffled value could be decoded from the ECoG signal recorded from the LPFC, which indicated that the LPFC may *not* include value-related information, but only processes the visual information. To examine this possibility, we performed the decoding analyses with the ECoG signals recorded from subareas of the LPFC. The results showed that the LPFC was in fact involved in both value-related and visual information and that these were localized, respectively, in the anterior and posterior parts of the LPFC. Furthermore, the peak timing of the value decoding performance was earlier in the posterior region than in the anterior region indicating that visual information was processed earlier in the LPFC than value-related information. We suggest that input signals from the visual cortex are converted to value information along a signal stream from the posterior part to the anterior part of the LPFC.

Disclosures: **S. Tanaka:** None. **K. Kawasaki:** None. **I. Hasegawa:** None. **T. Suzuki:** None. **M. Kawato:** None. **M. Sakagami:** None.

Poster

251. Prefrontal Cortex and Decision Making

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 251.19/SS20

Topic: H.01. Animal Cognition and Behavior

Support: The Spanish Ministry of Economy (BES-2011-049131)

The Spanish Ministry of Economy (SAF2013-46717-R)

The Spanish Ministry of Economy (SAF2010-15730)

The Spanish Ministry of Economy (RYC-2009-04829)

Marie Curie IRG PIRG07-GA-2010-268382

ERC-2015-CoG - 683209 PRIORS

Marie Curie IIF253873

Title: The dynamics of expectation build-up and its integration with stimulus evidence during perceptual discrimination

Authors: *A. HERMOSO MENDIZABAL[1], A. HYAFIL[1,2], P. E. RUEDA-OROZCO[3], S. JARAMILLO[4], D. M. ROBBE[5], J. DE LA ROCHA[1]
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Abstract: Prior experiences shape the way we perceive the world by creating expectations, a reference frame for future decisions and judgements. Little is known however about how these expectations are built and influence our perception. We trained rats in a reaction time (RT) two-alternative forced-choice (2AFC) task in which the two acoustic stimulus categories were presented in sequences exhibiting serial correlations: the probability to repeat the previous stimulus category varied between 0.7 and 0.2 in blocks of 200 trials. Rats adapted their behavior to the sequence correlations by developing a repeating choice bias after correct repetitions and a weaker but reliable alternating bias after correct alternations. The bias built up after each correct response but reset to zero after error trials independently of the number of previous correct trials. A GLM analysis, separately fitted for after correct and after error trials, revealed that these biases were the superposition of several history dependent terms: (1) repulsion of previous stimulus, possibly due to sensory adaptation; (2) a lateral bias towards (away from) the side of recently rewarded (unrewarded) responses, i.e. win-stay-lose-switch strategy; (3) a novel and strong

transition bias that reinforced recent correct repetitions and alternations. Intriguingly the transition bias was ignored after error trials, when the reliability of the internal model was possibly questioned, and recovered after the subsequent correct trial. As this nonlinear effect could not be captured by a unique GLM fit, we built a latent generative model of rats decisions, whereby lateral and transitions biases are updated at each trial and transition bias influence on current trials is gated by a reward-dependent signal. Thanks to this modulation the transition bias was not erased after errors, and a single correct trial was sufficient to recover the accumulated choice bias.
Stimulus expectations also lead to longer RT for unexpected compared to expected stimuli, but comparable to trials without a defined expectation. Finally expectation had in general a weaker impact on choice for trials with long RT, a feature that unveils how expectation and current stimulus evidence are integrated. We simultaneously conducted pharmacological inactivations and neural population recordings in dorso medial striatum and in medial prefrontal cortex. We have started to characterize how these circuits encode and combine priors with stimulus information. Overall, our findings reflect that expectations show consistent flexible build-up-and-reset dynamics across trials allowing rats to capitalize on the predictability of the stimulus sequence.

Disclosures: **A. Hermoso Mendizabal:** None. **A. Hyafil:** None. **P.E. Rueda-Orozco:** None. **S. Jaramillo:** None. **D.M. Robbe:** None. **J. de la Rocha:** None.

Poster

251. Prefrontal Cortex and Decision Making

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 251.20/SS21

Topic: H.01. Animal Cognition and Behavior

Support: National Natural Science Foundation of China (31571079)

Title: Short-term influence by recent trial history depends on stimulus difficulty

Authors: *W. JIANG, J. LIU, D. ZHANG, H. YAO
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Abstract: Previous studies have shown that perceptual decisions of humans and animals can be influenced by trial history as well as sensory evidence. However, the dependence of history influence on stimulus difficulty and the temporal window of history influence are less well understood. We trained freely-moving mice to perform a two-alternative forced choice task to detect the position of a light bar presented on the left or right side of the screen. The level of stimulus difficulty was controlled by stimulus contrast ranging from 20% to 100%. Different contrasts were presented in different blocks (80 trials per block). We modeled the mice’s choice

in each trial using a probabilistic choice model that integrated the influence of current stimulus contrast and the outcome of previous trials. For each block, we compared the accuracy of a simple model (without history influence) and the full model (with history influence) at predicting choices, and estimated the number of history trials (N trials back) that could influence current choice. We found that including trial history in the full model improved the accuracy of prediction relative to the simple model, and the improvement increased with stimulus difficulty. The number of history trials that could influence current choice also increased with stimulus difficulty, and such effect did not depend on the block sequence. For the most difficult stimulus, the number of history trials that could influence current choice did not change with trial duration, suggesting that the short-term memory load of trial history is limited. We are now performing electrophysiological recordings from the frontal cortex of behaving mice to examine whether neuronal activity is influenced by trial history and whether the influence is dependent on stimulus difficulty.

Disclosures: **W. Jiang:** None. **J. Liu:** None. **D. Zhang:** None. **H. Yao:** None.

Poster

251. Prefrontal Cortex and Decision Making

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 251.21/SS22

Topic: H.01. Animal Cognition and Behavior

Support: Grants-in-Aid for Scientific Research on Innovative Areas (26250003)

Grants-in-Aid for Scientific Research on Innovative Areas (25119004)

Title: Two distinct learning processes in rats, insight-like learning and trial-and-error learning

Authors: *K. MAKINO, Y. IKEGAYA
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Abstract: We have two types of learning processes, trial-and-error learning and insight learning, and that is, we sometimes learn gradually through trial and error (Thorndike, 1898), otherwise we learn suddenly through insight (Kohler, 1917). However, little is known about the neural mechanisms underlying two distinct learning processes and the difference between them. In this study, we designed the behavior task, in which a two-hole nose-poke test allowed to dichotomize the learning of each rat into insight-like learning or trial-and-error learning. During the behavior test, rats select either a left or right nose-poke hole in the front panel in the apparatus. One of two holes is illuminated by green light in a random manner from trial to trial. Nose-poking into the other hole delivers a food pellet as a reward. Using this task, we sought to search the brain regions that mediated insight-like learning or trial-and-error learning. First, we focused on the

anterior cingulate cortex (ACC), a part of the prefrontal cortex, because recent human researches had reported that the emergence of insight was coincident with increased ACC activity (Luo *et al*., 2004; Anderson *et al*., 2009). To investigate whether ACC was involved in insight, ACC activity was pharmacologically inhibited during the task by cannula injection of the $GABA_A$ receptor agonist muscimol. Unexpectedly, the ACC inhibition prevented trial-and-error learning but not insight-like learning. This result indicates that ACC plays an important role for gradual learning rather than insight. At the same time, our data suggest that distinct brain regions mediate insight-like learning and trial-and-error learning in rats.

Disclosures: K. Makino: None. **Y. Ikegaya:** None.

Poster

251. Prefrontal Cortex and Decision Making

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 251.22/SS23

Topic: H.01. Animal Cognition and Behavior

Support: NIH R01EY019273-01

Title: Foveal and response field information are multiplexed in the frontal eye field to form a neural representation for eye movement planning and execution

Authors: *K. MIRPOUR[1], Z. BOLANDNAZAR[1], J. W. BISLEY[1,2,3]
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Abstract: Neurons of the frontal eye field (FEF) of prefrontal cortex are known to play an important role in saccade planning and execution. Most previous studies of FEF have relied on single eye movements and have shown that neurons in FEF respond maximally to task relevant stimuli located in the response field. However in realistic situations, isolated eye movements to explicitly signaled goals rarely happen. Saccades usually connect two fixations as part of a stream of fixations to obtain information about the visual world or to find something or someone. Therefore information about the origin of a saccade may play an important role in deciding when to make the next saccade. Here we asked whether the identity of the stimulus at the focus of the gaze impacts the response of FEF neurons. We recorded the activity of 231 FEF neurons from two animals while they performed a visual foraging task with 5 possible targets and 5 distractors presented on the screen. As previously shown, we found that the identity of the stimulus in the response field modulated the population response. However, the identity of the stimulus at the fovea had a far greater effect that appeared to modulate the gain of the neuron. When the animals were fixating a potential target, neuronal responses were significantly and substantially less than when the animals were fixating a distractor. There was no interaction between the two effects,

suggesting that the neuronal response multiplexes information about what is in the response field and what is at the fovea. We propose that by strongly affecting the response to stimuli in the response field, this mechanism helps control the flow of saccades. When fixating something that may give a reward, responses across FEF are reduced and, thus, help maintain fixation. Conversely, when fixating a stimulus that is not the goal of search, activity across FEF is elevated, highlighting alternative saccade targets and leading to shorter fixation durations.

Disclosures: K. Mirpour: None. **Z. Bolandnazar:** None. **J.W. Bisley:** None.

Poster

251. Prefrontal Cortex and Decision Making

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 251.23/SS24

Topic: H.01. Animal Cognition and Behavior

Support: R01MH065658

Title: Contributions of OFC and mPFC to certain vs uncertain reversal learning

Authors: *P. MARTIN[1], M. L. SHAPIRO[2]
[1]Icahn Sch. of Med. At Mount Sinai, New York, NY; [2]Neurosci., Mt. Sinai Sch. Med., New York, NY

Abstract: Behavioral flexibility is the ability to adapt to a changing and uncertain environment (Kolb, 1990). Nature is inherently stochastic. For example, a stimulus (fruit tree) can often be predictive of reward (fruit), but not always (bad year). Nature is also volatile. It can change altogether without warning, so that a stimulus (fruit tree) predictive of reward (fruit), suddenly comes to predict nothing at all (fruit season is over). The prefrontal cortex (PFC) is the neural substrate of behavioral flexibility (Fuster, 2001), and its subcircuits may provide mechanisms to optimally navigate a dynamic environment that is both stochastic and volatile. For example, the orbitofrontal cortex (OFC), part of the ventral aspect of the PFC, is critical in guiding behavior when stimulus-outcome associations change (Schoenbaum et al., 2009b), specially when they are stochastic (Dalton et al., 2016). Another subregion of the PFC, the medial PFC (mPFC), is crucial for adaptive responses in a quickly changing, or volatile environment (Behrens, 2007; Guise & Shapiro, 2017). Whether the mPFC and OFC play complementary roles in responding to different types of uncertainty is unknown. To investigate this further, we trained rats in a rapid serial spatial reversal task in an automated plus maze, where one of two goal arms was initially rewarded. The identity of the rewarded spatial location was reversed quickly (volatility), when animals achieved 10 correct trials out of 12 consecutive trials. In one cohort, the spatial goals were reinforced deterministically (always/never), whilst in a different cohort they were reinforced stochastically (80% of the time/20% of the time). When animals were able to

complete 5 reversals per session, they were implanted with double bilateral cannula targeting the mPFC and lateral OFC. After recovery and retraining, rats received local infusions of either saline or the GABAA agonist muscimol into either the mPFC or lateral OFC. When spatial goals were reinforced deterministically, inactivating the mPFC produced severe deficits during reversal learning, but not during the initial spatial discrimination. Inactivating the OFC did not impair either the initial spatial discrimination or further spatial reversal learning, mirroring results of others (Schoenbaum, 2002; Dalton et al., 2016). A second cohort is undergoing training on the stochastic version of the task, after which the same schedule of inactivations will be performed. This data will shed light, in a within-subject study, on how two subregions of the PFC interact to provide behavioral flexibility in the face of different types of uncertainty.

Disclosures: P. Martin: None. **M.L. Shapiro:** None.

Poster

251. Prefrontal Cortex and Decision Making

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 251.24/SS25

Topic: H.01. Animal Cognition and Behavior

Support: MOST, Taiwan

Title: Risk-dependent choice affected by the lesion of lateral orbitofrontal cortex of the rat

Authors: Y.-H. YANG[1], Y.-C. CHANG[2], C.-Y. CHUANG[3], S.-F. CHEN[4], *R.-M. LIAO[5]
[1]Intitute of Neurosci., [2]Dept. of Psychology, [3]Inst. of Neurosci., [4]Intitute of Neuriscience, [5]Natl. Cheng-Chi Univ., Taipei, Taiwan

Abstract: Risk is a ubiquitous feature of the environment, such that decision making under risk or uncertainty is essential for all living organisms to survive. Lack of this kind of adaptive risk-based decision making have been shown to link with several psychiatric disorders such as substance abuse and schizophrenia. Although there is a growing body of research investigating the neural mechanisms underlying risk-associated decision making, only a few studies examined the risk-dependent choice by taking the variance in the desired reward outcome into account. The expected value (EV) set in equal for the binary choice options is required in the risk-dependent choice task. A T-maze with three different reward ratios set up to measure the risk-dependent choice in the rat has been reported by Yang and Liao (2015). In which, the nucleus accumbens has been shown to be critical for the development of this behavior; it is intriguing to test whether the orbital frontal cortex is also involved in risk-dependent choice behavior. In the present experiment, the experimental rats, following the operational recovery from an excitotoxic lesion in the lateral OFC (lOFC), received behavioral tests of locomotor activity, anxiety, reward discrimination and T-maze risk choice. In the risk choice, the rats choose between either large

reward but risky (LR) and small reward and certain (SC) for each trial. The probabilities of reward (50%, 25%, and 12.5%) and the reward magnitude given in LR option (2, 4, or 8 pellets) were correspondently manipulated to mimic three levels of risk (in low, medium, and high, respectively). From a 7-day post-lesion test of free choice, in the sham controls, risk-seeking performance appeared in low-risk group, whereas risk-averse pattern in high-risk group. A shift from an early risk-seeking to a later risk-averse was observed in the medium-risk group. The lOFC lesion caused the rat tested in medium-risk condition become risk-seeking in the 7-day test, and no significant post-lesion change was observed in the high- or low-risk group. The present lOFC lesion did not affect the gross motor function, neither producing anxiety-like response. Together, these data indicate that the lOFC is involved in risk-dependent decision making.

Disclosures: **Y. Yang:** None. **Y. Chang:** None. **C. Chuang:** None. **S. Chen:** None. **R. Liao:** None.

Poster

251. Prefrontal Cortex and Decision Making

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 251.25/SS26

Topic: E.07. Rhythmic Motor Pattern Generation

Support: JSPS KAKENHI 26242065

Title: Effect of cognitive load on self-paced periodic movements with different motor patterns

Authors: *W. QI[1], A. MIURA[2], K. KATO[2], K. KANOSUE[2]
[1]Sports Sci., [2]Waseda Univ., Tokorozawa-Shi, Japan

Abstract: Choosing appropriate movements depending on specific situations is the premise of keeping accurate and stable performance. Especially for periodic movements understanding differences in movement characteristics among different movements is important for improving sports and music performances. In order to analyze periodic movements, a model is generally utilized that is composed of two parts, temporal perception process (cognition) and motor execution process (movement). The purpose of this study was to test whether the accuracy and stability of periodic movements are influenced with cognitive load and movement types. Fifteen subjects were recruited in this experiment (20-40 years old, healthy, right-handed). The subjects sat at a table naturally, and a force sensor was fixed on their right index fingers by tapes. The right forearm was put on the table and set at a satisfied position while taping or pressing with the right index finger. Two periodic motor patterns (finger tapping and finger pressing) and two different lengths of inter-tap (or inter-press) intervals (375ms and 2500ms) were tested as the primary task. The secondary task backward counting was utilized. For the primary task, trials are

randomized across the subjects and each trial contained 31 taps or presses (30 intervals). For the secondary task, subjects had to continuously do the reverse counting from a random number given by the experimenter and vocalize answers. Signals from the force sensor and the metronome were fed into a computer through an A/D converter. CVs of single tasks were significantly smaller than those of dual tasks for the whole experiment ($P<0.01$). This result suggests that the extra cognitive load worsen the stability of performance in both finger tapping and finger pressing. In short time interval (375ms) of the single task, CV of tapping task was significantly smaller than that of pressing task ($P < 0.01$) while there was no significant difference in long time interval ($P > 0.05$). In dual tasks, there was no significant difference between CVs of tapping and pressing at both time intervals ($P > 0.05$). These results indicate that although the extra cognitive load of the secondary task was the same, it influenced the stability of tapping task more than that of pressing task. Thus, finger tapping and finger pressing can be considered as different type of movement and influenced differently with a same cognitive load. As a conclusion, we suggest that the difference of stability in periodic movement comes from both cognition and movement type.

Disclosures: **W. Qi:** None. **A. Miura:** None. **K. Kato:** None. **K. Kanosue:** None.

Poster

252. Learning and Memory: Hippocampal Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 252.01/SS27

Topic: H.01. Animal Cognition and Behavior

Support: NIH 5R01MH084038

Title: Out-of-context activation of memory: Limits of stress-induced memory enhancement

Authors: ***B. B. LEE**[1], A. A. FENTON[2]
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Abstract: BACKGROUND: The current work characterized some of the limitations of a previously reported phenomenon called “out-of-context activation of memory” (OCAM). Swim-stress raised serum corticosterone levels, and made labile previously acquired, consolidated memories in a context that is unrelated to the original learning situation. This stress-induced observation enhanced the expression of memory for tasks that were appetitively-conditioned, aversively-conditioned, short training regimens, and intensive training regimens (Ježek et al, 2010).
RATIONALE: We investigated the role of corticosterone in this stress-induced activation of memory, and the impact of swim-stress on memories of different ages and different types.

METHODS: Multiple behavioral regimens were used including aversively-conditioned left/right discrimination task, active place avoidance task, and administering exogenous corticosterone. RESULTS AND SUMMARY: We report that corticosteroids are necessary but not sufficient component of stress-induced OCAM phenomenon, its impact is limited to enhancing the expression of stable, unrelated memories that were acquired up to one week before, and has no observable effect on hippocampus-dependent memories.

Disclosures: B.B. Lee: None. **A.A. Fenton:** None.

Poster

252. Learning and Memory: Hippocampal Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 252.02/SS28

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant R01MH099128

NIH Grant R21NS091830

Title: Place learning induces persistent input-specific hippocampus circuit function changes in the freely-behaving mouse

Authors: *A. CHUNG, A. A. FENTON
Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: The synaptic plasticity and memory (SPM) hypothesis asserts that learning changes synaptic function of the neural circuits that store the information that is acquired in memory. This predicts it should be possible to detect long-term synaptic function changes that support persistent memory, but these changes have been elusive. We investigated, in freely-behaving mice, whether i) place learning causes synaptic circuit function changes in CA1 and DG of the hippocampus, ii) the circuit function changes are altered by subsequent place learning, iii) memory formation coincides with increased expression of PKMzeta, a molecule that is both necessary and sufficient for maintenance of late-LTP; iv) memory erasure by PKMzeta inhibition also reverses the long-term synaptic changes. Adult male mice were implanted with sets of stimulating electrodes in the angular bundle and 16- or 32-site recording electrodes that spanned the dorsal hippocampus somatodendritic axis. After a pretraining session of 30-min free exploration on day 1, mice received 30 min active place avoidance training each day for 3 days. Seven days later, mice received retention test to test memory. One day after retention test, they received additional training in a “conflict” trial with the shock zone relocated 180° or a “novel” trial in a new environment. DG and CA1 evoked potential responses to angular bundle 0-300 µA test stimuli were measured 2h before each training session and the site-specific fEPSP slope and

population spike amplitude were computed from the current source density to detect circuit function changes. Memory training (but not pretraining) decreased the fEPSP slope at the molecular layer of the upper but not the lower blade of DG. The fEPSP slope also decreased at CA1 stratum lacunosum moleculare (s.lm), whereas the poly-synaptic response (DG-to-CA3-to-CA1) at CA1 stratum radiatum was potentiated. These changes persisted at least 50 days. Conflict memory training in the same environment did not cause further changes but Novel memory training (but not pretraining) in a new environment decreased the fEPSP in the molecular layer of the lower blade of the DG. These data indicate that storage of conditioned memory causes input-specific hippocampus synaptic circuit function changes that are training specific and sufficiently large to be detected at the level of the fEPSP response. These changes in synaptic populations may dwarf the changes that are presumed to store the specific information in memory but the effect of PKMzeta inhibition that erases avoidance memory is being assessed.

Disclosures: A. Chung: None. **A.A. Fenton:** None.

Poster

252. Learning and Memory: Hippocampal Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 252.03/SS29

Topic: H.01. Animal Cognition and Behavior

Support: NIH-R25NS080686-06

NYU Dean's Undergraduate Research Funding

Title: Dendritic compartment specific morphological alterations in the dorsal hippocampus of the MAM model of neurodevelopmental insult

Authors: *K. C. O'REILLY, A. V. PATINO, A. A. FENTON
Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: Patients with neuropsychiatric disorders often express deficits in information processing and limbic circuit abnormalities. While these disorders appear to have diverse etiology, their common features suggest neurodevelopmental origins. Accordingly, we used the schizophrenia-related gestational day 17 methylazoxymethanol acetate (MAM) model to evaluate the hypothesis that a general gestational insult can alter the limbic neural circuit. We previously showed that adult MAM rats have problems accumulating memory over trials separated by approximately 10 min in a hippocampus-dependent active place avoidance task. We also find that metabolic functional coupling between the dorsal hippocampus and the medial entorhinal cortex is consistently higher in MAM rats, who also have reduced hippocampus area and altered hippocampus morphology.

To evaluate the possibility of a structural basis for the MAM-induced hippocampus dysfunction, we examined Golgi impregnated tissue. We completed our evaluation by measuring layer thickness along the somatodendritic axis of dorsal CA1 and dentate gyrus. CA1 is markedly shrunk in MAM rats in a dendritic compartment specific manner, with a significantly thinned stratum oriens, pyramidal layer and stratum radiatum. There were no differences in stratum lacunosum molecular or in any layer of the dentate gyrus.
We next evaluated principal cell morphology of the different dendritic compartments, recognizing that the various dendritic compartments receive segregated neocortical and intrahippocampal inputs. There is minimal impact of MAM exposure on granule cell morphology in the dentate gyrus. Dendritic length and branch order was not affected by MAM exposure in any portion of the molecular layer, but MAM rats have an increased number of spines in the inner third, where medial entorhinal cortex fibers terminate.
In MAM rats, CA1 pyramidal neurons do not extend as far from the cell body as in controls, and dendritic length and branching are reduced. Specifically, the dendritic length within stratum radiatum is reduced in MAM rats, while there is no difference in dendritic length of stratum lacunosum moleculare.
These data indicate that principal cells in the hippocampus have morphological differences that constrain their ability to receive neuronal input and that these differences are not global, but instead occur at input-specific locations. Because these alterations are input-specific, abnormal neurodevelopment after MAM exposure can bias information processing in neural circuits that underlie cognitive abilities.

Disclosures: **K.C. O'Reilly:** None. **A.V. Patino:** None. **A.A. Fenton:** None.

Poster

252. Learning and Memory: Hippocampal Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 252.04/SS30

Topic: H.01. Animal Cognition and Behavior

Support: Simons Foundation grant 294388

NIH grant R01MH099128

Title: Impaired learning-related dynamics of local field potentials and evoked responses in Fmr1-null mice

Authors: *D. DVORAK, A. CHUNG, A. A. FENTON
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Abstract: Fragile X Syndrome (FXS) and other autism spectrum disorders (ASD) are associated with reduced cognitive flexibility that manifests as difficulty when tasks require switching between relevant and irrelevant information in memory. We find that conditioned-place learning and memory is normal for the initial location of an avoidable shock in Fmr1-null mice but the mice are impaired on conflict trials when the shock is relocated opposite to the initial location. Fmr1-null mice also show normal responses to spatial novelty when the locations of two of four familiar objects are exchanged in the same environment but, unlike wild-type (WT) mice, they do not respond when the two objects are exchanged between environments. Finally, Fmr1-null mice have a normal preference for another mouse over an inanimate object but, unlike WT mice, they do not prefer novel mice over familiar mice.
In the effort to identify the pathophysiology of these abnormalities, we detected exaggerated rates of dentate spike (DS) events in Fmr1-null mice. DS events modulate activity in the memory-associated hippocampus CA3-CA1 network. Whereas the WT rate of DS decreases dramatically during conflict trials, Fmr1-null DS rates remain high. Place avoidance learning also differentially alters dentate responses to perforant path (PP) stimulation of the angular bundle in WT and Fmr1-null mice. While the field excitatory postsynaptic potential (fEPSP) slope is significantly reduced by avoidance learning at the molecular layer of the upper but not the lower blade in WT mice, it is reduced at the lower blade but not the upper blade in Fmr1-null mice.
We then expressed the inhibitory DREADD hM4Di selectively in medial entorhinal cortical layer 2 stellate cells that give rise to the PP. Dose-dependent CNO activation of hM4Di dose-dependently silences the fEPSP response to PP stimulation putting us in a position to test whether chemogenetic attenuation of the PP can reduce DS rates and correct the selective impairment of conflict learning in Fmr1-null mice.

Disclosures: **D. Dvorak:** None. **A. Chung:** None. **A.A. Fenton:** None.

Poster

252. Learning and Memory: Hippocampal Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 252.05/SS31

Topic: H.01. Animal Cognition and Behavior

Support: NSF Grant IOS-1146822

Title: How coordinated are representations of space in the MEC and hippocampus during navigation?

Authors: *E. PARK, A. A. FENTON
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Abstract: The spatial discharge of many medial entorhinal cortex (MEC) and hippocampus cells can be classified into functional classes that are hypothesized to collectively constitute a cognitive map, the unitary neural representation of space used for navigation. We evaluated whether MEC and hippocampus CA1 representations of space are coherent during navigation that requires two distinct representations of the environment. Rats navigating on a 1.2 diameter circular arena that rotated at 1 rpm were conditioned to avoid a part of the rotating floor as well as avoid a stationary region defined by room features.
Rat MEC and CA1 principal cells were recorded during active place avoidance navigation across three task phases: stable1 (S1)-rotating (R)-stable2 (S2). Basic features like the firing rates of all cells were unchanged across the phases. Despite excellent navigation, spatial tuning of MEC head-direction and grid cells, and CA1 place cells degraded during rotation and partially reverted when rotation stopped for S2.
We measured sub-second (e.g. 40 ms) temporal correlations in the discharge of cell pairs during each recording and used the correspondence between two recordings to estimate representational invariance across the conditions. Correlations within MEC ensembles were unchanged by rotation indicating representational invariance (S1xS2: r=0.98; S1xR: r=0.98). Invariance was confirmed by using the discharge of single head direction cells as an internal reference for computing the direction tuning of a second cell because internally-referenced direction tuning maintained, but was unstably registered to the environment. This instability is because the direction sense intermittently registers to different distant environmental features. This is a key feature of “etak” vector-based navigation that is practiced by Pacific Islanders. CA1 cell pair discharge correlations were less well maintained than MEC cells across two recordings (S1xS2 r=0.39; S1xR r=0.31) as were the correlations between MEC head-direction cell - CA1 place cell pairs (S1xS2: r=0.66; S1xR: r=0.33). These findings indicate that the discharge of MEC cells generates a strong internally-organized representation of space that is intermittently and variably registered to external features of the environment, whereas the CA1 place cell representation of space is less robustly organized as assessed 1) within the hippocampal network, 2) with respect to MEC cells, and by any single feature of the external environment, even during effective navigation.

Disclosures: E. Park: None. **A.A. Fenton:** None.

Poster

252. Learning and Memory: Hippocampal Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 252.06/SS32

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant R01NS39600

NSF Grant NSF IIS-1302256

Title: Comprehensive classification and phenotyping of firing patterns in hippocampal neuron types

Authors: *A. O. KOMENDANTOV, S. VENKADESH, C. L. REES, D. W. WHEELER, D. J. HAMILTON, G. A. ASCOLI
Krasnow Inst. for Advanced Study, George Mason Univ., Fairfax, VA

Abstract: Systematically organizing the structural, molecular, and physiological properties of hippocampal neurons is important for understanding their computational functions in the cortical circuit. Hippocampome.org identifies 122 neuron types in the rodent hippocampal formation (dentate gyrus, CA3, CA2, CA1, subiculum, and entorhinal cortex) based on their somatic, axonal, and dendritic locations, putative excitatory/inhibitory outputs, molecular marker expression, and biophysical properties such as time constant and input resistance. We augment the electrophysiological data of this knowledge base by collecting, quantifying, and analyzing the firing responses to depolarizing current injections for every hippocampal neuron type from available published experiments. We designed and implemented objective protocols to classify firing responses based on both transient and steady-state activity. Specifically, we identified 5 transients (delay, adapting spiking, rapidly adapting spiking, transient stuttering, and transient slow-wave bursting) and 4 steady states (non-adapting spiking, persistent stuttering, persistent slow-wave bursting, and silence). Leveraging this automated classification approach, we characterized the set of all firing responses reported for each hippocampal neuron type and defined 10 unique firing pattern phenotypes that reveal potential new neuronal subtypes. Several novel statistical associations emerge between firing responses and biophysical properties, morphological features, and molecular marker expression. The firing pattern parameters, stimulus conditions, digitized spike times, detailed reference to the original experimental evidence, and analysis scripts are released open-source through Hippocampome.org for all neuron types, greatly enhancing the existing search and browse capabilities. Collating this information online in human- and machine-accessible form will help design and interpret both experiments and hippocampal model simulations.

Disclosures: A.O. Komendantov: None. **S. Venkadesh:** None. **C.L. Rees:** None. **D.W. Wheeler:** None. **D.J. Hamilton:** None. **G.A. Ascoli:** None.

Poster

252. Learning and Memory: Hippocampal Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 252.07/SS33

Topic: H.01. Animal Cognition and Behavior

Support: NSF IIS-1302256

NIH R01NS39600

Title: Large-scale cellular count, distribution, and shape analysis in the mouse hippocampal formation from Allen Brain Atlas Nissl-stained images

Authors: *S. M. ATTILI[1], C. L. REES[2], M. F. M. SILVA[2], T.-V. NGUYEN[2], D. W. WHEELER[2], G. A. ASCOLI[2]
[1]Col. of Sci., George Mason Univ., Herndon, VA; [2]George Mason Univ., Fairfax, VA

Abstract: The number of neurons and glial cells is an important attribute in the characterization of distinct functional regions of the nervous system. Cell densities vary considerably between and within brain areas, across species and life-span development, and are susceptible to pathologies, pharmacological treatment, and genetic alterations. Quantifying the distribution of cells in every brain region is fundamental to attaining a comprehensive census of distinct neuronal and glial types. Until recently, estimating neuron numbers involved time-consuming procedures that made it unfeasible to consider routine comprehensive counting of neurons in an entire brain region without stereological sampling. Progress in open-source image recognition software, growth in computing power, and unprecedented neuroinformatics developments have altered this status quo. The Allen Brain Atlas provides free online access to high-resolution Nissl-stained images along with regional segmentations, offering potentially paradigm-shifting alternatives to stereological sampling. Together, automated cell segmentation and publicly shared complete series of raw histological sections enable reliable and reproducible high-throughput quantification of regional variations in cell number, density, size, and shape at whole-system scale. While this strategy is directly applicable to any and all regions of the mouse brain, we first deploy it on the closed-loop circuit of the hippocampal formation: the medial and lateral entorhinal cortex; dentate gyrus (DG), areas CA3, CA2, and CA1; and dorsal and ventral subiculum. We used two independent image segmentation pipelines, ImageJ and CellProfiler, and the coronal images from the standard Allen Brain Atlas of the adult mouse. We report the first cell-by-cell soma segmentation in every sub-region and layer of the left hippocampal formation through the full rostral-caudal extent, except for the (already well-characterized) principal layers of CA and DG whose cells are too densely packed for effective counting. The overall numbers (218,874 cells in CA1, 142,954 in CA2/3, 157,942 in DG, 461,282 in entorhinal cortex, and 221,446 in subiculum) well match existing sparse data from the published literature. In addition to comprehensive cell counts, our quantitative analysis reveals definitive regional and laminar variation of cell size, shape, and space occupancy.

Disclosures: S.M. Attili: None. **C.L. Rees:** None. **M.F.M. Silva:** None. **T. Nguyen:** None. **D.W. Wheeler:** None. **G.A. Ascoli:** None.

Poster

252. Learning and Memory: Hippocampal Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 252.08/SS34

Topic: H.01. Animal Cognition and Behavior

Support: NIH R01NS39600

NSF IIS-1302256

Title: Dynamical properties of multi-behavior neurons in the hippocampus

Authors: *S. VENKADESH, A. KOMENDANTOV, D. WHEELER, E. BARRETO, G. ASCOLI
Krasnow Inst. for Advanced Study, George Mason Univ., Fairfax, VA

Abstract: Hippocampome.org is a knowledge base of neuron types in the rodent hippocampal formation. In addition to information on morphology, membrane biophysics, molecular marker expression, and connectivity, this knowledge base includes firing pattern data digitized from peer-reviewed published articles for more than 80 neuron types. In previous work, we algorithmically classified these firing patterns and developed an evolutionary framework to quantitatively capture various firing patterns with optimized Izhikevich models. Leveraging and expanding this framework, our current work models multi-behavior dynamics, where a single neuron exhibits qualitatively different behaviors for different stimuli. For example, CA1 bistratified neurons display stuttering and spiking patterns at different input current levels. More than 10 neuron types in the hippocampus exhibit input-dependent multi-behaviors. Using Izhikevich models, we investigate the dynamical properties of these neuron types. We observed chaos in multi-behavior models that switch from bursting to spiking mode as the bifurcation parameter (input current) changes. Using Poincaré maps, we show period doubling cascades leading to chaos in a small region near the transition point. We also explore the Izhikevich model parameter space to identify regions of such chaotic behaviors. In addition, we analyze various transient features of firing patterns such as delay (to spike), spike frequency adaptation, and transient stuttering/bursting in the phase space, and we investigate how they lead to steady-states, such as a stable equilibrium or a limit cycle attractor. We attempt to generalize any existing associations between the transient and steady state elements of firing patterns based on their trajectories in phase space.

Disclosures: S. Venkadesh: None. **A. Komendantov:** None. **D. Wheeler:** None. **E. Barreto:** None. **G. Ascoli:** None.

Poster

252. Learning and Memory: Hippocampal Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 252.09/SS35

Topic: H.01. Animal Cognition and Behavior

Support: NIH R01NS39600

NSF IIS-1302256

Title: Hippocampome.org: Increasing open-access knowledge of rodent hippocampal neuron types and their properties

Authors: *D. W. WHEELER, C. M. WHITE, A. O. KOMENDANTOV, C. L. REES, D. J. HAMILTON, S. VENKADESH, K. MORADI, M. ATTILI, C. TECUATL, G. A. ASCOLI
Krasnow Inst. for Advanced Study, George Mason Univ., Fairfax, VA

Abstract: Hippocampome.org is an open-access knowledge base currently defining 122 neuron types by the patterns of axonal and dendritic presence across the parcels of the rodent hippocampal formation, as described in peer-reviewed literature. In addition to this morphological identification, Hippocampome.org includes information on molecular markers based on direct and inferential evidence, gene expression based on mouse *in situ* hybridization from the Allen Brain Atlas (ABA), electrophysiology (membrane biophysics and firing patterns), and known/potential connectivity. We are now augmenting this knowledge base in several new dimensions. 1) The connectivity domain will move beyond using the simple overlap of axons and dendrites to conclude potential connections, to a more nuanced assessment that takes into consideration the expanse of the neurites in a parcel. 2) We are adding information about the electrophysiology of synapses between neuron types. 3) The estimation of the counts of each of the neuron types will further leverage the cellular distribution from the mouse ABA reference Nissl images. 4) Modeling and simulation of diverse neuronal behaviors are being constrained by (and linked to) experimental recordings from different neuron types. In parallel with these developments, we are continuing to mine the literature for additional properties and new neuron types as needed. In this process, evidence from recent publications is integrated with previously annotated “on-hold” information. Last but not least, continuous improvements of the web portal aim to enhance the user experience, including an advanced search engine and the seed of an application program interface (API).

Disclosures: D.W. Wheeler: None. **C.M. White:** None. **A.O. Komendantov:** None. **C.L. Rees:** None. **D.J. Hamilton:** None. **S. Venkadesh:** None. **K. Moradi:** None. **M. Attili:** None. **C. Tecuatl:** None. **G.A. Ascoli:** None.

Poster

252. Learning and Memory: Hippocampal Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 252.10/SS36

Topic: H.01. Animal Cognition and Behavior

Support: NINDS (NIH) R01NS39600

NSF IIS-1302256

Title: Synapses in the clouds: augmenting Hippocampome.org with a knowledge base of glutamatergic and GABAergic signals

Authors: *K. MORADI, G. P. MADISON, C. L. REES, A. S. GAWADE, D. J. HAMILTON, G. A. ASCOLI
Krasnow Inst. For Advanced Study, George Mason Univ., Fairfax, VA

Abstract: The first intracellular synaptic signals were recorded in the late 1950s from the rodent hippocampus. Since then, numerous studies have recorded these signals from different hippocampal neuron types. The properties of synaptic transmission, such as amplitude, kinetics, and plasticity, depend both on pre- and post-synaptic neuron types. Thus, 100 neuron types could yield up to 10,000 synaptic types. In practice the number is smaller since circuits are not all-to-all connected. Recorded signals, however, are also a function of experimental covariates, including animal strain, sex and age, electrode type, slice orientation, bathing solution, stimulation protocol, and temperature. The exact measures defined by experimentalists to quantify synaptic transmission also vary notoriously across labs. Comparing two individual signals requires a systematic accounting of all above-mentioned parameters. To approach this problem, we first mapped hippocampal synaptic signals from 1168 peer-reviewed journal articles to neuron type pairs based on Hippocampome.org. We then designed and implemented a cloud-based collaborative graphical interface leveraging Google Apps Script, and carefully annotated each recording with its measure definitions and experimental covariates following the Petilla terminology. Next, we extended Hippocampome.Org with an Application Programing Interface (API) to search for potential connections based on axonal and dendritic morphology, refined as needed with neurochemical markers, membrane biophysics, and firing patterns. Finally, we devised a Python-based wrapper around the NEURON simulation environment to detect initiation point of digitized sparse synaptic signals to optimize synaptic models. This pipeline allowed the synaptic characterization of 2475 out of 3302 potential connections in the hippocampal formation from more than 700 distinct experimental settings. This unprecedented database encompasses all major excitatory and inhibitory pathways across the entorhinal cortex, dentate gyrus, CA3, CA2, CA1, and subiculum.

Disclosures: **K. Moradi:** None. **G.P. Madison:** None. **C.L. Rees:** None. **A.S. Gawade:** None. **D.J. Hamilton:** None. **G.A. Ascoli:** None.

Poster

252. Learning and Memory: Hippocampal Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 252.11/SS37

Topic: H.01. Animal Cognition and Behavior

Support: FAU Development/ Foundation Funding

Title: DREADD inactivation of dorsal hippocampus impairs object recognition memory in C57BL/6J mice

Authors: *D. A. CINALLI, JR, R. W. STACKMAN, JR
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Abstract: While it has long been established that, in rodents, the perirhinal cortex (PER) plays an essential role in object recognition memory, inconsistent findings render the answer to the question of what role the hippocampus plays in such memory a point of contention. Temporary inactivation and immunohistochemical studies in mice have implicated the CA1 region of dorsal hippocampus (dCA1) as critical for object recognition. Our lab has previously shown that if mice, presented with two identical novel objects explore each object for ~30s, then a strong memory is encoded that is dependent on dCA1 neuronal activity. In contrast, limited object exploration (~10s each object) leads to a weak memory dependent on PER neuronal activity, suggesting distinct yet critical roles for the two regions. We used designer receptors exclusively activated by designer drugs (DREADDs) to inhibit dorsal CA1 neurons to provide further support that the hippocampus play a crucial role in spontaneous object recognition (SOR) memory. Mice received bilateral infusions of the adeno associated virus expressing inhibitory DREADDs (AAV-CaMKIIα-hM4D[Gi]-mCherry) or a GFP control (AAV-CaMKIIα-GFP). After 7 wk postoperative recovery to allow optimal hM4Di expression, mice were placed into a familiar high-walled square arena that contained two novel objects during the sample session. Mice were allowed to explore until 30s of exploration of each object, or 38s of either object was acquired. During the test session 24 h later, one of the objects was replaced with a novel object. 30 minutes prior to the test session, mice received either clozapine N-oxide (CNO, a synthetic DREADD agonist; 10 mg/kg, i.p.), or vehicle. Preliminary data suggests that DREADD-induced inactivation of dCA1 neurons produced impaired memory for the familiar object. In order to further verify that the DREADDs system functionally impaired dCA1, mice subsequently were tested in the Morris water maze and contextual fear conditioning. We also investigated motor effects of CNO at 10mg/kg using an open-field assay. Together these data further support that CA1 neuronal activity plays an essential role in non-spatial object recognition memory.

Disclosures: **D.A. Cinalli:** None. **R.W. Stackman:** None.

Poster

252. Learning and Memory: Hippocampal Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 252.12/SS38

Topic: H.01. Animal Cognition and Behavior

Support: Medizinische Forschungskommission HHU Düsseldorf 37/2010

Title: Differences in glutamatergic, GABAergic and dopaminergic receptor densities along the longitudinal axis of the mouse hippocampal formation

Authors: *C. HEROLD[1], J. DEITERSEN[1], K. AMUNTS[1,2], K. ZILLES[2,3]
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Abstract: Gene-expression studies as well as cytoarchitectonical analysis have postulated the existence of discrete spatial boundaries between principal neurons in the different subdivisions along the longitudinal axis of the hippocampal formation, suggesting that the subdivisions reflect discrete entities. Recent evidence for differences in tuning and connectivity further supports the notion that the dorsal (dHF), the intermediate (iHF) and the ventral hippocampal formation (vHF) are functionally distinct. Beside the analysis of genetic markers, connectivity and cell types, the basis for these functional differences is largely unknown. Therefore, we analyzed binding site densities for glutamatergic AMPA, NMDA, kainate and $mGluR_{2/3}$ receptors, GABAergic $GABA_A$ (including benzodiazepine binding sites), $GABA_B$, and dopaminergic $D_{1/5}$ receptors using quantitative *in vitro* receptor autoradiography in the longitudinal axis of the hippocampal formation of mice.
We largely confirmed the borders of vHF, iHF and dHF and detected substantial differences in receptor densities between the dorsal and ventral dentate gyrus (dDG, vDG) and the dorsal, intermediate and ventral Cornu Ammonis fields (dCA1, iCA1, vCA1 and dCA3, iCA3, vCA3). Kainate, NMDA, $GABA_A$ and $D_{1/5}$ receptors showed higher densities in the dDG compared to vDG. For example, $GABA_A$ were three-fold and NMDA and $D_{1/5}$ receptors were two-fold higher expressed in dDG compared to vDG. In the CA fields, further AMPA and $mGlu_{2/3}$ receptors were distinctively expressed. No differences were observed for $GABA_B$ receptors. While most receptor densities were the highest in the dorsal regions and/or intermediate regions, kainate receptors showed the highest concentrations in the ventral portions. Additionally, AMPA receptors were higher in vCA3 and iCA3 compared to dCA3. Further, $D_{1/5}$ receptors were higher expressed in dCA3 and vCA3 compared to iCA3.

To our knowledge this is the first study that directly addressed neurochemical differences between areas in the HF along the longitudinal axis. We demonstrated that GABAergic, glutamatergic and dopaminergic receptors are unequally expressed and provide additional evidence for a neurochemical basis of the reported differential functional aspects that future studies should take into account.

Disclosures: C. Herold: None. **J. Deitersen:** None. **K. Amunts:** None. **K. Zilles:** None.

Poster

252. Learning and Memory: Hippocampal Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 252.13/SS39

Topic: H.01. Animal Cognition and Behavior

Support: NIH 4R37NS081242-05

NIH 5R01MH083686-08

Title: Spine imaging reveals direct synaptic inputs to CA1 neurons during navigation

Authors: *C. DOMNISORU, D. W. TANK
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Abstract: Hippocampal neurons must maintain a sufficiently stable and precise representation of an environment to be useful for behavior, while simultaneously remaining flexible enough to react to a changing external world. Recent studies have found that the tuning of individual neurons may be independently flexible, with cells developing new fields (Bittner *et al.*, 2015) or dropping in on out of an otherwise stable representation across recording days (Ziv *et al.*, 2013). How do individual place cells develop their narrow spatial tuning while retaining the ability to modify this tuning over time? Because place firing is thought to arise primarily from the spatial tuning and dendritic organization of the excitatory inputs to each cell, here we developed a strategy for spine imaging in individual CA1 neurons in awake behaving mice traversing linear tracks in virtual reality. Using sparse AAV-mediated labeling with GCamp6S combined with two photon imaging at 30- 60Hz framerates, we measured Ca^{2+} transients from somas as well as spines. On average, active spines exhibited very few Ca^{2+} transients during behavior (~0.25 transients per minute), but with sufficiently long recordings we were able to determine the place fields of individual spines. Spine spatial tuning revealed that CA1 place cells received direct synaptic inputs from cells with place fields that spanned the environment. Despite the broad distribution of input tuning, we found a higher fraction of inputs that aligned with the cell's place field. Moreover, inputs with different tuning were interspersed within individual dendritic branches, such that neighboring spines could have place fields that were far apart in the

environment. These findings suggest that hippocampal place cells maintain their flexibility by remaining synaptically connected with other place cells with unrelated tuning, and yet form precise spatial fields by having a higher fraction of, or by having stronger inputs from, similarly-tuned presynaptic partners. This type of mostly-random, weakly biased connectivity could present a general strategy for balancing flexibility with precision. Bittner, K.C., Grienberger, C., Vaidya, S.P., Milstein, A.D., Macklin, J.J., Suh, J., Tonegawa, S. & Magee, J.C. (2015) Conjunctive input processing drives feature selectivity in hippocampal CA1 neurons. *Nat Neurosci*, **18**, 1133-1142. Ziv, Y., Burns, L.D., Cocker, E.D., Hamel, E.O., Ghosh, K.K., Kitch, L.J., El Gamal, A. & Schnitzer, M.J. (2013) Long-term dynamics of CA1 hippocampal place codes. *Nat Neurosci*, **16**, 264-266.

Disclosures: C. Domnisoru: None. **D.W. Tank:** None.

Poster

252. Learning and Memory: Hippocampal Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 252.14/SS40

Topic: H.01. Animal Cognition and Behavior

Title: Mapping of activated synapses in the hippocampus after context exploration with a new optogenetic reporter for spine potentiation

Authors: F. GOBBO[1], L. MARCHETTI[2,1], B. PINTO[1,3], A. JACOB[1], C. ALIA[4], S. LUIN[1], L. CANCEDDA[3], *A. CATTANEO[1]
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Abstract: Increasing evidence points to the importance of dendritic spines in the formation and allocation of memories, and alterations of spine number and physiology are associated to memory and cognitive disorders. Modifications of the activity of subsets of synapses are believed to be crucial for memory establishment. In addition, theoretical models suggest the involvement of synapse clustering in memory-related neuronal activity. However, many aspects regarding the spatial arrangement and the activity of potentiated synapses in vivo are still poorly understood. By combining Arc RNA regulatory sequences and a protein tag interacting with components of the post-synaptic density, we engineered an expression cassette (pSynActive) to drive the translation of a light-sensitive membrane channel at activated synapses in a regulated, input-specific way. This hybrid approach provides a new methodology to (i) map and (ii) tag potentiated synapses with optogenetic probes, as well as other reporter proteins. By means of in utero electroporation, we delivered this potentiation reporter in mouse hippocampus. We were thus able to tag synapses in vivo in a defined time window, making use of a tetracycline-

inducible promoter. We mapped activated synapses in the hippocampal regions CA1 and dentate gyrus, and compared the resulting synaptic ensembles in mice that were maintained in the home cage to mice that explored a novel environment. We found significant differences in terms of number and spatial arrangement of activated synapses following the novel context exposure, and highlight peculiarities in their distribution between CA1 and the dentate gyrus. Hence, this approach looks promising for the mapping of potentiated synapses in the brain, and could make it possible to re-activate the neuron only at previously activated synapses, extending current neuron tagging technologies in the investigation of memory processes at the synaptic level.

Disclosures: F. Gobbo: None. **L. Marchetti:** None. **B. Pinto:** None. **A. Jacob:** None. **C. Alia:** None. **S. Luin:** None. **L. Cancedda:** None. **A. Cattaneo:** None.

Poster

252. Learning and Memory: Hippocampal Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 252.15/SS41

Topic: H.01. Animal Cognition and Behavior

Support: NIMH grant P50-MH0779720

Dr. Miriam and Sheldon G. Adelson Medical Research Foundation

Title: Pharmacological blocking of C-C chemokine receptor 5 (CCR5) enhances learning and memory

Authors: *M. ZHOU, L. CHIU, M. MIYASHIRO, H. SEKHON, C. ZHOU, Y. CAI, S. HUANG, T. SILVA, A. SILVA
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Abstract: Although the role of CCR5 in immunity and HIV infection has been widely studied, its role in neuronal plasticity and learning and memory is not well understood. Our recent study shows that genetically blocking CCR5 function by *Ccr5* knockout or hippocampal *Ccr5* knockdown results in increases in MAPK/CREB signaling and enhanced long-term potentiation (LTP), which leads to the enhancement of hippocampus dependent learning and memory. Importantly, *Ccr5* knockout reverses the LTP and memory deficits caused by HIV V3 loop peptide. Here, we report that pharmacological inhibition of CCR5 by maraviroc, an FDA approved CCR5 antagonist, enhances both contextual memory in the fear conditioning task and social memory in the social recognition test. When mice were treated with food pellets containing the same dose of maraviroc prescribed for patients, it rescued the social memory deficits in a mouse model of neurofibromatosis type I (*Nf1*), a genetic mutation that has been reported to cause emotional recognition and face perception deficits in children with this disease.

Our results suggest that besides its role as a critical co-receptor for HIV infection in the brain, CCR5 is a suppressor for learning and memory, and that brain permeable CCR5 antagonists can be used to treat memory deficits such as those associated with HIV infection or with neurofibromatosis type I.

Disclosures: **M. Zhou:** None. **L. Chiu:** None. **M. Miyashiro:** None. **H. Sekhon:** None. **C. Zhou:** None. **Y. Cai:** None. **S. Huang:** None. **T. Silva:** None. **A. Silva:** None.

Poster

252. Learning and Memory: Hippocampal Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 252.16/SS42

Topic: H.01. Animal Cognition and Behavior

Support: National Institutes of Health R37 AG013622

the Dr. Miriam and Sheldon G. Adelson Medical Research Foundation to A.J.S.

China Scholarship Council to S.H.

T32 MH19384-14 for A.F.

ERC Starting Grant dEMORY ERC-2012-StG-311435 to P.P.

Title: Hotspots of dendritic spine turnover facilitate learning-related clustered spine addition and network sparsity

Authors: ***S. HUANG**[1], A. FRANK[1], M. ZHOU[1], A. GDALYAHU[3], G. KASTELLAKIS[4], P. POIRAZI[4], X. WEN[2], T. SILVA[1], J. TRACHTENBERG[1], A. SILVA[1]
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Abstract: Structural plasticity mediated by addition and elimination of dendritic spines is thought to underlie the formation of long-term memory. However, the spatial relationship of those structural activities during learning remains unclear. Using *in vivo* two-photon microscopy, we track spine dynamics in mouse retrosplenial cortex (RSC) during contextual and spatial learning. We report that learning leads to addition of new spines that are spatially clustered, and the amount of clustering is predicted by spine turnover prior to learning. Both spine measures are correlated with learning performance. Accordingly, a genetic manipulation that enhances pre-learning spine turnover also enhances learning-related spine clustering and future learning performance. Remarkably, clustered new spines are usually added on dendritic segments with high spine turnover, revealing the presence of hotspots on dendritic tree where elevated rates of

spine turnover facilitate clustered spine addition associated with memory. Biophysically inspired modeling suggests turnover increases clustering, neuronal firing rate, network sparsity, and memory capacity. One implication of these findings is that increased spine turnover allow neurons to more efficiently sample the synaptic space during learning in order to optimize information acquisition. Once acquired, spine clustering may stabilize this information, thus strengthening memory circuits.

Disclosures: **S. Huang:** None. **A. Frank:** None. **M. Zhou:** None. **A. Gdalyahu:** None. **G. Kastellakis:** None. **P. Poirazi:** None. **X. Wen:** None. **T. Silva:** None. **J. Trachtenberg:** None. **A. Silva:** None.

Poster

252. Learning and Memory: Hippocampal Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 252.17/SS43

Topic: H.01. Animal Cognition and Behavior

Support: NRF-2015M3C7A1031969

NRF-2016R1A2B4008692

SRC-2014051826

BK21+ program

Title: Anatomical connectivity and physiological characteristics of the fasciola cinereum in the hippocampus

Authors: *S.-B. PARK, S.-W. YOO, H.-S. JUNG, I. LEE
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Abstract: The fasciola cinereum (FC) is a subregion of the hippocampus, located along the midline with its lateral boundaries adjoining the distal borders of the CA1. Although the FC was described in rats as early as in 1972 by Hjorth-Simonsen, its anatomical connectivity and physiological properties are largely unknown. Furthermore, knowing the anatomical characteristics of the FC is also important for practical reasons to define the distal boundaries of the CA1. In the current study, we characterized the afferent connections of the FC using retrograde tracing methods. We injected retrobeads into the FC (n=6) and distal CA1 (n=5) in rats (Sprague-Dawley). After 5-10 days of a resting and recovery period, rats were perfused transcardially to examine the histological results. In some rats (n=3), retrobeads in different colors were injected into the FC and distal CA1 to compare the results within subjects. Retrobeads were found retrogradely in the perirhinal cortex (PER), postrhinal cortex, lateral

entorhinal cortex (LEC), and supramammillary nucleus (SuM). Retrobeads injected into the FC and distal CA1 were found in layer II and layer III in the PER and LEC, respectively. It appears that the FC contained intrinsic connections among its cells because retrobeads were found remotely from the injection sites along the septotemporal axis in the hippocampus. We found no afferent connections of the FC in the medial entorhinal cortex and other subregions of the hippocampus including the dentate gyrus (DG), CA1, and CA3. We also examined the efferent connections of the FC by injecting AAVdj-CAG-mCherry or enhanced green fluorescent protein (eGFP) into the FC and distal CA1. In the hippocampus, the FC projected to the crest (i.e., the junction where the dorsal blade and ventral blade met) of the septal DG. We found no efferent projections of the FC to other subregions (e.g., CA1, CA3) of the hippocampus. When retrobeads were injected into the FC and DG, retrobeads in both regions were commonly found in the layer II of the LEC, PER, and SuM. Because principal cells in the FC resembled the granule cells in the DG, we tested whether the FC also showed selective vulnerability to colchicine as previously observed in the DG. Colchicine injected into the FC made selective lesions of the FC only, and the adjacent pyramidal cell layers in the distal CA1 was relatively intact. Such contrast in vulnerability to colchicine between the FC and CA1 made it fairly easy to discern the boundaries between the two areas. The FC-CA1 boundaries were also confirmed by other staining methods including the Timm's and myelin staining methods. Firing properties and functions of the cells in the FC are currently examined.

Disclosures: S. Park: None. **S. Yoo:** None. **H. Jung:** None. **I. Lee:** None.

Poster

252. Learning and Memory: Hippocampal Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 252.18/SS44

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant NS078434

Title: Topographic organization of canonical and non-canonical circuit inputs to hippocampal CA1 revealed by monosynaptic rabies tracing

Authors: *Y. SUN[1], X. XU[2]
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Abstract: Most of our knowledge of hippocampal topographic connections comes from conventional anatomical tracing studies which lack cell-type specificity and do not have quantitative measurements of circuit connectional strengths. Further, non-canonical circuit inputs to the hippocampus have been uncovered with new viral and genetic circuit mapping. Thus in the

present study, we re-evaluate and quantify intra- and para- hipppocampal input connections to different CA1 subfields (proximal, intermediate, and distal CA1) by using a novel monosynaptic rabies tracing system (Sun et al., 2014, 2017). In our experiments, excitatory pyramidal neurons in different subfields of dorsal CA1 are targeted, and retrogradely labeled direct presynaptic neurons are mapped in intact brains. Consistent with the previous description, our rabies tracing indicates that proximal CA1 (pCA1) receive most input connections from distal CA3, and distal CA1 (dCA1) receives most CA3 inputs from proximal CA3. Our quantitative analysis reveals that pCA1 receives 4 fold stronger input from CA3 than that of dCA1 in terms of their input connection strength indices (CSI: 9.03 vs 2.44; N=6 cases). pCA1 receives entorhinal cortex (EC) inputs mainly from medial EC (CSI: 1.51); intermediate CA1 receives more inputs from medial EC than lateral EC (CSI: 0.87 vs 0.62); dCA1 receives more inputs from lateral EC than medial EC (CSI: 0.98 vs 0.45). This shows changes of EC input strengths to CA1 subfields in a topographic manner. In addition to labeled neurons in EC layer III, we found ~15% of mapped EC input neurons are putative EC layer II stellate cells. We confirm and extend our previous finding of non-canonical subiculum inputs to CA1, and the data show that dCA1 receives stronger inputs than intermediate CA1 and pCA1 (CSI: 1.33, 0.55, and 0.31, respectively; N=8). Pre- and para- subiculum also projects to CA1 directly with pCA1 receiving stronger inputs than intermediate CA1 and dCA1 (CSI: 0.53, 0.28, and 0.24, respectively; N=8). Together, these results provide a new understanding of topographic organization of canonical and non-canonical inputs to CA1 excitatory neurons, and allows for functional considerations of how different intra- and para- hipppocampal inputs modulate CA1-associated spatial navigation and memory behaviors.

Disclosures: **Y. Sun:** None. **X. Xu:** None.

Poster

252. Learning and Memory: Hippocampal Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 252.19/SS45

Topic: H.01. Animal Cognition and Behavior

Support: The EPFL Blue Brain Project Fund

The ETH Board Funding to the Blue Brain Project

European Union Seventh Framework Program (FP7/2007-2013) under grant agreement no. 604102 (HBP)

Calculations were performed on the EPFL Blue Brain IV BlueGene/Q supercomputer hosted at the Swiss National Supercomputing Center (CSCS) in Lugano

Medical Research Council (MRC)

Novartis Pharma

Title: Reconstruction and simulation of a full-scale model of rat hippocampus CA1

Authors: *A. ROMANI[1], N. ANTILLE[2], L. L. BOLOGNA[3], J.-D. COURCOL[2], A. DEVRESSE[2], A. ECKER[2], J. FALCK[4], C. P. H. FAVREAU[2], M. GEVAERT[2], A. GULYAS[5], J. V. HERNANDO[2], S. JIMENEZ[2], S. KALI[5], L. KANARI[2], J. G. KING[2], S. LANGE[4,6], C. LUPASCU[3], A. MERCER[4], M. MIGLIORE[3], R. MIGLIORE[3], A. POVOLOTSKIY[2], S. RAMASWAMY[2], M. W. REIMANN[2], C. A. ROSSERT[2], Y. SHI[2], A. M. THOMSON[4], W. VAN GEIT[2], L. VANHERPE[2], H. MARKRAM[2], E. B. MULLER[2]
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Abstract: We present a digital reconstruction and initial validation of a full-scale rat hippocampus CA1 using methods developed in the Blue Brain Project (BBP) and made publicly available through the Human Brain Project (HBP) Brain Simulation Platform (BSP). In brief, the hippocampus CA1 volume, defined by publicly available atlases, is populated with a series of high fidelity reconstructions of well-characterized neuron types according to experimentally measured densities and composition. A connectome is generated by first detecting collisions between neurons and then pruning the exceeding synapses in order to match the biological data of bouton densities and number of synapses per connection. Electrical models of neurons and synapses were constrained by electrophysiological recordings and published data. Finally, each reconstruction step and emergent properties of the complete model is validated to assess the quality of the model predictions and plan the subsequent model refinements. The BSP facilitates the process of building, validating, and simulating the hippocampus circuit by providing access to web-based user-oriented interface. Furthermore, the BSP is designed to allow multiple teams to cooperate on the same model. Indeed, the reconstruction is intended to be the product of a larger community initiative involving groups beyond the HBP, which will periodically refine the model and make public releases. The reconstruction represents a resource for the community to integrate experimental data, perform *in silico* experiments, and test hypotheses on hippocampal function.

Disclosures: **A. Romani:** None. **N. Antille:** None. **L.L. Bologna:** None. **J. Courcol:** None. **A. Devresse:** None. **A. Ecker:** None. **J. Falck:** None. **C.P.H. Favreau:** None. **M. Gevaert:** None. **A. Gulyas:** None. **J.V. Hernando:** None. **S. Jimenez:** None. **S. Kali:** None. **L. Kanari:** None. **J.G. King:** None. **S. Lange:** None. **C. Lupascu:** None. **A. Mercer:** None. **M. Migliore:** None. **R. Migliore:** None. **A. Povolotskiy:** None. **S. Ramaswamy:** None. **M.W. Reimann:** None. **C.A. Rossert:** None. **Y. Shi:** None. **A.M. Thomson:** None. **W. Van Geit:** None. **L. Vanherpe:** None. **H. Markram:** None. **E.B. Muller:** None.

Poster

252. Learning and Memory: Hippocampal Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 252.20/SS46

Topic: H.01. Animal Cognition and Behavior

Support: NSERC

OMHF

Title: Egr1 expression in avian granule cells is consistent with pattern separation

Authors: *N. MILLER[1], C. C. DAMPHOUSSE[1], N. MICKS[1], E. KLEINHANDLER[1], D. F. MARRONE[1,2]
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Abstract: Previous work by our lab has demonstrated that the avian hippocampus expresses gene products of EGR1 (also called ZENK) in a context-dependent manner during a spatial learning task. Importantly, preliminary data show that granule cells (identified by the expression of Prox1) showed a much lower probability of repeated activation than non-granule counterparts, similar to the pattern observed in mammals, and consistent with a system geared for pattern separation. Further investigation under conditions susceptible to high interference will determine if the pattern of activated granule cells expressing *Egr1* is nearly orthogonal even under conditions in which external stimuli are changing minimally, as can be observed in mammals. This remains an important question, since the lack of a clear anatomical architecture consistent with a “hidden layer” may call into question the role of granule cells in the avian hippocampus in supporting spatial cognition.

Disclosures: N. Miller: None. **C.C. Damphousse:** None. **N. Micks:** None. **E. Kleinhandler:** None. **D.F. Marrone:** None.

Poster

252. Learning and Memory: Hippocampal Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 252.21/SS47

Topic: H.01. Animal Cognition and Behavior

Support: NSERC

OMHF

Title: Social preference alters Arc expression in the olfactory bulb

Authors: *C. DAMPHOUSSE[1], E. KLEINHANDLER[2], N. MICKS[2], N. MILLER[3], D. F. MARRONE[2]
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Abstract: It has long been known that rodents can impart preference for scents and flavors of food through social contact. While the social transmission of food preference (STFP) is a well characterized paradigm, relatively few experiments have investigated the neurobiological substrate that support STFP. Towards this goal, we investigate whether the development of STFP alters olfactory bulb activity. Studies have shown that another form of social preference (pairing odors with tactile stimulation in rodent pups), alters the olfactory bulb response to the preferred odor. More specifically, the preferred odor is represented by a larger and more reliably recruited ensemble of mitral cells. To test whether a similar process occurs in the adult following STFP, we expose adult male Sprague Dawley rats to two flavors (cocoa and cinnamon) and impart a preference for one of the flavors (counterbalanced) using a standard STFP protocol. The following day, groups of rats (n = 6/group) are exposed to either the preferred odor twice (P/P), the non-preferred odor twice (NP/NP), or both odors (P/NP), with each exposure space 30 min apart. The size and pattern of the ensemble activated by each odor can then be determined by examining the compartmental expression of Arc. If, as hypothesized, STFP causes the preferred odor to induce a larger and more specific pattern of mitral cell activity, this suggests that the large body of data on the mechanisms of preference development through tactile stimulation may also apply to the STFP paradigm.

Disclosures: C. Damphousse: None. **E. Kleinhandler:** None. **N. Micks:** None. **N. Miller:** None. **D.F. Marrone:** None.

Poster

252. Learning and Memory: Hippocampal Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 252.22/SS48

Topic: H.01. Animal Cognition and Behavior

Support: NSERC

OMHF

Title: Altered immediate-early gene expression predicts memory impairment in Goto-Kakizaki rats

Authors: *D. F. MARRONE[1], C. DAMPHOUSSE[2], J. MEDEIROS[1], N. MICKS[1]
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Abstract: Type 2 Diabetes mellitus (T2D) is a common metabolic disorder that has steadily increased in prevalence over the past five decades, and has been associated with cognitive decline and increased risk of dementia. To further investigate the link between T2D and cognitive ability, here we test both memory performance and hippocampal function in the Goto-Kakizaki (GK) rat, an animal model of T2D selectively bred to have persistent hyperglycemia in the absence of obesity. Relative to Wistar rats of the same age, GK rats show deficits in performance of a what-where-when test of episodic-like memory. Moreover, these deficits are predicted by the pattern of expression of *Egr1* (an immediate-early gene critical for memory function) in the dentate gyrus. These results, along with further analysis of the pattern of gene expression in the pyramidal cell layers will help to functionally link persistent hyperglycemia to changes in hippocampal physiology.

Disclosures: D.F. Marrone: None. **C. Damphousse:** None. **J. Medeiros:** None. **N. Micks:** None.

Poster

252. Learning and Memory: Hippocampal Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 252.23/SS49

Topic: H.01. Animal Cognition and Behavior

Support: NSERC Discovery Grant

Title: Interactions between adult-born and developmentally-born neurons during learning

Authors: *A. ASH, J. CLEMANS-GIBBON, T. O'LEARY, E. CHAHLEY, D. SEIB, J. SNYDER
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Abstract: One feature that sets the dentate gyrus (DG) of the hippocampus apart from other regions of the brain is its ability to produce new neurons throughout adulthood. This results in a heterogeneous population of cells of various ages and diverse properties. For example, immature neurons have a net inhibitory effect on downstream populations, and there is evidence that new and old neurons are differentially modulated by feedback circuitry in the DG in vitro. Recent reports indicate that feedback inhibition plays a powerful role in selecting which DG neuron are

recruited during memory formation. This raises the question of whether developmentally-born and adult-born neurons have distinct roles in feedback inhibition, particularly in vivo when neuronal ensembles are selected during memory encoding. To address this we combined chemogenetics and immunohistochemistry for BrdU+Fos to silence, and measure activity in, developmentally and adult-born neurons as rats learned a spatial water maze task. Specifically, retrovirus was injected into the DG of male rats at postnatal day 1 or 6 weeks of age to express the inhibitory DREADD receptor, HM4Di, in neurons born in early development or adulthood. The same rats were also injected with BrdU to label developmentally or adult-born neurons. At 10 weeks of age rats were injected with either the HM4Di agonist CNO or vehicle and then trained in the water maze (8 trials). One hour after water maze training brains were collected and processed immunohistochemically for BrdU, GAD67, GFP and c-Fos to identify neurons that were recruited during learning. We expect that silencing adult-born neurons will reduce activity (c-Fos) in inhibitory interneurons and, in turn, increase overall levels of neuronal recruitment in the DG, particularly in developmentally-born neurons. Since adult-born neurons receive less GABAergic inhibition, we expect their recruitment to be less impacted when populations of DG neurons are silenced. By manipulating and measuring activity in discrete populations of DG neurons, our findings will provide novel insights into the mechanisms by which subcircuits within the DG contribute to memory formation.

Disclosures: A. Ash: None. **J. Clemans-Gibbon:** None. **T. O'Leary:** None. **E. Chahley:** None. **D. Seib:** None. **J. Snyder:** None.

Poster

252. Learning and Memory: Hippocampal Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 252.24/SS50

Topic: H.01. Animal Cognition and Behavior

Title: Extracts of Ixeris dentata improve cognitive function on Trimethyltin-Induced memory deficit in the rats

Authors: *D. JANG[1], S. LEE[1], J. OH[1], H. LEE[1], D.-H. HAHM[1,2], I. SHIM[1,2]
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Abstract: The this study examined whether Extract of *Ixeris dentate*(EID) improved behavioral alterations, and hippocampal neuronal activity in rats induced by administration of trimethyltin (TMT), an organotin compound that is neurodegenerative to the animals. The effect of EID to improve cognitive efficacy in the TMT-induced rats was investigated using Morris water maze (MWM) test and using immunohistochemistry to detect components of the choline acetyltransferase (ChAT) and cAMP-response element-binding protein (CREB) expression. Rats

injected with TMT showed impairments in learning and memory and daily administration of EID (400 and 800 mg/kg, p.o.) markedly improved memory function demonstrated on the MWM test. Additionally, administration of EID significantly alleviated the TMT-induced loss of cholinergic immunoreactivity, and restored the hippocampal expression levels of CREB proteins. The findings thus suggest that EID might be useful for improving the cognitive function.

Disclosures: D. Jang: None. **S. Lee:** None. **J. Oh:** None. **H. Lee:** None. **D. Hahm:** None. **I. Shim:** None.

Poster

252. Learning and Memory: Hippocampal Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 252.25/SS51

Topic: H.01. Animal Cognition and Behavior

Support: NIMH Grant R00MH083044

Sackler Family Foundation

Title: Early-life serotonin transporter blockade blunts adult serotonergic enhancement of hippocampal memory

Authors: *A. A. MORGAN[1,5], I. Z. DINCHEVA[2,5], C. M. TEIXEIRA[3,5], Z. ROSEN[6], M. HERSH[3], S. A. SIEGELBAUM[6], M. S. ANSORGE[4,5]
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Abstract: Cognitive deficits constitute a primary impairment in several neuropsychiatric disorders, including depression and schizophrenia. The etiology of these disorders include developmental components, suggesting that the pathogenesis of cognitive impairment might relate to altered maturation of neurocircuitry. Serotonin (5-HT) has been established as a major regulator of neuronal wiring throughout development. We find that boosting 5-HT signaling during a sensitive period ranging from postnatal day (P) 2 - P11 reduces density of 5-HTergic innervation of the hippocampus in adult mice and impairs spatial learning in the Morris water maze task. To test for causality between these two consequences, we applied optogenetic techniques in mice and delineated the role of 5-HT signaling in hippocampal function, under normal conditions and after P2-11 5-HT interference. We find that stimulation of 5-HTergic terminals in the CA1 region of the dorsal hippocampus potentiates excitatory transmission at CA3-to-CA1 synapses. Furthermore, activation of 5-HTergic projections in dorsal CA1 (dCA1) enhances spatial memory. Conversely, optogenetic silencing of dCA1 5-HT terminals inhibits

spatial memory. Exposure to fluoxetine, a selective 5-HT reuptake inhibitor, from P2 - P11 blunts 5-HT-mediated potentiation of the CA3-CA1 synapse and abolishes the observed enhancement in spatial memory in adult mice optogenetically stimulated in the dCA1 region. Collectively, our data reveal a powerful modulatory influence of 5-HTergic synaptic input on hippocampal function and memory formation, and a blunting of this mechanism after early-life 5-HT transporter blockade.

Disclosures: A.A. Morgan: None. **I.Z. Dincheva:** None. **C.M. Teixeira:** None. **Z. Rosen:** None. **M. Hersh:** None. **S.A. Siegelbaum:** None. **M.S. Ansorge:** None.

Poster

252. Learning and Memory: Hippocampal Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 252.26/SS52

Topic: H.01. Animal Cognition and Behavior

Support: Christopher Newport University

Title: The impact of fornix lesions on place vs response learning in the open-field tower maze

Authors: *O. LIPATOVA, M. M. CAMPOLATTARO, J. PICONE, V. CAGLE
Christopher Newport Univ., Newport News, VA

Abstract: Prior studies have shown that the hippocampus is important for the acquisition of place- but not response-navigation. However, these experiments often contain stressful training conditions (e.g., forced swimming in the Morris Water Maze) or have a high chance performance level (e.g., left vs. right arm choice in the T-maze). The present study used a non-stressful land-based maze (i.e., the Open Field Tower Maze [OFTM]), which has a chance performance at twenty-five percent. After initial pre-training, rats received either an electrolytic fornix lesion surgery or a sham surgery. Half of the rats from each surgical group were given place-training or response-training in the OFTM. The results showed that (1) lesioned place-learners required more trails than sham place-learners to correctly solve the OFTM and (2) lesioned response-learners solved the OFTM at the same rate as sham response-learners. Our findings support the hypothesis that the hippocampus is necessary for place-learning but not response-learning on the OFTM task. The OFTM does not depend on a choice between restricted directions that a rat would be required to make on a T-maze or a plus-maze, and does not include aversive components inherent to a Morris Water Maze or Barnes Maze. Thus, the OFTM can be used to investigate manipulations of hippocampus-dependent spatial learning without confounding variables related to an animal’s stress level or direction-preference.

Disclosures: **O. Lipatova:** None. **M.M. Campolattaro:** None. **J. Picone:** None. **V. Cagle:** None.

Poster

252. Learning and Memory: Hippocampal Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 252.27/SS53

Topic: H.01. Animal Cognition and Behavior

Title: The effect of REV-ERB alpha in hippocampal synaptic plasticity

Authors: *J. CHOI, B.-K. KAANG
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Abstract: Circadian rhythms are driven by a circadian oscillator, and previous studies suggest that learning and memory are sensitive to circadian rhythms. One of the genes responsible for generating the circadian rhythm is Rev-erbα. REV-ERBα protein is a nuclear receptor that acts as a transcription repressor, and is a core component of the circadian clock. However, the role of REV-ERBα in neurophysiological processes of hippocampus has not been characterized yet. In this study, we examined the relationship between circadian rhythm and hippocampal synaptic plasticity, using REV-ERBα knock-out (KO) mice. Lacking REV-ERBα, the KO mice displayed abnormal synaptic plasticity in the night period (CT12 - C14), compared to the WT littermate. However, REV-ERBα KO mice exhibited normal long-term potentiation during the light period (CT0 - CT2). Taken together, these results provide evidence that REV-ERBα is critical for hippocampal synaptic plasticity during the dark period.

Disclosures: **J. Choi:** None. **B. Kaang:** None.

Poster

252. Learning and Memory: Hippocampal Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 252.28/SS54

Topic: H.01. Animal Cognition and Behavior

Support: CIHR 2011

Title: Impaired spatial memory following post-synaptic deletion of DCC expression in the adult mouse hippocampus

Authors: *E. WONG, G. THOMPSON-STECKEL, S. D. GLASGOW, T. E. KENNEDY
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Abstract: The receptor deleted in colorectal cancer (DCC) and its ligand netrin-1 are essential for normal neural development. Both are also expressed by neurons in the adult nervous system and enriched at synapses. While conditional genetic deletion of DCC expression from glutamatergic neurons in the hippocampus of adult mice results in deficits in long-term potentiation (LTP) and hippocampal-dependent spatial memory, the specific pre- and post-synaptic contributions of DCC have not been identified. Here, we show that adult mice with selective deletion of DCC from the post-synaptic CA1 hippocampal subregion exhibit impairment in spatial memory tasks. Conversely, selective genetic deletion of DCC from the pre-synaptic CA3 hippocampal subregion in adult mice does not result in impairments of spatial learning and memory. These findings indicate that post-synaptic DCC at the Schaffer collateral synapse is required for the synaptic plasticity underlying hippocampal-dependent spatial memory.

Disclosures: E. Wong: None. **G. Thompson-Steckel:** None. **S.D. Glasgow:** None. **T.E. Kennedy:** None.

Poster

252. Learning and Memory: Hippocampal Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 252.29/SS55

Topic: H.01. Animal Cognition and Behavior

Support: NNSF of China(31471079 to Y.Z.)

Title: GHS-R1a signaling modulates synaptic function and memory

Authors: *N. LI
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Abstract: The hippocampus plays important role in memory formation and spatial navigation. GHS-R1a, the only identified receptor for orexigenic peptide hormone ghrelin, was found to be expressed in the hippocampus. Our previous study showed that micro-infusion of ghrelin into the CA1 region of dorsal hippocampus impairs memory acquisition and GHS-R1a KO mice exhibits enhanced spatial memory, indicating that GHS-R1a signaling interferes with hippocampus-dependent memory formation. To explore the underlying cellular mechanisms, we first measured both synaptic transmission and plasticity in acute hippocampal slices of GHS-R1a KO and WT

control mice. Reduced inhibitory synaptic transmission and intact excitatory synaptic transmission was found in CA1 pyramidal neurons of GHS-R1a KO mice, although LTP was unchanged. Meanwhile, we investigated the effect of GHS-R1a overexpression on synaptic function of primary cultured hippocampal neurons. We found that over-expression of GHS-R1a with a viral vector (AAV-hM4Di-2A-GHS-R1a-GFP) facilitated glutamate-evoked intracellular [Ca^{2+}] elevation and CNO administration reversed the elevation of intracellular [Ca^{2+}]. Interestingly, immunostaining for PSD-95 and synapsin-1 showed that over-expression of GHS-R1a inhibited excitatory synaptic density while had no effect on dendritic morphology of infected hippocampal neurons. Therefore, our present findings suggested that GHS-R1a signaling modulates the excitatory and inhibitory synaptic input into hippocampal pyramidal neurons which may contribute to memory improvement observed in GHS-R1a KO mice.
This work was supported by NNSF of China (31471079 to Y.Z.)

Disclosures: N. Li: None.

Poster

253. Learning and Memory: Hippocampal Representations

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 253.01/SS56

Topic: H.01. Animal Cognition and Behavior

Support: NIMH Grant MH094263

NIMH Grant MH051570

Title: Hierarchical organization of memories in the prefrontal areas contrast with memory organizations in hippocampal regions

Authors: *C. MIKKELSEN[1], A. FAROVIK[1], M. D. BROCKMANN[2], S. MCKENZIE[3], H. EICHENBAUM[1]
[1]Boston Univ., Boston, MA; [2]Ctr. For Memory and Brain, Boston, MA; [3]Neurosci., NYUMC, New York, NY

Abstract: Previous studies in our laboratory have examined neural population coding in rats performing a task where they learn reward associations of objects in different locations and spatial contexts. Representational Similarity Analysis (RSA) has revealed distinct hierarchical organizations of key task dimensions in multiple brain areas. In particular, neural networks in orbitofrontal cortex (OFC) strongly distinguish events with opposing response and reward outcomes within which they link events that share outcomes and the locations in which they occur, and this pattern contrasts with networks in hippocampal areas that distinguish events by the spatial context in which they occur and link events associated with different outcomes. Here

we extended RSA to the medial prefrontal cortex (mPFC). While the overall pattern of hierarchical organization in mPFC was the same as that in OFC, mPFC neural networks more strongly distinguish events with opposing outcomes and more strongly associate events with the same outcome and across locations. These observations suggest that mPFC and OFC share a fundamental role in outcome-based mapping of related events, as contrasted with context-based mappings in hippocampal areas. Future studies on interactions between these complementary mappings will shed light on how the prefrontal-hippocampal system supports memory.

Disclosures: C. Mikkelsen: None. **A. Farovik:** None. **M.D. Brockmann:** None. **S. McKenzie:** None. **H. Eichenbaum:** None.

Poster

253. Learning and Memory: Hippocampal Representations

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 253.02/SS57

Topic: H.01. Animal Cognition and Behavior

Support: MH052090

Title: Learning paradigm influences the organization of memory in the hippocampus

Authors: *D. J. SHEEHAN[1], J. W. RUECKEMANN[2], H. B. EICHENBAUM[3]
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Abstract: The hippocampus is critical associating related events (Eichenbaum et al., 2012), and damage to this region consequently leads to a wide array of cognitive impairments (Eichenbaum & Cohen, 2014). Studies have demonstrated that the hippocampus is central to the rapid creation of relational representations within a given environment (Tse et al., 2007), which together form a schema necessary for solving a task (Preston & Eichenbaum, 2013). In the present study, we investigate the role of the hippocampus in the relational representation and flexible use of experiences in a radial maze task. Rats implanted with drivable tetrodes in the dorsal CA1 region of the hippocampus were trained to acquire rewards on select arms of a 12-arm radial maze, using either a go/no-go single-arm training or discriminative paired-arm paradigm. After several days of training, the flexibility of the representation of the maze was then tested as the rats were forced to choose between arms that had not been previously paired. Behavioral results show that single-arm training leads to a clear ability to choose the rewarded arm, while animals receiving paired-arm training cannot use past experiences in a flexible manner. Electrophysiological results show a difference in the population representational similarity across the arms of the maze as a consequence of training procedure. Neuronal activity patterns in animals trained with single-arm presentations reflect robust and sustained spatial information for individual arm identities

throughout training, whereas population activity patterns in animals trained on pairs of arms indicated decreased spatial information coding of the rewarded arms as a function of training. Taken together, these results demonstrate that the manner in which the relationships of a task are learned influences how the hippocampus schematizes task parameters, and dictates whether stored knowledge can be used flexibly in new situations.

Disclosures: D.J. Sheehan: None. **J.W. Rueckemann:** None. **H.B. Eichenbaum:** None.

Poster

253. Learning and Memory: Hippocampal Representations

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 253.03/SS58

Topic: H.01. Animal Cognition and Behavior

Support: NIMH Grant MH052090

Title: Dynamic representations of temporal context in hippocampal population coding

Authors: *J. H. BLADON[1], D. J. SHEEHAN[4], C. DE FREITAS[1], C. S. KEENE[2], H. B. EICHENBAUM[3]
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Abstract: The hippocampus is essential for associating events in space and time (Eichenbaum, Nat Rev Neurosci 2014). To characterize how event representations are mapped within a spatial framework, we previously employed a task where rats use spatial context to guide object-reward associations and found that hippocampal neural populations strongly code for spatial context, then successively code for the locations of objects, then their identities and reward associations (McKenzie et al. Neuron 2014). In the present study we asked whether hippocampal networks also code for temporal contexts when a series of common events over a period of time guides object choices. We recorded from ensembles of dorsal CA1 neurons as rats performed a novel version of our context-guided memory task wherein on each trial the animal had to use temporal context to guide choices between two objects randomly assigned to two locations in a testing arena. Temporal contexts consisted of 15 trial blocks where one object was rewarded and another object not rewarded, alternating with 15 trial blocks where the object- reward associations were reversed. Ensemble analysis revealed dynamic CA1 population coding of key task dimensions over the course of each trial. First, location was strongly coded as the animal approached an object, but location coding waned thereafter. Second, just before reaching the object, temporal context was strong coded and this coding persisted. Third, as the animal arrived at the object, its identity along with temporal context was coded. Furthermore, CA1 population coding of temporal context was related to accurate task performance and failed to occur on errors. These

observations suggest that hippocampal population representations reflect the coding temporal context when essential to decision making.

Disclosures: **J.H. Bladon:** None. **D.J. Sheehan:** None. **C. de Freitas:** None. **C.S. Keene:** None. **H.B. Eichenbaum:** None.

Poster

253. Learning and Memory: Hippocampal Representations

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 253.04/SS59

Topic: H.01. Animal Cognition and Behavior

Support: NIMH MH052090

Title: Large-scale hippocampal population representations: Coherent spatial maps that gradually evolve over time

Authors: *N. R. KINSKY[1], D. W. SULLIVAN[2], W. MAU[1], H. B. EICHENBAUM[3]
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Abstract: Rapidly acquired stable hippocampal representations of space may provide a framework for remembering where events occur in an environment. Early research on place cell firing patterns in mice, however, reported that spatial firing patterns were not stable unless strong attention was required over extended experiences (Kentros, et al. 2004). Yet, a more recent study indicated that mice use the geometry of the environment instead of local cues to orient in space (Keinath et al, 2017). Thus, the apparent instability of place cells observed by Kentros et al. might be explained by undetected realignment of otherwise stable spatial representations. To explore this possibility, we employed in vivo calcium imaging to simultaneously monitor the spatial activity patterns of hundreds of CA1 neurons as mice explored two distinct arenas over eight days, with the local cues rotated relative to distant (room) cues to determine alignment of the spatial representations. In addition, by connecting the arenas with a corridor, we also investigated how the CA1 population responds to new spatial learning when the arenas are joined. We observed a largely coherent population representation that mapped each arena both within and across arenas, and the population map was most commonly oriented either to the local arena cues or to another undefined orientation. In addition, new neurons were recruited and old neurons remapped over days, resulting in an overall gradual drift of the ensemble spatial representation. Also, when the arenas were joined, the spatial maps of the two environments aligned. Thus, the hippocampus maintains a largely coherent ensemble representation that can realign to different anchors and gradually drifts over time.

Disclosures: **N.R. Kinsky:** None. **D.W. Sullivan:** None. **W. Mau:** None. **H.B. Eichenbaum:** None.

Poster

253. Learning and Memory: Hippocampal Representations

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 253.05/SS60

Topic: H.01. Animal Cognition and Behavior

Support: NIH MN095297

NIMH R01MH112169

NIBIB R01EB022864

ONR MURI N00014-16-1-2832

Title: Temporal coding of hippocampal neurons across scales

Authors: ***W. MAU**[1], D. W. SULLIVAN[2], N. R. KINSKY[1], Z. TIGANJ[3], J. WEI[1], M. W. HOWARD[1], H. B. EICHENBAUM[4]
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Abstract: Time is an essential component of episodic memory. Consistent with its critical role in memory for temporal order, hippocampal “time cells” fire at sequential moments within specific episodes that occur over the order of seconds (Eichenbaum, Nat Rev Neuro 2014). In addition, longer timescales are represented by a gradual decorrelation of neural signals over hours and days (Mankin et al., Neuron 2015). To date, no studies have attempted to investigate these two encoding strategies in tandem. Here, we trained mice to run on a motorized treadmill for fixed delay periods while calcium imaging hundreds of neurons simultaneously in dorsal CA1. We present preliminary data reporting a neural representation composed of time cell sequences over the brief treadmill running periods. These cells either (1) stably encoded the same interval, (2) lost temporal specificity, or (3) gained temporal coding over the course of 4-5 days. This heterogeneity in stability could be the underlying basis for temporal coding across multiple timescales. Such a mechanism might support long-term maintenance of temporal information in service of episodic memory.

Disclosures: **W. Mau:** None. **D.W. Sullivan:** None. **N.R. Kinsky:** None. **Z. Tiganj:** None. **J. Wei:** None. **M.W. Howard:** None. **H.B. Eichenbaum:** None.

Poster

253. Learning and Memory: Hippocampal Representations

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 253.06/SS61

Topic: H.01. Animal Cognition and Behavior

Support: 2R01MH095297

Title: Intrinsic circuitry sharpens hippocampal time cell firing patterns

Authors: *R. J. PLACE[1], J. W. RUECKEMANN[3], H. B. EICHENBAUM[2]
[1]Boston Univ., Cambridge, MA; [2]Psychological and Brain Sci., Boston Univ., Boston, MA; [3]Univ. of Washington, Arcata, CA

Abstract: Interactions between the hippocampus and entorhinal cortices have been implicated in the creation of spatiotemporal trajectories used in organizing episodic memories. While both temporal as well as spatial coding is reflected in the activity patterns of neurons in the medial entorhinal cortex (MEC) and hippocampus (Kraus et al., 2013; Kraus et al., 2015), the mechanisms reponsible for generating these signals remains unclear. Here we report that transient disruptions of intrinsic hippocampal circuitry via stimulation of the ventral hippocampal commisural (vHC) fiber bundle corrupt hippocampal temporal firing patterns during the delay of a spatial working memory task. Rats were implanted with a single biphasic stimulus electrode in the vHC along with an array of recording tetrodes in CA1. We tested memory performance using a delayed alternation T-maze paradigm, wherein rats ran on a treadmill located on the center stem of the maze during an 8s memory delay period. After each treadmill run, the rat was rewarded for remembering its most recent trajectory and selecting the alternate route. During the treadmill run, CA1 neurons consistently fired at successive brief moments, such that “time cell” sequences spanned the entire delay. After a set of baseline trials (n = 20), rats ran a set of stimulation trials (n=20). Two seconds into the delay, we stimulated the vHC, which has been shown to inhibit CA1 pyramidal cell firing for durations ranging 100-200 ms (Zugaro et al., 2005). In contrast to previous reports of place cell stability in reponse to vHC stimulation (Jadhav et al., 2012), hippocampal time cells were susceptible to the transient disruption of intra-hippocampal processing. Consistent with previous findings that the elimination of CA3 inputs to CA1 resulted in a loss of spatial information within CA1 place cells, we observed less temporal information within baseline-defined time cells after the stimulation. Additionally, we found less precise temporal coding in neuronal ensembles for several seconds following the stimulation. In spite of the corruption of a baseline temporal signal, new time cell activity emerged as a result of the stimulation. Newly formed time cells spanned the delay with a temporal density profile similar to cells found at baseline conditions. However, these newly formed cell ensembles displayed less distinct temporal coding than

baseline ensemble activity. These results suggest that mechanisms within the hippocampus are crucial for stabalizing and refining the temporal signal within CA1, and yet the capacity for generation of a CA1 temporal signal persists despite of transient intrinsic disruption.

Disclosures: R.J. Place: None. **J.W. Rueckemann:** None. **H.B. Eichenbaum:** None.

Poster

253. Learning and Memory: Hippocampal Representations

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 253.07/SS62

Topic: H.01. Animal Cognition and Behavior

Support: NIMH MH052090

Title: Cognitive maps of memories and space in large hippocampal neural ensembles

Authors: *S. J. LEVY[1], N. R. KINSKY[2], D. W. SULLIVAN[3], H. B. EICHENBAUM[4]
[1]Grad. Program in Neurosci., [3]Psychology, [4]Psychological and Brain Sci., [2]Boston Univ., Boston, MA

Abstract: Recent work suggests that a major role of the hippocampus to disambiguate memories by forming unique neural representations when experiences involve overlapping elements. However, a previous study in which hippocampal neurons were recorded while animals foraged for food in different arenas within the same global environment reported that place cells distinguished local arenas only by firing rate and not by changes in the place field location (rate remapping), while population vectors distinguished the same arenas in different envrionments, interpreted as a mechanism for coding distinct episodic memories (Leutgeb et al. Science 2005). Other studies have suggested that, under distinct cognitive demands, memory representations are distinguished by a combination of rate and global remapping, comparable to the different global environments above. The extent to which remapping is characterized by rate and global changes has not been quantified. To quantify rate and global remapping under distinct cognitive demands in the same environment, we used in vivo calcium imaging to observe the activity of hundreds of CA1 neurons simultaneously while mice performed a hippocampus-dependent delayed non-match to place task on a continuous T maze. In this task, mice are forced to turn in one direction for reward in the sample phase, then after a 20 sec delay, must select the opposite direction in the choice phase to receive another reward. Population analyses of neuronal activity on the center segment of the maze common to both sample and test, and left-turn and right-turn trials, show that hippocampal cells employ a mixture of rate and global mapping to disambiguate trials by task phase and direction, composing an overall ensemble mapping of cognitive state (sample vs test), trajectory (left vs right), and space (stable place fields) that maintains these distinctions throughout two weeks of recordings.

Disclosures: **S.J. Levy:** None. **N.R. Kinsky:** None. **D.W. Sullivan:** None. **H.B. Eichenbaum:** None.

Poster

253. Learning and Memory: Hippocampal Representations

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 253.08/SS63

Topic: H.01. Animal Cognition and Behavior

Support: MH094263

MH050570

MH052090

MH095297

Title: TENASPIS: A fast, accurate, and improved tool for detecting ROIs and calcium transients from in-vivo single photon fluorescence microscopy

Authors: *D. W. SULLIVAN, N. R. KINSKY, W. MAU, H. B. EICHENBAUM
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Abstract: Recent advances in single-photon fluorescence calcium imaging offer the ability to monitor the activity patterns of hundreds of neurons simultaneously in behaving animals. A major challenge in data processing is the accuracy of detection and isolation of single-neuron regions of interest (ROIs) by video analysis, in particular in the CA1 area where neuron cell bodies are densely packed. Current techniques including PCA/ICA have the drawback of computational explosion due to supra-linear algorithmic complexity, resulting in very slow processing times. We have devised a technique, TENASPIS (Technique for Extraction of Neuronal Activity from Single Photon Imaging Sequences), which uses a heuristic approach to calcium transient detection via linear-time image segmentation, which avoids the computational explosion inherent in other techniques. TENASPIS produces results similar to PCA/ICA on real as well as simulated datasets, both in ROI detection accuracy and calcium transient detection accuracy. Recent improvements to TENASPIS include new approaches to movie pre-processing and avoiding type 1 and type 2 errors in calcium transient detection. TENASPIS is a free, open-source software tool that works with data from a variety of microscopes, species, and brain areas.

Disclosures: **D.W. Sullivan:** None. **N.R. Kinsky:** None. **W. Mau:** None. **H.B. Eichenbaum:** None.

Poster

253. Learning and Memory: Hippocampal Representations

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 253.09/SS64

Topic: H.01. Animal Cognition and Behavior

Support: NRF-2015M3C7A1031969

NRF-2016R1A2B4008692

SRC-2014051826

BK21+ program

Title: Firing patterns of the dorsal and ventral hippocampal neurons in representing place and its value

Authors: *S.-W. JIN, J. SHIN, I. LEE
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Abstract: Most hippocampal functions including spatial navigation have been studied in the dorsal hippocampus (dHP), but little is known about the roles of the ventral hippocampus (vHP). Although some prior studies reported that cells in the vHP contained larger place fields compared to those in the dHP, its functional significance is largely unknown. The functions of the vHP have been investigated mostly by using behavioral testing, focusing mostly on anxiety-related issues. However, it is unknown how positive values of different kinds and with different magnitudes are represented in association with places in the hippocampus. In the current study, we examined differential functions the dHP and vHP in representing a place and its significance (i.e., value). We recorded single units from the dHP and vHP simultaneously while the rat alternated between two adjacent arms of an 8-arm maze. Food wells at the ends of the arms were baited with sunflower seeds (SS) during pre-training. Once rats were trained to criterion (240 trials/hr), a 24-tetrode hyperdrive was implanted targeting the dHP and vHP simultaneously. After recovery from surgery, tetrodes were lowered to the putative pyramidal cell layers while the rat was trained in the alternation task. During this training period, the animal experienced different reward types (i.e., Froot Loops [FL] and Cheerios [CR]) for two days before the main recording began. When the main recording session started, the rat experienced different sessions as follows: (i) FRL-FRT (fixed reward location with fixed reward type) in which SS was provided as reward at the arm ends, (ii) VRL-FRT (variable reward location with fixed reward type) in which SS was provided as reward at variable locations along the arm, (iii) FRL-VRT (fixed reward location with variable reward type) in which FL, CR, and SS were alternately given as rewards only at the arm ends in a given block, and (iv) food preference task in a T-maze

(two choice arms of the T-maze were baited with SS and CR). Our preliminary analysis suggests that cells in the hippocampus dynamically represented reward-related information. Specifically, among the putative pyramidal cells that started firing immediately before the rat displaced the disc to uncover the reward, some cells increased or decreased their firing rates according to the reward type (e.g., SS or CR). Some putative interneurons also showed such reward-related modulations in their firing rates. The rate modulation associated with the reward type also appeared during reward consumption in some cells. We are currently collecting more data to analyze whether differential reward-related firing patterns appeared between the dHP and vHP.

Disclosures: S. Jin: None. **J. Shin:** None. **I. Lee:** None.

Poster

253. Learning and Memory: Hippocampal Representations

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 253.10/SS65

Topic: H.01. Animal Cognition and Behavior

Support: NRF-2015M3C7A1031969

NRF-2016R1A2B4008692

SRC-2014051826

NRF BK21+ program

Title: Neural correlates of visual contextual memory in CA3 following lesions in the dentate gyrus

Authors: *C.-H. LEE, S.-H. JEON, I. LEE
Dept. of Brain & Cognitive Sci., Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: The hippocampus is necessary for remembering visual context (i.e., visual scene) in the animal's background and its associated behavior. However, little is known about information processing for visual contextual memory in different subfields of the hippocampus. Our previous study (Ahn and Lee, 2014) suggests that the dentate gyrus (DG) is critical in both learning a new visual context and recognizing modified old contexts, but not in retrieving familiar contextual memories. In the current study, we made neurotoxic lesions using colchicine in the DG and recorded single units from the CA3 as the rat performed a visual contextual memory (VCM) task. A T-maze with a start box attached at the end was used, and an array of three 17-inch LCD monitors surrounded the two arms of the maze for displaying visual stimuli. In the VCM task, the rat chose either the left or right arm based on the visual context presented on the monitors. Once rats were trained to criterion (above 70% correct for two consecutive days) for both context

pairs, we injected colchicine in the DG bilaterally using custom-made glass pipettes. Then, we implanted a hyperdrive with 24 tetrodes targeting the dorsal CA3. When rats recovered from surgery, tetrodes were lowered to CA3 while rats were retrained in the same task. Once most tetrodes were positioned in the cell layers, the main recording began with four standard contexts (STD) for two days. Afterward, rats experienced the following contextual manipulations sequentially across days: (i) blurred, (ii) overlaid, (iii) masked, and (iv) novel contexts. In blurred sessions, five levels (0%, 30%, 40%, 50% and 70%) of Gaussian blurred contexts were used. In overlaid sessions, two contexts in each context pair were overlaid with each other with four levels of opacity ratios (original, 8:2, 7:3, and 6:4). In masked sessions, only parts of the visual context were visible only through circular hole masks with five diameter sizes (original, D1, D2, D3 and D4). Following masked sessions, new contextual stimuli were used for two days using a pair of novel visual contexts. Except for STD sessions in which rats were presented with four contexts within a single session, only a single pair of contexts were used in a given session. Based on our preliminary data, compared to controls (n=2), rats with DG lesions (n=3) seemed impaired in the VCM task with novel contexts while performance in other ambiguous scene sessions appeared relatively intact. We plan to run more rats in the same task and analyze electrophysiological data acquired during the VCM task to examine the firing patterns of CA3 neurons recorded when the rat processed various visual contexts in the presence or absence of DG inputs.

Disclosures: C. Lee: None. **S. Jeon:** None. **I. Lee:** None.

Poster

253. Learning and Memory: Hippocampal Representations

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 253.11/SS66

Topic: H.01. Animal Cognition and Behavior

Support: NIH R15 AREA Award 1R15AG045820-01A1

Title: Hippocampal LFP and single unit recording in juvenile rats during Barnes maze navigation

Authors: *D. G. MCHAIL[1], C. KIMBALL[2], N. COSTELLO[2], T. C. DUMAS[3]
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Abstract: Electrophysiological recording from the brain in awake and behaving rodents is beginning to reveal the neural substrates that support spatial navigation. In particular, coordinated activities in networks of cells in the hippocampus sensitive to spatial context (i.e. place cells) have been linked to the recall, planning, and execution of trajectories through space. Because spatial navigation ability comes online at postnatal day (P) 21 in rodents, investigating

physiological differences in animals just under and just over P21 during maze exploration is a powerful tool to help determine which components of the system are sufficient to enable this complex cognitive skill. We recently reported that age-dependent differences in hippocampal theta and gamma rhythms were associated with superior performance during free exploration in a Y-maze (SfN, 2016, manuscript submitted). However, there is no explicit goal in this task. In the current work, we paired hippocampal LFP and single unit recording with performance in a Barnes maze in the juvenile rat. We have already validated the Barnes maze as a behavioral tool that exposes developmental differences in spatial learning and memory from P17 and P24 (manuscript submitted). Surgery to implant tetrodes into the hippocampus occurred at P19. Three days following surgery, single units and LFPs were recorded during maze performance and learning of the goal location was observed. We will report relationships between developmental stage, place cell activity (i.e. size and stability) and oscillatory activities (i.e. theta and gamma rhythms and sharp-wave ripples), and maze performance (i.e. learning parameters, vicarious trial and error, and memory scores). These findings will help elucidate the roles of specific hippocampal networks properties in the developmental emergence of distinct aspects of spatial cognition.

Disclosures: D.G. McHail: None. **C. Kimball:** None. **N. Costello:** None. **T.C. Dumas:** None.

Poster

253. Learning and Memory: Hippocampal Representations

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 253.12/TT1

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant MH101198

NIH Grant MH105427

Title: Optogenetic manipulation of hippocampal dorsal CA1 during an olfactory working-memory task

Authors: *A. L. MYLAVARAPU[1], J. TAXIDIS[1], K. SAMADIAN[1], E. HOFFBERG[1], N. SABOORI[1], M. BEDROSSIAN[1], T. TAIMOORAZY[1], B. NOSRATI[1], J. SADIK[1], P. GOLSHANI[2]
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Abstract: Working memory (WM) is a crucial aspect of cognition, allowing for active retention of information during a short period of time to complete an action. Even though the neurophysiological hallmark of WM is persistent neuronal firing across a delay period in prefrontal and parietal cortical areas, WM is thought to incorporate a larger network of cortical

and subcortical structures, including the hippocampus (Sreenivasan et al. 2014). Instead of persistent firing, hippocampal neuronal ensembles typically fire in sequences during delayed-response tasks, encoding time, spatial trajectories, or other task-related information (Pastalkova et al. 2008, MacDonald et al. 2011). However, it remains unclear whether there is a causal link between such sequences and WM. Which elements of the circuitry are necessary for retention of a stimulus during a delay period? What role do these circuits play during learning or while increasing the memory load? How would disrupting excitation/inhibition balance in the hippocampus affect performance? To gain more insight into these questions, we trained Gad2-Cre:Ai32 head-fixed mice to perform a delayed non-match-to-sample (DNMS) olfactory WM task (Liu et al. 2014). Using in vivo two photon calcium imaging in dorsal CA1 during the task, we observed spiking sequences that encode the identity of the first olfactory stimulus throughout the delay following it. We thus conducted a series of optogenetic manipulation experiments, exciting channelrhodopsin-expressing GABAergic interneurons to determine the effect of disrupting these sequences during the DNMS task. We observed a small but significant reduction in behavioral performance during optogenetic stimulation of GABAergic neurons in the hippocampus bilaterally, compared to non-stimulated controls. Moreover, to assess the role of CA1 sequences during learning, we will stimulate mice during training of the task and compared their learning curves with those of controls. Finally, we will optogenetically silence CA1 in well-trained mice while prolonging the delay (from 5 up to 15 seconds) to address the link of CA1 sequences with memory load. Employing such time-precise manipulation of subpopulations in the dorsal CA1 during a WM-dependent task will shed light into the role of excitation/inhibition balance in the hippocampus and the circuit-level underpinnings of WM. This will be crucial for further understanding of how hippocampal dysfunction may be related to observed WM-impairments in brain conditions like schizophrenia or Alzheimer's' disease.

Disclosures: A.L. Mylavarapu: None. **J. Taxidis:** None. **K. Samadian:** None. **E. Hoffberg:** None. **N. Saboori:** None. **M. Bedrossian:** None. **T. Taimoorazy:** None. **B. Nosrati:** None. **J. Sadik:** None. **P. Golshani:** None.

Poster

253. Learning and Memory: Hippocampal Representations

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 253.13/TT2

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant MH101198

NIH Grant MH105427

Title: Hippocampal spiking sequences during an olfactory working-memory task

Authors: *J. TAXIDIS[1], A. MYLAVARAPU[1], K. SAMADIAN[1], E. HOFFBERG[1], N. SABOORI[1], M. BEDROSSIAN[1], T. TAIMOORAZY[1], B. NOSRATI[1], J. SADIK[1], P. GOLSHANI[2]
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Abstract: How does the brain actively retain information in memory for short time intervals, and compare this information with incoming input to execute an action? Studies in rodents suggest that the hippocampus is involved in working-memory, with neuronal population activity organized in spiking sequences, encoding different trial elements. Such sequences have been observed in dorsal CA1, during the delay, in a match-to-sample olfactory task (MacDonald et al. 2013) and a spatial alteration task (Pastalkova et al. 2008) in head-fixed and freely-moving rats respectively. These sequences may be critical for task performance, but their link to working-memory is not well understood. Are they associated with the actual memory of the stimulus? How do they relate with learning and performance? How do they evolve over time? What are key elements of hippocampal neuronal circuits in generating and sustaining them? To gain more insight into these questions, we trained Gad2-Cre:Ai9 head-fixed mice to perform an olfactory delayed non-match-to-sample task, requiring working-memory activation (Liu et al. 2014). We performed in vivo two-photon calcium imaging (with GCaMP6f calcium indicator) of the same population of dorsal CA1 pyramidal layer neurons during both early stages of training and in the well-trained phase. We recorded the activity of hundreds of neurons over multiple consecutive days, while mice performed the task, using a variety of delay periods (5-15 seconds). We observed that several neurons were activated only during the presentation of specific odors (‘odor-cells’), while others encoded for specific timepoints during the delay period following a given stimulus (‘delay-cells’). Collectively, this activity formed spiking sequences, involving both pyramidal cells and GABAergic interneurons, that cover the entire duration between the two olfactory stimuli. We describe how such sequences adjust to prolonging the delay duration; how they relate to correct versus error trials and how the firing field of each cell evolves during learning and in the well-trained stage. Understanding whether and how such population dynamics emerge and are linked to working-memory processes provides a critical step to understanding brain mechanisms of memory formation and consolidation.

Disclosures: J. Taxidis: None. **A. Mylavarapu:** None. **K. Samadian:** None. **E. Hoffberg:** None. **N. Saboori:** None. **M. Bedrossian:** None. **T. Taimoorazy:** None. **B. Nosrati:** None. **J. Sadik:** None. **P. Golshani:** None.

Poster

253. Learning and Memory: Hippocampal Representations

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 253.14/TT3

Topic: H.01. Animal Cognition and Behavior

Title: Comparing hippocampal oscillations in the macaque across free and constrained experimental contexts using wireless recordings

Authors: *O. TALAKOUB[1], P. SAYEGH[1], K. L. HOFFMAN[2,3]
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Abstract: The most versatile experimental paradigms to study the neurophysiological mechanisms underlying animal cognition and behavior involve recording the neural activity in the awake and behaving animal. Imposing behavioral limitations may alter brain states and consequently the underlying neural selectivity. For example, hippocampal responses in rats that are freely moving can differ from those reported during movements through immersive virtual space, or under various levels of immobility (Foster et al., *Science*, 1989; Terrazas et al., *J Neurosci*, 2005; Aghajan et al., *Nat. Neurosci*, 2015). In humans, a recent study highlighted the possibility that this may also occur for human navigation (Bohbot et al., *Nat Comm* 2017; Aghajan et al., *BioRxiv*, 2016), and in monkeys, hippocampal molecular imaging showed differences in neuronal activation as a function of mobility (Thome et al., *J Neurosci*, 2017). To determine the dependence of hippocampal oscillations on experimental context, we compared hippocampal activity of two macaques in laboratory isolation booths and their housing environments during visual exploratory, inactive, and quiescent periods. Field potentials were recorded from multi-channel electrodes, AD converted at either 32 kHz sampling rate and sent to a Neuralynx Digital Lynx system ('tethered') or sampled at 30 kHz, and transmitted wirelessly to the same system ('wireless'). Differences in hippocampal activity between the stationary-and-fixed versus free-behaving states were most notable in sharp-wave ripple rate. In contrast to hippocampal oscillations in the freely moving rat and mouse, we rarely observed reliable occurrence of ripples during ingestive behaviors, despite regular SWR appearance in the booth during various task behaviors including drinking. Surprisingly, ambulatory behavior was not associated with continuous stretches of 7-10 Hz theta band activity, at least during slow movements, and in general, low (<25 Hz) oscillatory activity in macaques was shorter-lived in all experimental contexts compared to durations reported in rats and mice. Due to similarities in neuroanatomy and general functional conservation between macaques and humans, the results shown in this study are predicted to be preserved in humans. This raises important methodological questions about how to compare neural activity across experimental contexts in primates, and how to compare hippocampal activity across primate and rodent orders.

Disclosures: O. Talakoub: None. **P. Sayegh:** None. **K.L. Hoffman:** None.

Poster

253. Learning and Memory: Hippocampal Representations

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 253.15/TT4

Topic: H.01. Animal Cognition and Behavior

Support: HFSP Young Investigators Grant RGY0088

NSF CAREER Grant CBET-1351692

NSF BRAIN EAGER IOS-1550994

NSF Grant 1250104 (IGERT: Neuroengineering from Cells to Systems)

Title: Continuous neural recordings for long-term temporal dynamics in the rodent hippocampus

Authors: *J. CHU, E. ACKERMANN, S. DUTTA, C. KEMERE
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Abstract: Much is still unknown about the mechanisms underlying learning and memory, as well as the functional significance of associated hippocampal replay sequences. There is strong evidence supporting the roles of these replay sequences in a number of cognitive functions, including memory consolidation and behavioral planning. However, a statistical understanding of replay events, including the long-term temporal dynamics, is still lacking. To this end, we collected hippocampal data by chronically and continuously recording from animals over multiple days. In this way, we can determine the temporal decay of replay events, and better understand the contextual prevalence of such events.

Indeed, replay is expected to occur throughout the day, presumably representing recent, past, distant past, and never-before-experienced experiences, yet existing analyses of replay have primarily considered recording sessions shortly before and after short term (approximately one hour) behavioral experiments. As the memory consolidation process extends beyond these short-term periods, we examined the replay events in other contexts.

In addition to the scientific investigations enabled by our neural data acquisition system, our wireless setup eliminates experimental failure modes such as a tether disconnection. Overall, these continuously collected recordings provide new insights into the temporal and contextual dynamics of spatial representations during memory encoding, consolidation, and recall.

Disclosures: J. Chu: None. **E. Ackermann:** None. **S. Dutta:** None. **C. Kemere:** None.

Poster

253. Learning and Memory: Hippocampal Representations

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 253.16/TT5

Topic: H.01. Animal Cognition and Behavior

Support: NSF CAREER award (CBET-1351692)

NSF BRAIN EAGER award (IOS-1550994)

HFSP Young Investigator's award (RGY0088)

Ken Kennedy Institute for Information Technology

Title: Latent variable models for hippocampal sequence analysis

Authors: *E. ACKERMANN[1], K. MABOUDI ASHMAN KAMACHALI[3], K. DIBA[4], C. KEMERE[2]
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Abstract: The activity of ensembles of neurons within the hippocampus is thought to enable memory formation, storage, and recall, and even potentially decision making. During offline states (associated with sharp wave ripples, quiescence, or sleep), some of these neurons are reactivated in temporally-ordered sequences which are thought to enable associations across time and episodic memories spanning longer periods. However, analyzing these sequences of neural activity remains challenging for several reasons, including the (i) lack of animal behavior, and (ii) limitations of prevailing analysis approaches to sufficiently quantify metrics of sequential activity.

Here we build on recent approaches using latent variable models for hippocampal population codes, to detect and score so-called "replay events", and to build models of hippocampal sequences independent of animal behavior. In particular, we show that these models, trained on only a few seconds of offline ripple-associated data, can be used to accurately decode waking behavior. This reversal of the inference direction (i.e., starting with models trained on quiescent data and decoding active wake behavior, as opposed to the prevalent Bayesian approach of training models on awake behavior and decoding quiescent activity) is important because the ground truth for the quiescent periods cannot be established. In this way, we can quantitatively assess the extent to which waking behavior fits the quiescent model, and discover additional structure in the quiescent data that might represent remote or even hypothetical experiences. Furthermore, we demonstrate that these latent variable models are comparable to state-of-the-art Bayesian methods for detecting replay, and we characterize those instances where the latent variable model approach outperforms the Bayesian approach, e.g., to detect trajectories with non-constant running speed, or nonlinear trajectories in more complex environments.

Overall, the latent variable model approach provides an attractive framework for studying and analyzing sequential neural activity, but perhaps more importantly, they provide an alternative "sequential" view of hippocampal activity that may shed new light on how memories are formed, stored, and recalled.

Disclosures: E. Ackermann: None. **K. Maboudi Ashman Kamachali:** None. **K. Diba:** None. **C. Kemere:** None.

Poster

253. Learning and Memory: Hippocampal Representations

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 253.17/TT6

Topic: H.01. Animal Cognition and Behavior

Support: HFSP Young Investigators (RGY0088)

NSF CAREER (CBET-1351692)

NSF BRAIN EAGER (IOS-1550994)

Title: Low-latency, open-source, closed-loop system for sharp-wave ripple detection

Authors: *S. DUTTA, E. ACKERMANN, C. KEMERE
Electrical and Computer Engin., Rice Univ., Houston, TX

Abstract: Transient neural activity pervades electrophysiological activity within the hippocampus. Particularly, sharp-wave ripples (SWRs), transient coordinated bursts of ~150-250 Hz oscillations present in the local field potential in hippocampal area CA1 that last approximately 60-150 ms. Within the network, SWRs co-occur with ensemble spiking of pyramidal neurons in the area. Together, SWRs and concomitant neural activity are associated with information propagation relating to memory consolidation, recall, and memory-guided decision making. Selective interaction with the brain upon online hippocampal SWR detection has been established to cause behavioral and cognitive alterations in animal memory consolidation and working memory. However, null results of behavioral or physiological alterations have also been reported. Additionally, investigations of cortical regions post-SWR have been studied in order to examine the extent of SWR based coordination within the brain. As such, to further probe SWR contributions to the learning and memory processes, we evaluate the performance and discuss the capabilities of an open-source, plug-and-play, online ripple detection system. Our system has been developed to interface with an open-source software platform (Trodes) and two hardware platforms (OpenEphys and SpikeGadgets). We show that our in vivo results, ~35-60 ms detection latencies with ~2 ms closed-loop latency while detecting >95% of events with <10 false detections per minute, are dependent upon both algorithmic tradeoffs and acquisition hardware. We discuss the potential limitations of online ripple disruptions and explore further strategies to improve detection accuracy. Finally, we look to employ this detection algorithm with behavioral traces, multiunit activity, and a wireless system. Overall, we anticipate our modular, open-source, real-time system will facilitate causal closed-loop neuroscience experiments.

Disclosures: S. Dutta: None. **E. Ackermann:** None. **C. Kemere:** None.

Poster

253. Learning and Memory: Hippocampal Representations

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 253.18/TT7

Topic: H.01. Animal Cognition and Behavior

Support: HFSP young investigators grant

Title: Fiber photometry micro-drive array for recording neural activity of hippocampus of freely moving rat

Authors: *Z. CHEN[1], C. KEMERE[2]
[1]Electrical And Computer Engin., [2]Rice Univ., Houston, TX

Abstract: Fiber photometry is a novel optical recording tool that can report collective activity of a specific population of neurons as single scalar value in real time, similar to local field potential (LFP) that is usually acquired through non-trivial computation of electrical recording and from non-specific population of neurons, thus it would help assisting electrophysiological method in studying hippocampal projections to other brain areas during forming memory. However, the understanding of distinction and relation between the optical and electrical signature in hippocampal activity remains lacking. Here I developed a fiber photometry system for recording optical signal from genetically encoded fluorescent calcium sensors in hippocampus of a free moving rat. In order to analyze both optical and electrical signals from a freely moving rat, I integrated photometry system with current electrophysiological recording system, a micro-drive array with 8 tetrodes. I implemented this method on a rat during spatial task in a linear track and open space exploration for recording.

Disclosures: Z. Chen: None. **C. Kemere:** None.

Poster

253. Learning and Memory: Hippocampal Representations

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 253.19/TT8

Topic: H.01. Animal Cognition and Behavior

Support: PSC-CUNY 68159-00 46

Title: Functional lateralization of c-Fos expression in the mouse dorsal dentate gyrus

Authors: *J. JORDAN[1], M. R. SHANLEY[1], K. TINEO[2], M. KAHN[2], A. WINTER[3], R. MURATORE[3], C. PYTTE[1,2]
[1]Biol., Grad. Center, The City Univ. of New York, New York, NY; [2]Psychology, Queens College, CUNY, Flushing, NY; [3]Paul D. Schreiber High Sch., Port Washington, NY

Abstract: Lateralization is an organizing principle of nervous systems across taxa. The hippocampus is essential for the formation of new declarative memories and spatial navigation and is known to be lateralized in many forms of anatomy, physiology, and cognitive function. The dentate gyrus (DG), a structure within the hippocampus, is important for the encoding of new memories. While activity in human hippocampus is known to be left-lateralized with respect to episodic memory and right-lateralized with respect to virtual spatial navigation, it is not clear if the rodent hippocampus, which allows researchers to study the cellular underpinnings of hippocampal function, shows similar functional lateralization. Further, human studies are limited by restrictions on body movement during imaging. Here, we used expression of the immediate early gene c-Fos, a marker of neuronal activity, in the dorsal DG of mice following object-exploration, wheel running, or homecage rest to determine whether behavioral state modulated DG c-Fos lateralization. We compared the degree of hemispheric lateralization of DG c-Fos expression between groups and found that object-exploring mice were significantly more left-lateralized than both wheel runners and mice at rest. The latter groups did not differ. These data indicate that activity in the mouse DG may be lateralized with respect to behavioral state. For instance, lateralized processing of extrasensory versus path integration inputs into the hippocampus may lead to lateralized processing of declarative memory versus spatial navigation. We suggest that taking into account hemispheric lateralization may greatly enhance our understanding of hippocampal function and may even resolve some decades-long debates in hippocampal literature.

Disclosures: J. Jordan: None. **M.R. Shanley:** None. **K. Tineo:** None. **M. Kahn:** None. **A. Winter:** None. **R. Muratore:** None. **C. Pytte:** None.

Poster

253. Learning and Memory: Hippocampal Representations

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 253.20/DP14/TT9 (Dynamic Poster)

Topic: H.01. Animal Cognition and Behavior

Title: Dedicated hippocampal inhibitory networks for locomotion and immobility

Authors: *M. W. ARRIAGA[1], E. B. HAN[2]
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Abstract: Hippocampal network activity is controlled by the ambulatory state of the animal; however, how locomotion is represented in hippocampal circuits remains poorly understood. Here we examined whether distinct locomotor states are encoded differentially in genetically defined classes of hippocampal interneurons. To characterize the relationship between interneuron activity and movement, we used in vivo, two-photon calcium imaging in genetically identified populations of mouse CA1 hippocampal interneurons as animals performed a virtual reality track running task. We found that activity in the majority of somatostatin- and parvalbumin-expressing interneurons positively correlated with locomotion. Surprisingly, nearly one in five somatostatin or one in seven parvalbumin interneurons were inhibited during locomotion and activated during periods of immobility. Anatomically, somatostatin immobility-activated neurons were distinguished by having smaller somata than movement-activated neurons. Furthermore, immobility-activated interneurons were distributed across cell layers, with somatostatin-expressing cells predominantly in stratum oriens and parvalbumin-expressing cells mostly in stratum pyramidale. Importantly, each cell's correlation between activity and movement was stable both over time and across virtual reality environments. Our findings suggest that hippocampal interneuronal microcircuits operate with preferential activity during either movement or immobile periods. These inhibitory networks may regulate information flow in "labeled lines" within the hippocampus to process information during distinct states of locomotion.

Disclosures: M.W. Arriaga: None. **E.B. Han:** None.

Poster

253. Learning and Memory: Hippocampal Representations

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 253.21/TT10

Topic: H.01. Animal Cognition and Behavior

Support: BMBF Grant 01GQ1506

NIH Grant R01MH109170

Title: Modeling replay and theta sequences in a 2-d recurrent neural network with plastic synapses

Authors: A. AZIZI[1], K. DIBA[2], *S. CHENG[1]
[1]Inst. for Neural Computation, Ruhr Univ. Bochum, Bochum, Germany; [2]Dept. of Psychology, Univ. of Wisconsin-Milwaukee, Milwaukee, WI

Abstract: During immobility awake states or when rats are asleep, place cells are reactivated in a sequential order. This reactivation co-occurs with sharp wave/ripples in the local field potential (LFP) in the hippocampus and reflect the sequence of the animal's prior spatial behaviour or the upcoming trajectory to a goal location. During running, the LFP shows characteristic theta oscillations, whose phase modulates the activity of place cells. This modulation, called phase precession, is accompanied by the activity of place cells occurring in a sequential order within a theta cycle. One possible connection is that phase precession leads to sequential ordering within theta cycles. Alternatively, phase precession might be the result of the directional activation of a group of cells with overlapping place fields. Romani and Tsodyks [2015] recently modelled phase precession using an unstable moving bump of activity in a 1-d continuous attractor neuronal network. The driving force of the sequential activity is the short-term plasticity in the synaptic connections. This model also generates offline replay activity in a different operating mode. Since no long-term plasticity was included in the model, the resulting replay and theta sequences only reflected the recent behavior of the animal within the last few seconds and the associated span of phase precession was limited. Recent studies, however, point to a separation of phase precession and theta sequences. Although phase precession can be found immediately in novel environment, the development of theta sequences requires experience [Feng et al. 2015] and the goal location, rather than the extent of phase precession, appears to determine the length of theta sequences [Wikenheiser and Redish 2015]. Furthermore, a recent study suggests a dissociation between replay and theta sequences [Wu et al. 2017]. Only replay activity decoded portions of an environment that the animal had learned to avoid, while theta sequences did not penetrate into the avoided region. Here we study phase precession, theta and replay sequences, and the relationship between these phenomena in a 2-d continuous attractor network model. The units in the network exhibit spike-frequency-adaptation that destabilizes the bump attractor and synapses with long-term plasticity. This model can generate enhanced replay after exposure, theta sequences, and phase precession. The spatial extent of theta sequences is controlled by the running speed of the virtual animal as hypothesized by Wu et al. Our preliminary findings suggest that replay and theta sequences can be accounted for within a single model.

Disclosures: A. Azizi: None. **K. Diba:** None. **S. Cheng:** None.

Poster

254. Learning and Memory: Limbic Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 254.01/TT11

Topic: H.01. Animal Cognition and Behavior

Support: MEXT KAKENHI JP 25115002

JSPS KAKENHI JP 23220009

CREST JPMJCR13W1

Title: Complete erasure of memory trace from engram cells

Authors: *K. M. ABDOU[1,2], M. H. SHEHATA[1,2], Q. ZHAO[1,2], H. NISHIZONO[2,3], M. MATSUO[3], S. MURAMATSU[4], K. INOKUCHI[1,2]
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Abstract: Memories are stored in specific subsets of cells called memory engram cells. The recent finding that engram cells still retain memories even after retrograde amnesia, drew attention towards finding approaches for irreversible removal of fear memories. We have shown previously that autophagy induction enhances synaptic and memory destabilization induced by reactivation, and when combined with protein synthesis inhibition, complete retrograde amnesia is attained. However, whether the erased memory is still stored, yet dormant, is enigmatic.
In this study, using auditory fear conditioning in c-fos-tTA transgenic mice, we tagged the activated neurons during conditioning in the auditory cortex (AC) and the medial geniculate nucleus (MGm), or in the lateral amygdala (LA) with opsins (oChIEF) for optogeneic recall. Complete retrograde amnesia was attained by anisomycin treatment with the help of autophagy induction and the deficit in memory retrieval was long-lasting. Optogenetic stimulation of either LA engram cells or the terminals of AC and MGm engram cells in LA failed to recall the memory, indicating that engram cells in LA were no longer store the fear memory. Optogenetic induction of LTP in specific synapses between engram cells of AC-LA & MGm-LA pathways partially reinstated a cue-specific freezing response.
Our study sheds light on the capability of the total removal of memory engram. Also, based on the effect of autophagy on the synaptic destabilization, our study strongly suggests the importance of synaptic plasticity for the engram cells to retain the memory.

Disclosures: K.M. Abdou: None. **M.H. Shehata:** None. **Q. Zhao:** None. **H. Nishizono:** None. **M. Matsuo:** None. **S. Muramatsu:** None. **K. Inokuchi:** None.

Poster

254. Learning and Memory: Limbic Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 254.02/TT12

Topic: H.01. Animal Cognition and Behavior

Support: JSPS KAKENHI 16H04653 to N.O.

CREST JPMJCR13W1

JSPS KAKENHI JP23220009

MEXT KAKENHI JP25115002 to K.I.

Title: Unraveling the dynamism of engram cells during contextual memory processing

Authors: *K. GHANDOUR[1,2,3], N. OHKAWA[1,2,3], C. FUNG[2,4], Y. SAITOH[1,2,3], T. TAKEKAWA[2,5], H. ASAI[1,2], R. OKUBO-SUZUKI[1,2], M. NOMOTO[1,2], S. SOYA[6], S. TSUJIMURA[1,2], H. NISHIZONO[7], M. MATSUO[7], M. SATO[4,8,9], M. OHKURA[8,9], J. NAKAI[8,9], Y. HAYASHI[4,9,10], T. SAKURAI[6], M. OSANAI[11,12], T. FUKAI[2,4], K. INOKUCHI[1,2]
[1]Univ. of Toyama, Toyama, Japan; [2]CREST, Jst, Japan; [3]PRESTO, Jst, Japan; [4]RIKEN, Bsi, Japan; [5]Fac. of Informatics, Kogakuin university, Japan; [6]WPI-IIIS, University of Tsukuba, Japan; [7]Life Sci. Res. Center, Univesity of Toyama, Toyama, Japan; [8]Grad. school of Sci. and Engin., Saitama University, Japan; [9]Brain and Body Syst. Sci. institute, Saitama University, Japan; [10]Grad. school of Med., Kyoto University, Japan; [11]Grad. school of Med., Tohoku University, Japan; [12]Grad. school of Biomed Eng, Tohoku University, Japan

Abstract: It is hypothesized that a memory is encoded in a subset of neurons, which is activated by physiological input derived from a corresponding event, called engram. The c-fos-TetTag system has been used to prove the engram theory, by manipulation of cells that showed activity-dependent gene expression driven by learning. However, it remains unclear how memory is allocated to a specific subpopulation of neurons. Here we show that the engram cells possess several characteristic features compared to non-engram cells. We define engram cells as those expressing c-fos during learning, because optogenetic stimulation of c-fos-Tet-Taged cells, which were established in the hippocampal CA1 during context exposure, triggered recall of the contextual memory. A compatible imaging system was established to observe the labelled engram cells and the neuronal activity of hippocampal CA1 neurons through Ca2+ influx in freely-moving animals by miniature head-mount fluorescent microscopy. The engram cells showed characteristic activity during contextual learning by exposure to a novel context, in which the engram cells exhibited remarkable synchrony and higher Ca2+ influx compared to non-engram cells. Non-negative Matrix Factorization (NMF) analyses extracted characteristic patterns that were constructed by subgroup of engram cells, representing the persistent synchronous activity even during pre- and post-learning resting sessions. These results suggest that there are several fundamental characteristics of the engram cells that give them superiority in encoding the ongoing event. Our imaging system of engram cells and non-engram cells will provide deeper insights into the dynamics of the neural activity during learning.

Disclosures: K. Ghandour: None. **N. Ohkawa:** None. **C. Fung:** None. **Y. Saitoh:** None. **T. Takekawa:** None. **H. Asai:** None. **R. Okubo-Suzuki:** None. **M. Nomoto:** None. **S. Soya:** None. **S. Tsujimura:** None. **H. Nishizono:** None. **M. Matsuo:** None. **M. Sato:** None. **M. Ohkura:** None. **J. Nakai:** None. **Y. Hayashi:** None. **T. Sakurai:** None. **M. Osanai:** None. **T. Fukai:** None. **K. Inokuchi:** None.

Poster

254. Learning and Memory: Limbic Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 254.03/TT13

Topic: H.01. Animal Cognition and Behavior

Support: UGC RFSMS F.4-1/2006 (BSR)/5-94/2007

Title: Neuropotential role of taurine: Neurotransmitters, oxidative stress, mitochondrial dysfunctioning and histopathological evidences

Authors: *M. BHARDWAJ, SR
Neuropharm., Panjab Univ., Chandigarh, India

Abstract: Rationale: Alterations in neurotransmitters levels is the main culprit of the epilepsy. With the antioxidant effects, taurine cause the alterations in the Glutamate and GABA levels. So, it can be beneficial in epilepsy.
Objective: Aim of present study is to investigate the neuroprotective role of taurine and its modulation by minocycline in the kindling epilepsy
Method: PTZ (40 mg/kg, i.p.) was administered alternatively for 29 days until animal exhibited full motor seizures. Taurine was given orally at a dose of 25, 50 and 100mg/kg by dissolving it in distilled water once a day 1h prior to PTZ treatment and minocycline at the dose of 50 and 100mg/kg and its combination (Taurine+Mino50mg/kg) and (Taurine + Mino 100mg/kg) for the period of 29 days. Various neurobehavioral parameters followed by biochemical, mitochondrial respiratory enzyme complexes (I-IV), neurotransmitter examinations (Glutamate, GABA, Serotonin, Dopamine and Norepinephrine) and histopathological alterations were assessed.
Results: PTZ administration significantly impaired the cognitive performance in the morris water maze (MWM) performance test, increase the seizure score, cause the oxidative stress, mitochondrial dysfunctioning and also cause alterations in the neurotransmitter levels and in the histopathology of hippocampus and cortex. Treatment with the taurine (25, 50 and 100mg/kg), minocycline (50 and 100mg/kg) for 29 days significantly improve the seizure score, reduced AChE activity, oxidative damage (reduced LPO, nitrite level and elevate the SOD, catalase and GSH levels) and also restore the mitochondrial complexes (Complex I, II and IV) and improve the neurotransmitter levels (Glutamate, GABA, Serotonin, Dopamine and Norepinephrine). Combination of taurine with minocycline showed more significant effects as compared to the per se effect. Further, histopathological alterations showed the significant improvement effects in the combination of taurine with minocycline.
Conclusion: Taurine when combined with minocycline show the neuroprotection against the PTZ induced kindling epilepsy.

Disclosures: M. Bhardwaj: None.

Poster

254. Learning and Memory: Limbic Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 254.04/TT14

Topic: H.01. Animal Cognition and Behavior

Support: NIH grant R01 NS084324

Title: Genetically targeted expression of APP to subpopulations of hippocampal principal neurons leads to neuronal network dysfunction and impairment in hippocampus-dependent memory

Authors: *S. VIANA DA SILVA[1], M. G. HABERL[1], K. GAUR[1], M. LEDAKIS[1], M. FU[1], M. BRY[1], J. K. LEUTGEB[1], E. KOO[2], S. LEUTGEB[1,2]
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Abstract: Alzheimer's disease is a neurodegenerative disorder characterized by progressive mnemonic deficits. In humans, synapse and neuron loss are pronounced in the hippocampal formation, a region known to have an essential role for spatial learning and navigation. We used transgenic mice that over-express human amyloid precursor protein preferentially in CA1 or CA3 pyramidal cells (CA1-APP and CA3-APP, respectively) as models to investigate how amyloid-beta peptide (Aβ) induced dysfunction of synaptic plasticity affects the hippocampal circuitry and memory function during early phases of the disease. To test for memory deficits, we performed a spatial alternation task on a figure-8 maze with either no delay or brief delays (i.e., 2 s or 10 s) at the beginning of the center alley. The delay period is known to make the task hippocampal-dependent, in contrast to the continuous version. In 4-6 months old CA1-APP animals, we observed a decrease in the number of correct trials in only the hippocampal-dependent versions of the task. In 4-6 months old CA3-APP mice the hippocampal memory deficit was present only in the initial days of testing, and the transgenic mice reached control levels after 5 days of behavioral testing. To understand changes in network function that may underlie these behavioral phenotypes, we recorded local field potentials before, during, and after the CA1-APP and CA3-APP mice and control littermates performed the spatial alternation task. In LFP recordings from CA1, we assessed the abundance and structure of sharp-wave ripple events (SWRs) during rest and behavior. SWRs are high frequency oscillations that are believed to emerge locally in the CA1 region by the interaction of autoassociative CA3 network inputs with interneuron networks. SWRs are believed to support memory consolidation as sequences of cells active in behavior are reactivated during these events. We observed differences in SWR organization with APP over-expression and hypothesized that these changes could serve as a potential mechanism underlying the cognitive impairments observed in CA1-APP and CA3-APP

mice. We also investigated spatial and temporal firing patterns of hippocampal CA1 neurons in order to complete our understanding of the effect of amyloid-beta induced toxicity on hippocampal information processing. Our data indicate that synaptic toxicity induced by Aβ restricted to subpopulations of hippocampal principal cells resulted in substantial hippocampal network dysfunction and in impaired hippocampus-dependent behavior, which raises the possibility that reducing Aβ levels during early phases of the disease could reinstate normal neural circuit function.

Disclosures: **S. Viana Da Silva:** None. **M.G. Haberl:** None. **K. Gaur:** None. **M. Ledakis:** None. **M. Fu:** None. **M. Bry:** None. **J.K. Leutgeb:** None. **E. Koo:** None. **S. Leutgeb:** None.

Poster

254. Learning and Memory: Limbic Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 254.05/TT15

Topic: H.01. Animal Cognition and Behavior

Support: NIH grant R01MH100349

Title: Spatial representations in medial entorhinal cortex remain stable over the course of hours in contrast to hippocampal CA1 and CA2 network ensembles

Authors: *G. W. DIEHL[1], O. J. HON[1], S. LEUTGEB[1,2], J. K. LEUTGEB[1]
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Abstract: Formation of episodic memories relies on successful encoding of the *where*, *what*, and *when* components of an experience by the hippocampus and medial entorhinal cortex (mEC). Recent work has identified systematic changes in hippocampal network activity over time as a likely mechanism for representing the temporal aspects of experience over time scales of minutes to hours (Ezzyat & Davachi, *Neuron*, 2014; Eichenbaum, *Nat Rev Neurosci*, 2014; Nielson et al., *PNAS*, 2015; Hsieh et al., *Neuron*, 2014). Further investigation determined that not all hippocampal subregions represented elapsed time equally. Our laboratory proposed that a time-varying neural code in CA1 emerged from the integration of a stable CA3 representation and a time-varying CA2 representation (Mankin et al., *Neuron*, 2015), highlighting CA2 as a potential key player in the formation of the hippocampal representation of elapsed time. However, mEC superficial layer 3 has also been implicated in memory for temporal associations (Suh et al., *Science, 2011*), raising the possibility that a time-varying signal could be forwarded to CA1, and CA2, directly from mEC. To distinguish between the possibilities that the time-varying signal in CA1 arises directly from mEC, or that it requires the CA2 region, we recorded from principal cells in the superficial layers of mEC and examined how their firing patterns for the same

environment changed over the course of many hours. Rats performed multiple random foraging sessions in an open field, repeatedly returning to the same environment many times over the course of several days. The identity of each cell was tracked across successive sessions to determine how the firing properties of individual mEC cells, systematically changed over time. We found that the firing patterns of grid cells did not change systematically as a function of time when considering both spatial firing location and firing rate. Firing patterns of non-grid cells were also unaffected by elapsed time, exhibiting stability across hours that was comparable to the stability across minutes. Although we did observe significant changes as a function of time for 10-20% of the non-grid cell population, the degree of change was small (< 10 % change after 24 hours) and comparable to network changes observed in CA3, the most stable of the three hippocampal subregions. Thus, mEC firing patterns remained stable over the course of hours, limiting the extent to which mEC may contribute to the time-varying code in CA1 or CA2. Instead, the substantial changes over time observed in hippocampus may emerge as a result of local computations, or in response to inputs from sources other than mEC.

Disclosures: **G.W. Diehl:** None. **O.J. Hon:** None. **S. Leutgeb:** None. **J.K. Leutgeb:** None.

Poster

254. Learning and Memory: Limbic Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 254.06/TT16

Topic: H.01. Animal Cognition and Behavior

Support: NIH T32 AG00216

NIH R01 NS086947

Title: CA3 cells remain informative about the current spatial location in medial entorhinal cortex lesioned rats

Authors: *M. SABARIEGO[1], A. SCHOWALD[1], B. L. BOUBLIL[1], D. T. ZIMMERMAN[1], N. GONZALEZ[1], J. K. LEUTGEB[1], R. E. CLARK[2,3], S. LEUTGEB[1,4]
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Abstract: Spatial memory performance requires information about current and future locations. Recent studies have shown that hippocampal place cells contain information about both of these dimensions. The medial entorhinal cortex (mEC) projects directly to the hippocampus and is thought to be a key source of spatial and temporal information to hippocampal place cells. However, the specific contributions of the mEC to memory performance remain unclear, and we

therefore used mEC-lesioned rats to understand the contribution of mEC to hippocampus-dependent memory and hippocampal physiology. MEC and sham lesioned rats were trained to perform a spatial alternation task in which the animals alternated between left and right sides of a figure-8-maze to receive a food reward. Both groups performed similarly during the trials without delay, but when a delay was imposed, the mEC lesion group made significantly more errors. After further training, the behavioral performance of the mEC lesion group improved for trials with a 10-second delay but showed a long-lasting impairment for trials with delays of 60 seconds. Recordings of hippocampal single units and local field potentials were performed during the spatial alternation task to investigate the circuit dysfunction that underlies the memory impairment as well as to identify which neuronal firing patterns could support the spared memory function in mEC-lesioned rats. CA1 cells in mEC lesioned rats discriminated less well between left and right return arms than control animals. Unexpectedly, CA1 cells of control and lesioned rats distinguished equally well between left and right trajectories on the center stem before the decision point. We therefore examined whether CA3 is a possible source for maintaining separate neural codes for left and right trajectories such that this information could be provided to CA1 on the stem. We found that a subpopulation of CA3 cells in mEC lesioned rats consistently distinguished between right and left sides of the maze. These data indicate that mEC inputs are critical for distinct CA1 neuronal activity patterns on the return arms of the maze, while CA3 inputs more effectively retain differences. By forwarding this information, CA3 inputs could contribute to the reemergence of distinct CA1 firing patterns on the center arm, such that left-turn and right-turn trajectories are successfully distinguished in mEC lesioned rats. Taken together, our results suggest that intrahippocampal processing of inputs from sources other than mEC can support spatial working memory and that spatial computations can thus partially recover in a circuit without mEC projections to the hippocampus.

Disclosures: **M. Sabariego:** None. **A. Schowald:** None. **B.L. Boublil:** None. **D.T. Zimmerman:** None. **N. Gonzalez:** None. **J.K. Leutgeb:** None. **R.E. Clark:** None. **S. Leutgeb:** None.

Poster

254. Learning and Memory: Limbic Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 254.07/TT17

Topic: H.01. Animal Cognition and Behavior

Support: JFDP Fellowship

Title: Ventral CA1 neurons store social memory

Authors: *T. OKUYAMA[1], T. KITAMURA[1], D. S. ROY[1], S. ITOHARA[2], S. TONEGAWA[1]
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Abstract: For social animals, it is crucial to remember and recognize different conspecific individuals (social memory), and exhibit appropriate social behaviors, such as preference behavior or avoidance behavior, to each individual. However, it remains unknown which parts of these brain regions and their circuits hold social memory. In humans, lesion of the hippocampus leads to multiple memory deficits including social memory, suggesting that the hippocampus, at least in part, stores memory information on the individual as well as other components of episodic memory such as spatial or temporal memory. However, in rodents, the literature has not reached a consensus regarding the role of the hippocampus in social memory formation. Some studies using lesion experiments or electrophysiological recording concluded that the hippocampus is dispensable for recognizing a familiar conspecific, whereas other studies suggested the contrary.
Since mice naturally tend to spend more time interacting with novel mice, rather than familiar mice (social discrimination behavior), we can quantify the degree of memory of individuals by calculating the total duration of time spent with novel versus familiar individuals. Using this behavioral assay, we found that ventral hippocampal CA1 (vCA1) neurons of a mouse and their projections to nucleus accumbens (NAc) shell play a necessary and sufficient role in social memory. Both the proportion of activated vCA1 cells and the strength and stability of the responding cells are greater in response to a familiar mouse than to a novel mouse. Optogenetic reactivation of vCA1 neurons that respond to the familiar mouse enabled memory retrieval and the association of these neurons with unconditioned stimuli. Thus, vCA1 neurons and their NAc shell projections are a component of the storage site of social memory. Our research gives us new insights and clues into the neural mechanisms underlying social memory and social familiarity.

Disclosures: **T. Okuyama:** A. Employment/Salary (full or part-time):; JFDP fellowship. **T. Kitamura:** None. **D.S. Roy:** None. **S. Itohara:** None. **S. Tonegawa:** None.

Poster

254. Learning and Memory: Limbic Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 254.08/TT18

Topic: H.01. Animal Cognition and Behavior

Support: RIKEN Brain Science Institute

Howard Hughes Medical Institute

JPB foundation

Title: Basolateral to central amygdala neural circuits for appetitive behaviors

Authors: *X. ZHANG[1], J. KIM[1], S. MURALIDHAR[1], S. LEBANC[1], S. TONEGAWA[2]
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Abstract: Basolateral amygdala (BLA) principle cells are capable of driving and antagonizing behaviors of opposing valence. BLA neurons project to the central amygdala (CeA), which also participates in negative and positive behaviors. However, the CeA has primarily been studied as the site for negative behaviors and the causal role for CeA circuits underlying appetitive behaviors is poorly understood. Here we identified several genetically distinct populations of CeA neurons that mediate appetitive behaviors and dissected the BLA to CeA circuit for appetitive behaviors. The BLA to CeA pathway for promoting appetitive behaviors involves Dopamine Receptor 1^+ ($Drd1^+$) neurons, while the BLA to CeA pathway for suppressing appetitive behaviors involves Dopamine Receptor 2^+ ($Drd2^+$) neurons. These data reveal genetically defined neural circuits in the amygdala that promote and suppress appetitive behaviors are analogous to the direct and indirect pathway of the basal ganglia.

Disclosures: X. Zhang: None. **J. Kim:** None. **S. Muralidhar:** None. **S. LeBanc:** None. **S. Tonegawa:** None.

Poster

254. Learning and Memory: Limbic Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 254.09/TT19

Topic: H.01. Animal Cognition and Behavior

Support: RIKEN Brain Science Institute

Howard Hughes Medical Institute

JPB Foundation

Title: Distinct neural circuits for the formation and retrieval of episodic memories

Authors: *D. ROY[1], T. KITAMURA[2], T. OKUYAMA[3], S. OGAWA-KITAMURA[2], C. SUN[4], Y. OBATA[6], A. YOSHIKI[6], S. TONEGAWA[5]
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Abstract: The formation and retrieval of a memory is thought to be accomplished by activation and reactivation, respectively, of the memory-holding cells (engram cells) by a common set of neural circuits, but this hypothesis has not been established. The medial temporal-lobe system is essential for the formation and retrieval of episodic memory for which individual hippocampal subfields and entorhinal cortex layers contribute by carrying out specific functions. One subfield whose function is poorly known is the subiculum. Here, we show that dorsal subiculum and the circuit, CA1 to dorsal subiculum to medial entorhinal cortex layer 5, plays a crucial role selectively in the retrieval of episodic memories. Conversely, the direct CA1 to medial entorhinal cortex layer 5 circuit is essential specifically for memory formation. Our data suggest that the subiculum-containing detour loop is dedicated to meet the requirements associated with recall such as rapid memory updating and retrieval-driven instinctive fear responses.

Disclosures: D. Roy: None. **T. Kitamura:** None. **T. Okuyama:** None. **S. Ogawa-Kitamura:** None. **C. Sun:** None. **Y. Obata:** None. **A. Yoshiki:** None. **S. Tonegawa:** None.

Poster

254. Learning and Memory: Limbic Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 254.10/TT20

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant MH107970

Whitehall Foundation Grant

Title: Dynamic changes of silent synapses and plasticity in the prefrontal-amygdala synapses: Witnessing others' fear augments plasticity whereas subsequent inhibitory avoidance training abolishes it

Authors: *A. Y. MOROZOV, W. ITO
Virginia Tech. Carilion Res. Inst., Roanoke, VA

Abstract: The observational fear paradigm in mice (OF), in which the subject is briefly exposed to a conspecific receiving electrical footshocks, enhances retention of inhibitory avoidance (IA) learning and causes the formation of silent synapses in the prefrontal-amygdala pathway (1). To better understand the possible role of silent synapses in the enhanced avoidance learning, the dynamics of silent synapses and plasticity of the pathway between the dorsomedial prefrontal cortex (dmPFC) and principal neurons of basolateral amygdala (BLA) was examined *ex vivo* along the behavioral sequence: OF - IA training - IA testing. Channelrhodopsin 2 (ChR2) was expressed in the dmPFC by injecting an AAV-ChR2-Venus vector at p21-25. The animals were subjected to the behavioral training at p70-p90. The amygdala slices, prepared at different time

points along the OF-IA training - IA testing behavioral sequence, were analyzed. To evaluate plasticity, whole cell recording and an LTP protocol based on the spike-timing dependent plasticity rules was employed. The slices from mice 24 h after OF exhibited higher LTP than slices in the control group or slices from mice that underwent OF followed by inhibitory avoidance training 24 h later. To quantify silent synapses, whole cell recordings of synaptic responses elicited by minimal-like stimulation were performed from putative BLA principal neurons held at the membrane potentials of -75 mV and +40 mV. The slices from mice after OF exhibited a higher proportion of silent synapses than slices from control animals, whereas IA training decreased the proportion of silent synapses. The findings suggest that the OF-generated silent synapses enable plasticity in the dmPFC-BLA pathway, which may be responsible for the enhanced IA retention.

1. (2015). Observation of Distressed Conspecific as a Model of Emotional Trauma Generates Silent Synapses in the Prefrontal-Amygdala Pathway and Enhances Fear Learning, but Ketamine Abolishes those Effects Neuropsychopharmacology, 40(11), 2536-2545.

Disclosures: **A.Y. Morozov:** None. **W. Ito:** None.

Poster

254. Learning and Memory: Limbic Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 254.11/TT21

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant MH112093

Title: Suppression of the somatostatin, but not parvalbumin-expressing interneuron allows generating LTP in the prefrontal-amygdala synapses *In vitro* and *In vivo*

Authors: *B. FUSCO[1], ***B. FUSCO**[1], A. Y. MOROZOV[2], W. ITO[2]
[1]Morozov Lab., Virginia Tech. Carilion Sch. of Med., Roanoke, VA; [2]Virginia Tech. Carilion Res. Inst., Roanoke, VA

Abstract: Artificial manipulation of synaptic efficacy in a specific neuronal circuit is the next promising strategy for investigating the causal link between circuits and behaviors. In order to identify generic rules for obtaining LTP/LTD in specific circuits, here, we report development of methodology for LTP induction in the synapses formed by the projections from the dorsomedial prefrontal cortex (dmPFC) to basolateral amygdala (BLA) in mice. Because these synapses are surrounded by the extensive inhibitory network in BLA, it is difficult to induce plastic changes by standard high frequency or theta-burst stimulation of axons. We hypothesized that a temporary interference with the local BLA inhibition by a subset of interneurons would enable LTP induction by the axonal stimulation. To this end, either chemogenetic inhibitor hM4Di or

optogenetic inhibitor ArchT were expressed in one of the two classes of local GABAergic neurons that express parvalbumin (PV-INs) or somatostatin (SOM-INs), and an excitatory opsin with fast kinetics, Chronos, was expressed in the BLA afferents from dmPFC. LTP was measured by recording field EPSP in BLA slice preparation. Both the chemogenetic and optogenetic suppression of SOM-INs enhanced LTP induction by trains of 50 Hz blue light stimulation of the dmPFC axons, whereas suppression of PV-INs attenuated LTP induction. Furthermore, recording of LFP evoked in BLA of free moving mice by stimulation via our disposable miniature LED blue light source showed robust LTP induced by the identical combination of high frequency stimulation and chemogenetic suppression of SOM-INs. These findings reveal distinct roles of PV-INs and SOM-INs in gating amygdala LTP and provide a method for artificial facilitation of the dmPFC-BLA pathway in vivo.

Disclosures: B. Fusco: None. **A.Y. Morozov:** None. **W. Ito:** None.

Poster

254. Learning and Memory: Limbic Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 254.12/TT22

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant MH112093

NIH Grant MH107970

Title: Disposable miniature LED light source for *In vivo* optogenetic stimulation reveals dynamic changes of synaptic transmission *In vivo* in dmPFC-BLA synapses during observational fear and subsequent inhibitory avoidance

Authors: *W. ITO[1], A. MOROZOV[2]
[1]Virginia Tech. Carilion Res. Inst., Roanoke, VA; [2]Virginia Tech. Carilion Res. Inst., roanoke, VA

Abstract: Observational fear paradigm (OF) as a rodent model of emotional trauma is becoming popular. We have found that a single exposure of a subject mouse to the cagemate receiving electrical foot shocks for 4 min (1mA, 1s, x24 shocks) enhances memory retention in a subsequent inhibitory avoidance learning paradigm. We have been investigating the underlying mechanisms by focusing on the properties of synaptic transmission in the dmPFC-BLA circuitry (1, 2). Based on our finding that (1) Gi-DREADD (hM4Di) suppression of glutamatergic transmission in the dmPFC to BLA synapses during the OF paradigm blocks the OF-induced enhancement of inhibitory avoidance retention, and that (2) plasticity in the dmPFC-BLA synapses during the behavioral sequence (OF paradigm, IA training, IA testing) undergoes

dynamic changes detectable ex vivo, we hypothesized that dynamic change of synaptic transmission occurs in the synapses. To test the hypothesis, we recorded directly the dmPFC-BLA synaptic transmission in vivo during the entire behavior sequence. The recording became possible by development of a disposable miniature optogenetic light source, which consists of a miniature blue light LED coupled with a short rod of a high-NA optic fiber (diameter 230 micro meter) by index-matched UV-cured glue and emits maximum 8 mW at the tip of fiber for a few second as maximum duration of pulse. The simple design allowed us to make the miniature LED light sources reliably and with high yield using equipment available in a common biological laboratory. Using the light source bundled with recording wires (tungsten, diameter 30 micro meter), we recorded light-evoked fEPSP from BLA bilaterally in mice expressing ChR2 in dmPFC using 0.5ms light pulses at about 3mW. As we predicted from the ex vivo slice physiology results, the OF paradigm suppressed the dmPFC-BLA synaptic transmission, whereas IA training enhanced it. At the presentation, we will also discuss the details of constructing the disposable light source and sharing one LED-driver among multiple optrodes.

1.Ito, W., Erisir, A., & Morozov, A. (2015). Observation of Distressed Conspecific as a Model of Emotional Trauma Generates Silent Synapses in the Prefrontal-Amygdala Pathway and Enhances Fear Learning, but Ketamine Abolishes those Effects. Neuropsychopharmacology, 40(11), 2536-2545.

2.Liu, L., Ito, W., & Morozov, A. (2017). GABAb Receptor Mediates Opposing Adaptations of GABA Release From Two Types of Prefrontal Interneurons After Observational Fear. Neuropsychopharmacology, 42(6), 1272-1283.

Disclosures: W. Ito: None. **A. Morozov:** None.

Poster

254. Learning and Memory: Limbic Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 254.13/TT23

Topic: B.07. Synaptic Transmission

Support: NIH Grant GM118801

NIH Grand MH095905

Title: Etomidate suppresses LTP in the CA1 region of the hippocampus *In vitro* by targeting α5-$GABA_A$ receptors on interneurons

Authors: *A. G. FIGUEROA[1], G. SURGES[1], D. A. RUHL[2], C. LOR[1], M. PERKINS[1], U. RUDOLPH[3], R. A. PEARCE[1]

[1]Anesthesiol., Univ. of Wisconsin, Madison, WI; [2]Neurosci., Univ. of Wisconsin - Madison, Madison, WI; [3]Lab. of Genet. Neuropharm., McLean Hosp. / Harvard Med. Sch., Belmont, MA

Abstract: Background: Suppression of Long-Term Potentiation (LTP) in the CA1 region of the hippocampus by etomidate (ETOM) is thought to result from drug modulation of $GABA_A$ receptors that incorporate α5-subunits (α5-$GABA_AR$). Our recent finding that enhancement of tonic inhibition (TI) in pyramidal neurons and suppression of LTP can be dissociated indicated that ETOM suppresses LTP through other mechanisms (Zarnowska et al., 2015). Eliminating α5-$GABA_A$Rs only in pyramidal cells did not render mice resistant to etomidate in behavioral studies *in vivo* or LTP *in vitro* (Rodgers et al., 2015), suggesting that ETOM acts on α5-$GABA_A$Rs in non-pyramidal cells to suppress LTP, perhaps by disrupting disinhibitory interneuron circuits. We tested this hypothesis by knocking α5-$GABA_A$Rs out of interneurons.
Methods: Mutant mice were generated by utilizing a conditional knock out strategy involving expression of Cre-recombinase under the control of the GAD65 promoter, resulting in pseudo-wildtype (WT) mice carrying a 'floxed' α5-$GABA_AR$, and GAD-α5-KO mice. We assessed possible expression of Cre-recombinase in astrocytes by crossing tdTomato (GAD) x GFP (GFAP) mice, and examining for colocalization using fluorescent confocal microscopy. We measured LTP of coronal hippocampal slices *in vitro* by stimulating the Schaffer collateral pathway while recording from the *stratum radiatum* of the CA1 region. We used a theta-burst stimulation (TBS) paradigm to induce LTP and recorded EPSPs at a stimulus intensity that produced half the maximum EPSP response for 30 minutes prior to TBS and 60 minutes post-TBS. Slices were treated with control aCSF or 1μM ETOM solution. One-tailed Student's t-tests were performed to compare LTP in groups of 8 brain slices in the presence of absence of ETOM, in WT and GAD-α5-KO mice.
Results: There was no overlap in fluorescence between tdTom (GAD) and GFP (GFAP), indicating little or no expression of Cre-recombinase in astrocytes. There were no differences in LTP under drug-free conditions between WT and GAD-α5-KO mice (38.7% ± 2.5 vs 35.0% ± 5.5; $p > 0.05$). ETOM resulted in suppression of LTP in the WT mice (18.6% ± 6.3; $p = 0.01$), but not in the GAD-α5-KO mice (23.7% ± 6.4; $p > 0.05$).
Conclusions: Our results show that GAD-α5-KO mice are resistant to ETOM suppression of LTP *in vitro*. As the expression of Cre-recombinase in the GAD-Cre mice is limited to interneurons, the finding supports the hypothesis that ETOM targets α5-$GABA_A$Rs on interneurons to suppress LTP.

Disclosures: A.G. Figueroa: None. **G. Surges:** None. **D.A. Ruhl:** None. **C. Lor:** None. **M. Perkins:** None. **U. Rudolph:** None. **R.A. Pearce:** None.

Poster

254. Learning and Memory: Limbic Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 254.14/TT24

Topic: B.07. Synaptic Transmission

Support: NIH Grant GM118801

NIH Grant AA10422

Title: β2(N265M)-GABA$_A$R mice resist suppression of LTP by etomidate *In vitro*

Authors: *G. SURGES[1], A. FIGUEROA[1], C. LOR[1], M. PERKINS[1], N. KUNZ[2], G. E. HOMANICS[2], R. A. PEARCE[1]
[1]Anesthesiol., Univ. of Wisconsin, Madison, WI; [2]Anesthesiol., Univ. Pittsburgh, Pittsburgh, PA

Abstract: Background: Modulation of α5-subunit containing GABA$_A$Rs (α5-GABA$_A$Rs) has been shown to be essential in bringing about the amnestic endpoint of etomidate (ETOM). These subunits preferentially pair with β3 subunits, though α5β2-GABA$_A$Rs do also exist. In previous studies of mice carrying a mutation of the β3-subunit that confers insensitivity to ETOM (β3-N265M), we found that ETOM failed to enhance tonic inhibition (TI) in CA1 pyramidal neurons. Surprisingly, these mice remained susceptible to ETOM-induced suppression of LTP. Here we tested the hypothesis that ETOM suppresses LTP by modulating β2-GABA$_A$Rs.
Methods: We compared LTP in the CA1 region of the hippocampus in 60-80 day old WT mice and mice carrying the N265M point mutation in the β2-subunit of the GABA$_A$R (β2-N265M). LTP was measured by recording field EPSPs in the stratum radiatum *in vitro*, in response to theta-burst stimulation of the Schaffer collateral pathway. We performed one-tailed Student's t-tests to compare LTP in groups of 8 brain slices in the presence or absence of ETOM.
Results: As expected, ETOM (1μM) greatly suppressed LTP in 400μm brain slices of WT mice (CTRL 155±8% vs. ETOM 118±5%, p=.001). However, ETOM failed to suppress LTP in β2-N265M mice (CTRL 154±5% vs. ETOM 148±5%, p=.213). No significant difference between genotypes was observed under drug-free conditions (WT 155±8% vs. β2-N265M 154±5%, p=0.44).
Conclusions: This finding supports the hypothesis that ETOM suppresses LTP by modulating GABA$_A$Rs that incorporate β2-subunits. Since α5-GABA$_A$Rs have also been found to be essential for the amnestic effects of ETOM, this finding implicates α5β2-GABA$_A$Rs as the molecular target for ETOM suppression of LTP in the CA1 region of the hippocampus *in vitro*.

Disclosures: G. Surges: None. **A. Figueroa:** None. **C. Lor:** None. **M. Perkins:** None. **N. Kunz:** None. **G.E. Homanics:** None. **R.A. Pearce:** None.

Poster

254. Learning and Memory: Limbic Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 254.15/TT25

Topic: H.01. Animal Cognition and Behavior

Support: RSCF Grant 14-15-00685

Title: Differential activation of layers and neuronal subtypes of mouse neocortex in fear memory acquisition and retrieval

Authors: *O. I. IVASHKINA[1,2], K. TOROPOVA[1,2], T. KUNITSYNA[1], A. GRUZDEVA[1,2], K. ANOKHIN[1,2,3]
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Abstract: Associative learning is a fundamental mechanism for experience-dependent cortical modification. Though synaptic aspects of this process has been thoroughly studied, less is known about how it is implemented at the level of cortical circuits. Predictive coding theories suggest that classical conditioning leads to formation of cortical representations that differentially affect supragranular (L2/3) and infragranular (L5/6) cortical layers. While deep layers of the sensory cortex mediate top-down predictions from anticipatory model generated by frontal areas, superficial layers convey bottom-up prediction error signals that update prior representation according to sensory input. To study these processes we used auditory fear conditioning and c-Fos neuroimaging of layer-specific activation of different associative (infralimbic, prelimbic, cingular, retrosplenial, frontal associative and parietal associative) and sensory (primary auditory, ventral and dorsal areas of the secondary auditory) cortices after memory acquisition and retrieval in mice. We found that presentation of auditory CS and footshock during training leads to activation of cingulate cortex and the ventral part of secondary auditory cortex. Retrieval of associative memory about CS a day later produces preferential activation of cingulate, prelimbic, infralimbic and parietal associative cortices. This activation was specific in L2/3, L5 and L6 of cingulate cortex and L5 and L6 of prelimbic cortex. Layer-specific analysis of the primary auditory cortex showed that memory acquisition involved proportionally more L2/3 neurons, while CS presentation during retrieval involved proportionally more L5 neurons. Thus, our data suggest that cued conditioning can lead to shift from activation of supragranular layers during acquisition phase to infragranular layers during retrieval phase in the primary auditory cortex and overall preferential activation of associative areas during memory retrieval versus sensory cortex activation during memory acquisition.

Disclosures: O.I. Ivashkina: None. **K. Toropova:** None. **T. Kunitsyna:** None. **A. Gruzdeva:** None. **K. Anokhin:** None.

Poster

254. Learning and Memory: Limbic Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 254.16/TT26

Topic: H.01. Animal Cognition and Behavior

Support: RSCF grant #141500685

Title: Reorganization of memory engram over time: Cortical neuronal activity during fear memory formation and retrieval of recent and remote memory

Authors: *A. GRUZDEVA[1,2], O. IVASHKINA[1,2], K. TOROPOVA[1,2], K. ANOKHIN[1,2,3]
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Abstract: According to the standard model of systems consolidation memories or engrams are initially temporary stored within the hippocampus (recent memory) and, eventually, consolidated within the neocortex for permanent storage (remote memory). However, little is known about cellular mechanisms of reorganization of cortical memory engram over time. To study this issue, we first compared populations of activated neurons in the same area of parietal associative cortex during learning and recent memory retrieval using in vivo two-photon imaging of Fos-EGFP expression in parietal associative cortex of transgenic mice. The largest proportion of neurons, that were not active before learning, but were activated during learning, were also activated during recent memory retrieval (12% of all identified neurons). The small parts of identified neurons were activated only during learning or memory recall (4% or 2% respectively). Thus we found that neurons that were specifically activated during learning were then preferentially reactivated during retrieval of recent memory. We next compared neuronal populations that were active during retrieval of recent memory and remote memory in different brain structures. For this purpose we used transgenic Fos-Cre-tdTomato mice for targeted recombination in active populations (TRAP) to capture neurons that were active during recent memory recall and identified neurons that were active during remote memory recall with c-Fos immunohistochemical staining. Our results suggest preferential stability of neuronal engram population during retrieval of the recent memory.

Disclosures: A. Gruzdeva: None. **O. Ivashkina:** None. **K. Toropova:** None. **K. Anokhin:** None.

Poster

254. Learning and Memory: Limbic Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 254.17/TT27

Topic: H.01. Animal Cognition and Behavior

Support: RSCF Grant 14-15-00685

Title: Conditioning of contextual memory: Properties and imaging of neural circuitry in the mouse brain

Authors: *N. VOROBYEVA[1,2], O. IVASHKINA[1,3], K. TOROPOVA[1,3], K. ANOKHIN[1,2,3]
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Abstract: The ability to form associations is a fundamental feature of higher brain functions. Here we used a paradigm of preexposure facilitation effect (Fanselow, 1990; Rudy and O'Reilly 2001) to explore associability of an engram of a distant past event to a footshock in mice - specificity of such associative memory, its ongevity and neural circuits activated at its retrieval. Mice were first allowed to explore a new context A for 5 min and then at different delays (from 30 minutes to 30 days) received a 2 sec immediate footshock after being repeatedly placed in this context. We showed that the contextual engram in mice can be fear conditioned in all tested intervals. This association persisted for at least 30 days following such engram conditioning. The fear for the context A was specific, there was no freezing if immediate footshock was delivered in a context B or in a novel context C. Next, we used c-Fos mapping to reveal patterns of brain activity during conditioned engram retrieval. For this purpose we compared c-Fos expression induced by exploration of context A in mice from the conditioned and unconditioned groups. All groups explored the context 6 days before being tested, but the conditioned group also received immediate footshock in this context 3 days before the test. Expression of c-Fos was significantly elevated in the conditioned engram group in the areas of associative neocortex (frontal associative cortex, prelimbic and infralimbic cortex, cingular, retrosplenial and parietal cortex), in central and lateral amygdala and in CA1 area of hippocampus. Interestingly, dentate gyrus and CA3 had similar c-Fos activation in all engram groups. We also show that such conditioned contextual engram engages mainly pyramidal neurons (*EMX1+*), rather than interneurons (*GAD+*) at the time of its subsequent retrieval. At the next step, we performed *c*-Fos TRAP imaging (Guenthner et al., 2013) combined with c-Fos immunohistochemical staining in transgenic *Fos-Cre-tdTomato* mice to reveal overlap in cellular populations activated during context engram acquisition and its conditioning in the same animals. Our results suggest that the overlap of populations activated by conditioned and unconditioned stimuli in the the areas of associative neocortex (frontal associative cortex, prelimbic and infralimbic cortex, cingular, retrosplenial and parietal cortex), amydgala, and regions of hippocampus (CA1, CA3 and dentate gyrus).

Disclosures: N. Vorobyeva: None. **O. Ivashkina:** None. **K. Toropova:** None. **K. Anokhin:** None.

Poster

254. Learning and Memory: Limbic Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 254.18/TT28

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant F32MH090671

Title: Hippocampal phase precession results from cholinergic gating of entorhinal input

Authors: *S. C. VENDITTO[1,2], E. L. NEWMAN[2]
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Abstract: An important, unanswered question is how new memories are formed and stabilized in behaving animals. The hippocampal and parahippocampal circuits are recognized to be key contributors to memory formation. Within the hippocampus, temporally structured activity of individual cells, in the form of phase precession with respect to the local theta rhythm, is thought to play a critical role in converting neural activity into memories (O'Keefe & Recce, 1993; Mehta et al., 2002). Phase precession in CA1 neurons is likely the result of a shift from entorhinal drive to CA3 drive as animals move through a cell's firing field (Fernández-Ruiz et al., 2017). The mechanism that drives this shift remains unknown. Here, we test the hypothesis that cholinergic modulation serves to gate processing of entorhinal inputs by CA1 neurons in behaving animals. Our rationale for this hypothesis was our recent finding that cholinergic antagonism reduces phase precession in CA1 neurons (Newman et al., *under review*). We rationalized that the observed reduction to phase precession could have been the result of cholinergic antagonism reducing the excitatory drive from entorhinal cortex, leaving CA3 as the predominant driver of CA1. We refer to this as the cholinergic gating hypothesis. However, it is also possible that the cholinergic antagonist generally disrupted the temporal coding dynamics, causing a breakdown of the structured activity of the hippocampal ensemble. We refer to this as the degenerate ensemble hypothesis. To test between these hypotheses, we applied Bayesian reconstruction analysis the ensembles dynamics of CA1 neurons recorded before, during, and following the influence of the muscarinic acetylcholine receptor antagonist scopolamine to assess the effect on the quality and content of the decoded trajectories. Reduced decodability of the ensemble dynamics would support the *degenerate ensemble hypothesis*. Preserved decodability but reduced 'look-ahead', previously shown to occur during epochs of high entorhinal input, during each theta cycle would support the *cholinergic gating hypothesis*. The analysis found no significant change in the quality of ensemble coding but revealed a significant reduction in the amount of 'look-ahead'. That is, prior to the influence of scopolamine, the trajectories started near the animal and swept forward within each theta cycle. Under the

influence of scopolamine, however, the trajectories remained largely centered on the animal throughout the theta cycle, failing to sweep forward. These results provide clear support for the hypothesis that acetylcholine serves to gate entorhinal processing.

Disclosures: S.C. Venditto: None. **E.L. Newman:** None.

Poster

254. Learning and Memory: Limbic Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 254.19/TT29

Topic: H.01. Animal Cognition and Behavior

Title: Hippocampus required for retrieval practice induced memory improvements in rats

Authors: *D. M. LAYFIELD, N. P. SIDELL, A. T. ABDULLAHI, E. L. NEWMAN
Indiana Univ., Bloomington, IN

Abstract: The act of retrieving a memory benefits the long-term stability of that memory trace, this is known as the retrieval practice effect. Empirical investigations into the retrieval practice effect have focused largely on the phenomenology through study of human subjects (e.g., Karpicke & Roedgier, 2008). The basic neurobiological mechanisms underlying the retrieval practice effect, however, remain unknown. A foundational question in this regard is whether the hippocampus, putative home of newly formed memory traces, is required for the generation of this effect. To address this open question, we used a rodent variant of the retrieval practice paradigm (Crystal et al., 2013) to ask if hippocampal inactivation during retrieval practice reduces the stabilization of the target memory. Procedurally, rats were trained to visit all arms of a radial 8-arm maze each day over the course of two trials. In the first trial (i.e., study trial), only four arms were open. In the second trial (i.e., test trial), run one hour later, the rat was challenged to remember which four arms they had not yet visited when all arms were opened. Retrieval practice was implemented by placing the animals onto the maze with all arms closed for one minute shortly after the study trial. Behavioral performance on the test trial was compared in a 2x2 design: with or without retrieval practice; and with or without hippocampal inactivation. Inactivation was done with bilateral lidocaine infusions into the dorsal hippocampus (dHPC), timed so that the dHPC could be expected to be inactivated throughout the retrieval practice epoch but not during the test trial. When we analyzed the behavioral data, we found that retrieval practice improved performance at test when no activation was performed, replicating the rodent form of the retrieval practice effect. With dHPC inactivation, however, we observed a significant reduction in test performance. From these results, we conclude that the dHPC is required to reap the long-term benefits from retrieval practice.

Disclosures: **D.M. Layfield:** None. **N.P. Sidell:** None. **A.T. Abdullahi:** None. **E.L. Newman:** None.

Poster

254. Learning and Memory: Limbic Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 254.20/TT30

Topic: H.01. Animal Cognition and Behavior

Title: Neural computation by strong connections in cortical networks

Authors: *S. P. FABER[1], N. M. TIMME[2], J. M. BEGGS[1], E. L. NEWMAN[1]
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Abstract: How do networks of neurons process information? Connectomic studies suggest that information processing is distributed non-uniformly at both the whole-brain and circuit levels. However, little is known about how information processing varies with network topology. The goal of the current study was to test if neural computation has a predictable relationship between each of two specific topological network features: connection strength and rich clubs (sets of highly interconnected hubs). To do this, we analyzed spiking activity, recorded using a high-density 512-microelectrode array, of spontaneously active organotypic cultures of mouse somatosensory cortex. Spike trains of well-isolated units (98 - 594 cells per recording) were analyzed to identify connected pairs of neurons (i.e., those with significant transfer entropy in the 1.6 - 14 ms range). From these pairs, we constructed weighted, directed networks wherein nodes corresponded to spiking neurons and edges (connections between nodes) corresponded to directed information flows between neurons. Within these networks we identified triads, sets of three neurons, where the output of two neurons converged on a third neuron. For each triad, we used the Partial Information Decomposition, a tool from information theory, to quantify neural computation within that triad. To test whether neural computation is predicted by connection strength, we computed the correlation between the two. This revealed a strong, positive correlation between the connection strength and the amount of computation. That is, more converging information leads to increased neural computation within a triad. Given that stronger connections are more likely to exist in rich clubs, sets of neurons with many strong connections who also connect to each other, one would expect that rich clubs would be likely to perform increased levels of neural computation. To test this, we explored the relationship between computation and rich clubs. We found that computation occurred in rich clubs more than expected by chance. These findings inform our understanding of how network topology shapes neural information processing. We discuss these results in the context of learning and memory by considering how experience-dependent weight changes may alter neural computation.

Disclosures: **S.P. Faber:** None. **N.M. Timme:** None. **J.M. Beggs:** None. **E.L. Newman:** None.

Poster

254. Learning and Memory: Limbic Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 254.21/TT31

Topic: H.01. Animal Cognition and Behavior

Support: NSF IOS:1558121

Title: Trial restricted silencing of ventral hippocampal communication with the amygdala during the formation of a trace fear memory

Authors: *M. HERBST[1], R. C. TWINING[2], M. R. GILMARTIN[3]
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Abstract: The association of a neutral conditional stimulus (CS) and aversive footshock unconditional stimulus (UCS) in fear conditioning critically depends on the amygdala. However, if the CS and UCS are separated by several seconds, additional brain areas are needed, including the prelimbic cortex and the ventral hippocampus (VH). We have identified a putative role for the prelimbic cortex in providing sustained firing during the CS-UCS interval (Gilmartin & McEchron, 2005; Gilmartin et al., 2013); however, the contribution of the VH to memory formation is not clear. Given the importance of hippocampal networks in spatial and temporal encoding, it is possible that the ventral hippocampus provides a temporal context to the amygdala to promote the association of the cue and shock across time. If so, VH-BLA communication at the time of training will be necessary for the acquisition of trace fear conditioning. To test this, we selectively silenced VH inputs to the basolateral amygdala (BLA) in rats using projection-targeting optogenetics. Specifically, the VH-BLA connection was silenced during each of six paired trials by delivering laser light to ArchT-expressing terminals in the BLA 8 weeks after virus injection into the VH. Light was delivered 1s prior to CS onset to 1s following UCS offset in ArchT rats (n=10) or GFP control rats (n=10). All animals were tested for cued and contextual fear memory the following day in the absence of laser stimulation. Initial results suggest that VH inputs to the BLA during paired stimulus presentations are not necessary for the acquisition of cued or contextual fear. Follow-up chemogenetic experiments will test the alternative hypothesis that VH-BLA communication is necessary for the consolidation of trace fear memory.

Disclosures: **M. Herbst:** None. **R.C. Twining:** None. **M.R. Gilmartin:** None.

Poster

254. Learning and Memory: Limbic Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 254.22/TT32

Topic: H.01. Animal Cognition and Behavior

Support: Whitehall Foundation 2014-08-67

Title: Selective silencing of inputs to prefrontal cortex alter cortical encoding of trace fear memory

Authors: *R. C. TWINING[1], M. HERBST[2], D. DURIGAN[1], K. LEPAK[1], M. R. GILMARTIN[3]
[2]Neurosci. -Biomedical sciences, [3]Biomed. Sci., [1]Marquette Univ., Milwaukee, WI

Abstract: Trace fear conditioning (TFC) requires a neural network that is distinct from standard delay fear conditioning. In delay conditioning, an auditory conditional stimulus (CS) co-terminates with a shock unconditional stimulus (UCS). This association is largely supported by converging auditory and somatosensory input in the amygdala. Trace conditioning differs from delay conditioning in that the CS and the shock are separated by a temporal gap. We have shown that imposing this temporal complexity renders the acquisition of associative fear dependent on both the hippocampus and the prefrontal cortex. In addition, we described a subset of neurons in the prelimbic (PL) area of the prefrontal cortex that exhibit sustained increases in learning-related neuronal spiking that bridges the empty trace interval, reminiscent of a working memory buffer. Indeed, we optogenetically silenced neuronal activity in the PL cortex specifically during the trace interval and blocked the formation of a trace fear memory. What remains unknown, however, is which subcortical inputs to the PL cortex are necessary to support TFC, when precisely they are important, and to what extent these inputs control learning-related neuronal spiking. Here we recorded single unit activity in awake-behaving rats in both the prelimbic and infralimbic cortex and optogenetically silenced afferent input to the PL cortex during TFC. Results indicate that phasic, learning related bridging activity manifests as either sustained increases (20-30%) or decreases (17-22%) in neuronal spiking and occurs with greater frequency during training trials relative to probe (no US) trials (33% vs 22%). Moreover, sustained excitations are increased 2-fold when silencing ventral hippocampal input to the PL cortex during the cue and trace period (65%). This finding suggests that the VH may exert a net inhibitory influence on bridging activity in the PL cortex during TFC and, thus, its removal may enhance TFC or, alternatively, modulate attention to available cues leading to reductions in memory accuracy and enhanced negative affect in anticipation of environmental threat. Experiments are underway to determine the extent to which bridging activity and fear learning are modulated by brief optogenetic silencing of this pathway during weak training and during

longer trace intervals. Moreover, ongoing studies will determine the extent to which selective chemogenetic silencing of VH inputs to PL for longer durations can control the prelimbic encoding of a trace fear memory as well as the behavioral specificity, persistence, and magnitude of cue-evoked fear.

Disclosures: R.C. Twining: None. **M. Herbst:** None. **D. Durigan:** None. **K. Lepak:** None. **M.R. Gilmartin:** None.

Poster

254. Learning and Memory: Limbic Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 254.23/TT33

Topic: H.01. Animal Cognition and Behavior

Support: Whitehall Foundation Research Grant 2014-08-67

National Science Foundation IOS:1558121

Title: Prefrontal cortex communication with the basolateral amygdala in the formation of a trace fear memory

Authors: *A. J. KIRRY, A. ROTHWELL, H. GAINER, R. C. TWINING, M. R. GILMARTIN
Biomed. Sci., Marquette Univ., Milwaukee, WI

Abstract: The association of a neutral conditional stimulus (CS) and aversive footshock unconditional stimulus (UCS) in fear conditioning critically depends on the amygdala. However, if the CS and UCS are separated by several seconds as in trace fear conditioning, additional brain areas are needed, including the prelimbic area (PL) of the medial prefrontal cortex. A subset of PL cells exhibit sustained firing in response to a CS that persists until UCS delivery, and this trace interval activity is required for memory formation (Gilmartin & McEchron, 2005; Gilmartin et al., 2013). While this suggests that the PL may provide a bridging signal to link the CS and UCS in memory, it is unclear how and when the PL must communicate with the amygdala for learning to occur. Here we selectively manipulated PL inputs to the amygdala using projection-targeting optogenetics during training. The PL-BLA connection was silenced during the trace interval by delivering laser light to PL ArchT-expressing terminals in the BLA on each of six training trials. ArchT and GFP controls (n = 5/group) were tested for memory retention the following day in the absence of laser stimulation. In a separate study, we activated this PL-BLA pathway during training by stimulating PL ChR2-expressing terminals in the BLA (n = 8/group). Neither manipulation affected the formation of a trace fear memory, but stimulating this pathway enhanced the expression of a previously acquired fear memory. These results suggest that direct input to the BLA from the PL is not a means by which prefrontal firing

promotes learning across time. Additional support for this conclusion comes from a separate experiment in which we inhibited firing in PL cell bodies during the trace interval and quantified changes in Arc expression in the BLA. While PL silencing disrupted associative learning, it did not reduce learning-related Arc protein in the BLA. These findings do not rule out the possibility that BLA activity is upstream of the PL bridging signal. Indeed, the BLA can modulate post-conditioning CS responses or signal an unexpected UCS in the prefrontal cortex (Sotres-Bayon et al., 2012; Klavir et al., 2013, 2017). Our follow-up experiments are testing whether direct BLA to PL communication is necessary for trace fear memory formation.

Disclosures: A.J. Kirry: None. **A. Rothwell:** None. **H. Gainer:** None. **R.C. Twining:** None. **M.R. Gilmartin:** None.

Poster

254. Learning and Memory: Limbic Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 254.24/TT34

Topic: H.01. Animal Cognition and Behavior

Support: Grants-in-Aid for Science Research on Innovative Areas (25119004; 26250003)

Title: Random activation of a small population of CA1 neurons disrupts memory retrieval

Authors: *S. IWASAKI, Y. IKEGAYA
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Abstract: Memory retrieval requires reactivation of specific memory encoding cells, and higher reactivation of these neurons is linked to stronger memory retrieval. On the other hand, inadvertent activation of cells that are dispensable for memory retrieval may act as disturbing noise against memory retrieval. No studies, however, demonstrate that noisy activity inhibits memory retrieval. In this study, we report that sparse activation of a randomly selected subset of CA1 neurons disrupts memory retrieval. We injected a mixture of AAV-CaMKIIα-Cre and AAV-EF1α-DIO-ChR2 unilaterally into the mouse hippocampal CA1 region and introduced ChR2 into a small subset of cells. *In situ* hybridization elucidated that less than 5% of cells in the CA1 pyramidal cell layer co-expressed *ChR2* and *Arc*, an immediate early gene, after optical stimulation, indicating that we succeeded in optically manipulating the activity of a sparse cell population. When this cell subset was optically stimulated during contextual fear memory retrieval, the freezing score decreased. Optical stimulation *per se* did not affect the locomotor activity. *Arc* catFISH (cellular compartment analysis of temporal activity by fluorescence *in situ* hybridization) showed that optical stimulation alters neural activity that is essential for memory retrieval. These results indicate that sparse activation of randomly selected neurons was

sufficient to disrupt memory retrieval via inhibition of specific neural activity. The data are the first to show that noise-like activity indeed disrupts memory retrieval.

Disclosures: S. Iwasaki: None. **Y. Ikegaya:** None.

Poster

254. Learning and Memory: Limbic Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 254.25/TT35

Topic: H.01. Animal Cognition and Behavior

Support: NIMH Intramural Research Program (ZIAMH002887)

Title: Amygdala lesions do not disrupt familiarity memory in monkeys

Authors: *B. M. BASILE, C. L. KARASKIEWICZ, D. R. LUCAS, E. A. MURRAY
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Abstract: Dual-process accounts of item recognition posit two memory processes: slow but detailed recollection, and quick but vague familiarity. It has been proposed, based on prior rodent work, that the amygdala is critical for the familiarity aspect of item recognition. Here, we evaluated this proposal in rhesus monkeys (*Macaca mulatta*) with selective bilateral excitotoxic amygdala damage. We used a variety of visual memory tests designed to assess different aspects of familiarity, all administered on touchscreen computers. Specifically, we assessed monkeys' tendencies to make low-latency false alarms, to make false alarms to recently-seen lures, to produce curvilinear ROC curves, and to discriminate stimuli based on repetition across days. Across these metrics, monkeys with selective amygdala damage performed like unoperated control monkeys. However, amygdala damage did produce an anticipated deficit in rapid stimulus-reward learning in a three-arm-bandit gambling task, verifying the effectiveness of the lesions. Together, these results contradict prior rodent work and suggest that the amygdala is not critical for the familiarity aspect of item recognition.

Disclosures: B.M. Basile: None. **C.L. Karaskiewicz:** None. **D.R. Lucas:** None. **E.A. Murray:** None.

Poster

254. Learning and Memory: Limbic Circuits

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 254.26/TT36

Topic: H.01. Animal Cognition and Behavior

Support: MOST Grant 2012YQ03026007

NSFC Grant 91632103

Title: Fear extinction regulated by GABAergic interneurons in basolateral amygdala

Authors: *X. ZHANG[1], Y. ZHOU[2], W. LI[1]
[1]Shanghai Jiao Tong Univ., Shanghai City, China; [2]Bio-X Institutes,Shanghai Jiao Tong Univ., Shanghai, China

Abstract: Learning to contend with threats in the environment is essential for survival, but dysregulation of memories for traumatic events can lead to disabling psychopathology, for instance the depression and post-traumatic stress disorder (PTSD). How to forget these negative emotional memory is the key point for the treatment of these two kinds of diseases? Previous studies have found that the GABAergic interneurons in BLA (Basolateral amygdala) play key roles in fear extinction. However, mechanism of fear extinction has not involved in regulating animal behavior level, and there is no more direct evidence showing the role of interneurons. So our team successfully constructed ArcCreERT2, c - FosCreERT2 and GAD67CreERT2 transgenic mice, which can be crossbreed with R26RSTOP-floxed-tdTomato mice to mark various types of neural circuits activated by negative emotions extinction such as fear memory. Our double transgenic mice successfully labeled the neurons activated during fear extinction. We found that freeing time percent increased in the test period after extinction while we chemically inhibited these neurons. The results suggest that inhibition of the neurons responsible for extinction block the forgetting of aversive memories, indicate the key role GABAergic neurons in fear extinction.

Disclosures: X. Zhang: None. **Y. Zhou:** None. **W. Li:** None.

Poster

255. Cognitive Control in a Clinical Population

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 255.01/TT37

Topic: H.02. Human Cognition and Behavior

Support: PepsiCo, Inc

Title: Water intake improves working memory and executive function in women

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Abstract: Water is a vital nutrient. Cognitive function is impaired after 2% body water (BW) loss, but some research suggests impairments at ~1% to executive function. The purpose of this study was to determine the impact of daily insensible water loss on executive function in women. We hypothesized that 1) women lose $\geq$ 1.0% BW during daily activities, and 2) that insensible water loss impairs memory and executive function in healthy women [n= 12, 26 (5) yrs, 22.5 (2.6) kg/m^2 BMI, follicular phase]. The study took place over four session days; the first was a control (CON) session, during which the subject monitored her food and fluid intake (diary) and activity (Fitbit®). The next two sessions were applied in random order: a dehydration (DEH) session, where subjects minimized drinking (500ml/day), and the third was a euhydration (EUH) session, where subjects drank recommended fluid intake (~ 2500 ml/day). We compared mood, emotion (Visual Analog Scales, VAS), sensory perception (VAS) and cognition tests using computer based cognitive tasks (Cogstate) at 5 PM on the day prior to the session, at 7AM, 12 PM, and 5 PM on the session day. Water manipulations did not impact reported food or caloric intake. Cumulative fluid intake independent of what we controlled was also similar across sessions, as was physical activity. Further, body weight changes during CON was similar to EUH, indicating little insensible water loss during the CON session. Tests that measured attention and pattern recognition (Detection, Identification, One-Card Learning) were unaffected by water challenges, but executive function (Groton Maze Learning Test) varied according to test condition. There were the least errors with EUH; total errors: CON 40.1 (11.1), DEH 40.5 (10.1), EUH 33.9 (10.9), $P< 0.05$. Another test of executive function [Set Shifting (SETS)] also improved under EUH condition; total errors: baseline 22.6 (13.2) vs. final 18.8 (6.16)], $P< 0.05$, and DEH impaired executive function [SETS: CON 20.5 (13.2)] vs. DEH 24.6 (15.2) total errors]. There were no changes in mood or emotion across sessions, so improvement in cognition was independent of changes in mood (VAS). Our data do not support significant insensible water loss during daily activities as indicated by urine osmolality, but suggest that water intake can improve visual and working memory and executive function in young, healthy women. Future studies should examine mechanisms for these findings, and whether these findings apply to other cohorts.

Disclosures: **N. Stachenfeld:** 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.; PepsiCo. **S. Mitchell:** A. Employment/Salary (full or part-time):; PepsiCo, Inc. **E. Freese:** A.

Employment/Salary (full or part-time):; PepsiCo, Inc. **C. Leone:** None. **L. Harkness:** A. Employment/Salary (full or part-time):; PepsiCo, Inc.

Poster

255. Cognitive Control in a Clinical Population

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 255.02/TT38

Topic: H.02. Human Cognition and Behavior

Support: Canadian Institutes for Health Research

Natural Sciences and Engineering Research Council of Canada

Title: Hemispheric asymmetry of reward activity in obesity

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Abstract: Hemispheric asymmetry plays an important role in various cognitive functions, for example, left dominance for language processing and right dominance for spatial attention. Such an asymmetric effect has been reported within dopamine systems. For instance, researchers found that asymmetric D2 receptor availability in ventral striatum was associated with incentive motivation (Tomer et al., 2008) and right dominant dopamine release after receiving monetary awards (Martin-Soelch et al., 2011). An asymmetric effect of striatal activity was also reported in fMRI tasks, which was related to bias in approach–avoidance learning rate (Aberg et al., 2015), spatial attention to reward (Aberg et al., 2016a), even creativity and associative processing (Aberg et al., 2016b). We sought to explore hemispheric asymmetry in terms of BOLD activity and functional connectivity in obesity. In total, 360 participants were selected from the Human Connectome Project (Van Essen et al., 2013), separated into an “obese” group (n=180, BMI>30), and a “lean” group (n=180, 20<BMI<25). To control for the effect of impulsivity, the two groups were matched for delay-discounting rate and inhibitory control measures. The event-related gambling task fMRI paradigm was chosen to investigate brain response to monetary gains vs losses. Overlapping brain activation was detected between groups, including ventral tegmental area (VTA), striatum, thalamus, insula and anterior cingulate cortex (ACC). Among them, an asymmetry effect was observed in VTA and ACC, which was additionally modulated by decisional impulsivity. Specifically, obese subjects showed significantly higher BOLD activity in left than right VTA, but the opposite effect in left vs right ACC. The asymmetry index, i.e. difference in BOLD response to gains vs losses between brain areas in the two hemispheres, was significantly correlated with delay-discounting in both VTA (r= -0.1677, p=0.02) and ACC (r= 0.1927, p=0.01). Moreover, BMI was significantly related to the BOLD asymmetry in VTA

among all subjects (N=360, r= 0.1658, p=0.0017), and in both VTA (N=170, r= 0.3191, p<0.0001) and ACC (N=170, r= -0.2286, p=0.0027) among impulsive subjects. The functional connectivity between the two areas was estimated by using generalized psychophysiological interaction analysis (gPPI) (McLaren et al., 2012). This was also a predictor of BMI among impulsive subjects (N=170, r= -0.2155, p=0.0049). Our findings suggest that functional hemispheric asymmetry is an indicator of obesity specifically among impulsive subjects, and that top-down modulation from anterior cingulate cortex might play a role in obesity and impulsivity.

Disclosures: **Y. Zhang:** A. Employment/Salary (full or part-time):; Montreal Neurological Institute, McGill University. **A. Michaud:** A. Employment/Salary (full or part-time):; Montreal Neurological Institute, McGill University. **K. Larcher:** A. Employment/Salary (full or part-time):; Montreal Neurological Institute, McGill University. **A. Dagher:** 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.; Montreal Neurological Institute, McGill University.

Poster

255. Cognitive Control in a Clinical Population

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 255.03/TT39

Topic: H.02. Human Cognition and Behavior

Support: CONACYT (251309)

PAPIIT (IN204613)

CONACYT(BECARIO: 622343)

Title: Arithmetic verification processing in children with dyscalculia

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Abstract: Dyscalculia (DYS) is a learning disorder that affects the ability to learn math. Among 5%-15% school-age children across different languages and cultures have DYS. We compared the arithmetic verification processing between two groups of children of 8-10 years old, one with dyscalculia (DYS, n = 30) and another with normal academic performance (NAP, n = 20). All children were right-handed, without neurological or psychiatric alterations. We recorded Event-Related Potentials (ERP) during a sum verification task. Each trial corresponds to one-digit sum followed by a correct or incorrect probe. ERP were obtained time-locked to onset of the probe

(1000ms). In the 280-360ms window a N400-arithmetic effect (higher amplitudes to incorrect-probes than correct-probes) was observed in both groups: DYS presented a slightly more distributed topography than the NAP; at 360-440ms this effect was observed only in DYS. In the 440-540ms window NAP presented a P600-effect (higher amplitudes to incorrect-probes than correct-probes) with disseminated topography; at 550-700ms the NAP continued to show the effect at center-parietal-temporal distribution, whereas the DYS had a wide distribution. There were no differences between groups in reaction times, although the response time was higher for incorrect-probes. The percentage of right answers was higher in NAP compared to DYS, without difference between conditions. The results suggest that the N400-arithmetic effect, associated to arithmetic fact-retrieval was less focused and had longer duration in DYS than in NAP, probably because children with dyscalculia require more cognitive effort and because the fact-retrieval strategy in the long-memory is less strengthened. The P600 effect, associated to a re-evaluation process of the itself response is delayed and more distributed in DYS, suggesting a lower specialization and maturation of this process. Acknowledgments: PAPIIT- (IN204613), CONACYT- (251309), Milene Roca, Elena Juárez, Héctor Belmont.

Disclosures: C.S. Sonia Yanin: None. **T. Fernandez harmony:** None. **J. Silva pereyra:** None. **D. Prieto corona:** None. **S. Cárdenas Sánchez:** None.

Poster

255. Cognitive Control in a Clinical Population

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 255.04/TT40

Topic: H.02. Human Cognition and Behavior

Title: TMS evoked potential over the right prefrontal cortex and response inhibition ERP provide a biomarker for ADHD

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Abstract: Background: Attention-deficit-hyperactivity-disorder (ADHD) is partly characterized by impaired inhibitory control that manifests behaviorally and as a weaker right prefrontal cortex event related potential (ERP) signal during inhibitory control tasks. We ask whether the weaker ERP signal is associated with right prefrontal aberrant excitability as induced by Transcranial Magnetic Stimulation (TMS).
Methods: Neural activity of 49 healthy and 52 ADHD adults was recorded using Electroencephalography (EEG) during 2 experimental protocols: (1) a session of TMS over the right prefrontal cortex, and (2) while performing a Stop Signal task. ADHD severity was measured by standardized psychiatric assessment.

Results: ADHD subjects displayed significantly reduced amplitudes of P30 component of TMS-evoked potential (TEP) as well as N2 and P3 ERP components in the Stop Signal task than that of matched controls. Interestingly, the TEP P180 amplitude in ADHD was significantly higher than that of matched controls. Significant correlations were found between these components and ADHD severity.
Conclusion: Electrophysiological and TEP related abnormalities are evident in ADHD subjects. These findings further implicate the right PFC in the pathophysiology of ADHD.

Disclosures: I. Hadas: None. **A. Lazerovitz:** None. **U. Alyagon:** None. **A. Zangen:** None.

Poster

255. Cognitive Control in a Clinical Population

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 255.05/TT41

Topic: H.02. Human Cognition and Behavior

Support: CONACYT,CB-2012#178811

Title: Oculomotor inhibition in psychostimulant dependents and its relationship with ADHD-like behaviors on childhood

Authors: *E. J. NUNEZ MEJIA[1], O. INOZEMTSEVA[2], J. JUAREZ[3], E. MATUTE VILLASEÑOR[4], Y. CHAMORRO[5]
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Abstract: The inhibitory control is a cognitive process involved in the regulation of behavior. It has been reported that deficits in this process are related with substances dependence, specifically psychostimulants, and at the same time, with other disorders such as ADHD. Some studies report that the presence of ADHD symptoms on childhood may be a risk factor for the consumption of drugs. The oculomotor inhibitory control is a type of inhibitory control related to the same brain areas where the psychostimulants take place of action in the central nervous system (predominantly prefrontal cortex and basal ganglia) and these regions are compromised in people with ADHD. In addition, oculomotor tasks have been considered as a sensitive tool to assess inhibitory control alterations since it is not affected by other cognitive processes. Therefore, the aim of the study was to establish the relationship between oculomotor measures and the presence of ADHD behavioral symptoms on childhood in a group of psychostimulant dependents. We assessed a group of 39 psychostimulant dependents (PDG) and a control group (CG) (n=22) with a pro-saccade and an anti-saccade task under the overlap and gap conditions.

All participants answered the Wender UTAH scale for detecting ADHD-like behaviors on childhood. The results revealed that PDG presented significantly higher scores in Wender UTAH scale than CG. Moreover, PDG vs. CG displayed significantly higher error rates under the pro- and anti- gap conditions; higher rates of express saccades under the pro- and anti- overlap conditions, and anticipatory saccades rates under all of the conditions. There were no correlations between ADHD behaviors scores and the execution of oculomotor inhibition tasks. The results point out that the deficit on inhibitory control in psychostimulant users is associated to alterations in the oculomotor inhibitory system given by toxic effect of drugs on the brain structures involved in the inhibitory control and it is not directly related to antecedents of neurodevelopment problems as reported before.

Disclosures: E.J. Nunez Mejia: None. **O. Inozemtseva:** None. **J. Juarez:** None. **E. Matute Villaseñor:** None. **Y. Chamorro:** None.

Poster

255. Cognitive Control in a Clinical Population

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 255.06/TT42

Topic: H.02. Human Cognition and Behavior

Title: Frontal lobe oxyhemoglobin levels in patients with depressive disorder and healthy controls during cognitive tasks assessed using the NIRSIT functional near-infrared spectroscopy (fNIRS) device

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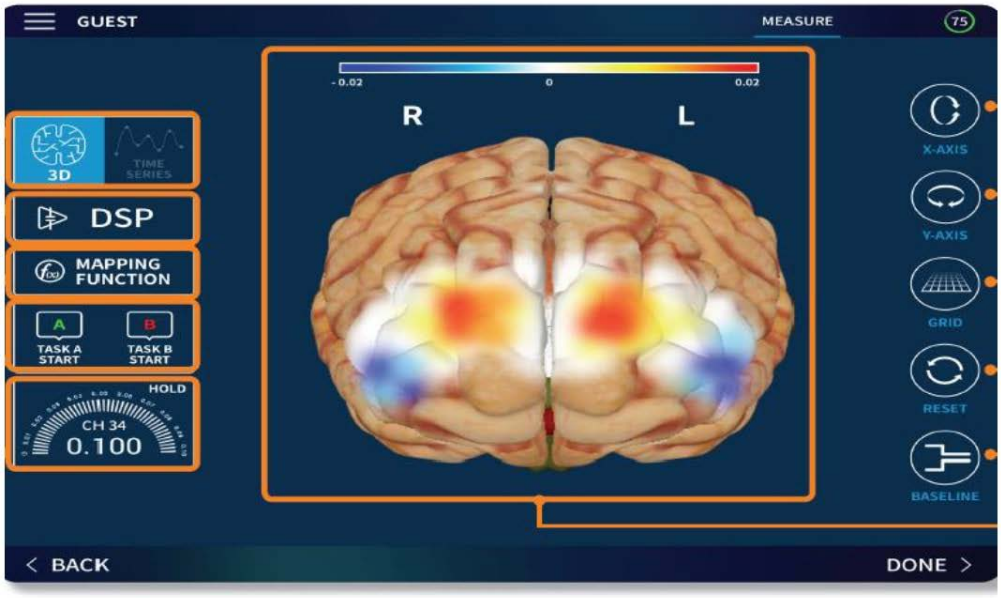
Abstract: Introduction: Neuropsychiatric illnesses contribute to significant health burden but there is no portable neuroimaging device for diagnostic use and clinical monitoring. The most widely used neuroimaging modality is functional magnetic resonance imaging, noted for its difficulty-of-use and high cost. Functional near infrared spectroscopy (fNIRS) offers a cost - effective solution. Methods: Enrolled subjects involve 10 patients with depressive disorder and 10 healthy controls. They perform the following cognitive tasks including Trail Making Test, N-back Test as well as Digit-symbol substitution. Real time measurement of oxyhemoglobin and deoxyhemoglobin are measured by NIRSIT device (OBELAB, Korea) which is a protable 200-channel fNIRS imaging system for the frontal cortex (see Figure 1). The obtained data will be analysed using the “integral mode”: the pre-task baseline will be determined as the mean over 10s just prior to each cognitive task, and the post-task baseline will be determined as the mean over the last 5 s of the post-task period. The average measurement of oxy-Hb and deoxy-Hb will be calculated after excluding data on the channels indicated as “bad channels” (i.e., those affected by motion artifacts) by the automatic algorithm. We will select oxy-Hb as the candidate

biomarker of depressive symptomatology. The integral value of oxy-Hb will be calculated for patients with depressive disorder and healthy controls. A value of $p<0.05$ (two-tailed) will be considered to be statistically significant. Results: We will provide graphical demonstrations to illustrate the differences between patients with depressive disorder and healthy controls during each cognitive task. We will present the mean integral values for patients with depressive disorder and healthy controls during each cognitive task. Conclusion: Our results support blood flow in the frontal lobe as a potential biomarker of depressive disorder and the NIRSIT fNIRS device can be applied in psychiatric practice as an adjunct diagnostic tool.



Disclosures: **R. Ho:** None.

Poster

255. Cognitive Control in a Clinical Population

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 255.07/TT43

Topic: H.02. Human Cognition and Behavior

Support: AA023165

AA017347

AA017168

Title: Functional networking differences in HIV infection, alcohol use disorder, and their comorbidity

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Abstract: HIV-1 infection and alcohol use disorder (AUD) affect separate brain systems and have the potential to disrupt neural communication between different sets of brain systems that contribute to successful cognitive and motor functioning. HIV+AUD comorbidity, which is highly prevalent, could disrupt both constellations of neural systems and possibly exacerbate disruption of systems overlapping the two diseases. We compared neural network communication in 29 HIV, 33 AUD, 22 comorbid patients, and 22 controls using resting-state functional connectivity MRI (rs-fcMRI). Functional connectivity (fc) was determined using the Stanford 90ROI functional atlas (findlab.stanford.edu/functional_ROIs.html) for ROI-to-ROI analysis testing differences in interregional fc among the 4 groups (pFDR<0.05, 2-tailed). Groups did not differ in age or sex distribution. Composite neuropsychological normative Z-scores for verbal/language, executive functions, learning/memory, information processing, and motor skills showed impairments among patient groups in all performance domains but verbal/language. Significant group differences were observed for cerebellar-frontal and cerebellar-parietal fc and between sensorimotor-parietal and orbitofrontal cortical fc. Follow-up analysis revealed different cerebellar-cortical connectivity patterns for HIV and AUD, marked by stronger fc in AUD and by weaker fc in HIV with the comorbid group in-between relative to controls, who only moderately synchronized activity between these regions during rest. Longer time since HIV infection correlated with weaker cerebellar-parietal fc in HIV (r=-.50, p=.008) and in comorbid patients (r=-.66, p=.003), and greater lifetime alcohol consumption moderately correlated with the observed stronger cerebellar-frontal connectivity in AUD (r=.41, p=.017). Comorbid patients with stronger cerebellar-supramarginal fc had lower executive function scores (r=-.56, p.008). Later onset of AUD correlated with higher motor skill scores (r=.45, p=.012). These findings indicate differentiated neurofunctional consequences of HIV infection and AUD for intrinsic interregional brain networking that have meaning for executive functional impairment in comorbid patients and for motor skills in AUD. Further, better motor skill performance, associated with later AUD onset, appeared enhanced by parietal-motor cortical reciprocal activation synchrony, unique to AUD and not seen in controls. Support: AA023165, AA017347, AA017168

Disclosures: T. Schulte: None. **E.V. Sullivan:** None. **A. Pfefferbaum:** None. **E.M. Müller-Oehring:** None.

Poster

255. Cognitive Control in a Clinical Population

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 255.08/TT44

Topic: H.02. Human Cognition and Behavior

Title: Creativity and clinical markers of OCD

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Abstract: Introduction: Individuals with moderate-to-severe form of OCD symptoms may display exceptional creativity and productivity (Andreasen, 1987); the underlying neurobehavioral mechanism of this phenomena is unknown. This study aimed to define the characteristics of individuals who demonstrate high life achievement/creativity and display clinically significant OC symptomatology. The main hypothesis was that the presence of OC symptoms is significantly correlated with high levels of creativity, and that individuals displaying this characteristic will demonstrate neurocognitive profiles similar to subjects with clinical OCD. **Methods:** Cognitive, intellectual, emotional and clinical characteristics were examined in real-world high-achievers (HAs, n=28) and "standard achievers" (SAs, n=29); measures included Y-BOCS, BDI, Creativity Achievement Questionnaire (Carson, Peterson, & Higgins, 2005), Verbal and Visual-Spatial Reasoning and WASI. Using the clinical cut-off scores for Y-BOCS we identified: High-High Achievers (HH) and High Standard Achievers (SH) with the highest scores of OC symptoms (8-19 points). Between-groups independent samples t-test analysis and within-groups Kendall's Tau b correlations were performed. **Results:** HAs had higher IQ scores, significantly higher verbal and perceptual reasoning scores, and significantly less depressive answers on the BDI than SAs; statistically significant positive correlation of IQ with Creativity, Creativity with Y-BOCS, and a negative correlation of high IQ with low depression in HAs. HHs scored significantly higher than SHs in Y-BOCS, IQ, Creativity, Verbal Reasoning, and displayed strong positive correlations between their Creativity and Y-BOCS. **Conclusion:** A unique group of individuals, High Functioning OCD (HFOCD), real life High-Achievers, displaying clinically severe OC symptoms and high creativity was identified. This correlative relationship between creativity and OC emerged when OC symptoms reached a clinical level of severity. HFOCDs showed no similarity to the clinical/cognitive profile of subjects with clinical OCD, with no symptoms of depression and no deficits in visual-spatial tasks, but with good verbal proficiency and high psychometric IQ. HFOCD may constitute an entirely unique OC Spectrum population with etiology and underlying specific

brain mechanisms different than in subjects with clinical OCD. **References:** Andreasen, N. C. (1987). *American Journal of Psychiatry*, *144*(10), 1288-1292. Carson, S. H., Peterson, J. B., & Higgins, D. M. (2005). *Creativity Research Journal*, *17*(1), 37-50.

Disclosures: S. Meyer: None. **M. Self:** None. **K. Jupiter:** None. **I. Solis:** None. **P. Lesnik:** None. **K. Rewin Ciesielski:** None.

Poster

255. Cognitive Control in a Clinical Population

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 255.09/TT45

Topic: H.02. Human Cognition and Behavior

Support: McDonnell Foundation Collaborative Action Award 220020387

Title: Lesion-derived network mapping of patients with non-prefrontal damage helps explain impaired performance on the Wisconsin card sorting test

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Abstract: The Wisconsin Card Sorting Test (WCST) has been described as a test of prefrontal cortex functions, especially planning, set shifting, and other executive functions. However, patients with damage outside prefrontal regions can also present with impaired performance on the WCST. These cases have widely varying patterns of damage, preventing parsimonious lesion-deficit explanations. Here we examined 62 patients with focal damage outside of the prefrontal lobes, all of whom completed the standard 124-card WCST. We used these cases to perform lesion-derived network mapping (c.f. Sutterer et al., 2016 *Cortex*, Boes et al., 2015 *Brain*), which uses healthy subject resting-state functional connectivity data to infer the areas that would be connected with each patient's lesion area in healthy adults. Specifically, each patient's lesion mask was used as a separate region-of-interest seed for resting-state functional connectivity in 198 healthy subjects to characterize typical patterns of functional connectivity with each lesion location. We examined the overlap of these "lesion-derived network maps" based on WCST performance, using permutation-based voxel-lesion symptom mapping. Lower performances on several WCST variables (e.g., percent perseverative errors, percent non-perseverative errors) were associated with an overlap in the lesion-derived connectivity with the left dorsolateral prefrontal cortex. Other WCST variables, such as failure to maintain set, were associated with lesion-derived connectivity with the left and right caudate. Meanwhile, traditional voxel-lesion symptom mapping did not demonstrate a high lesion-symptom correspondence. Overall, these preliminary results may reflect chronic diaschisis between prefrontal areas involved in executive functioning and damage to non-frontal areas that are

functionally connected with prefrontal regions. Healthy connectivity profiles of brain lesions have the potential to better inform cognitive neuropsychological studies in patients with ostensibly idiosyncratic patterns of damage and deficits.

Disclosures: M.J. Sutterer: None. **J. Kamm:** None. **J. Bruss:** None. **D. Tranel:** None.

Poster

255. Cognitive Control in a Clinical Population

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 255.10/TT46

Topic: H.02. Human Cognition and Behavior

Support: Carlos III: CD15/00092

Title: Stopping natural desires: the hypersexuality network in impulse control disorders in Parkinson´s disease

Authors: *I. OBESO[1], J. PINEDA-PARDO[1], J. MOLINA[2], L. VELA[1], F. ALONSO[1], J. OBESO[1]
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Abstract: Objectives: Humans are prone to approach natural stimuli with positive connotation such as food or sex. Impulse control disorders (ICD) is a side-effect of dopamine agonist medication to treat motor symptoms in Parkinson´s disease (PD) whereby desire towards natural rewards increases and uncontrolled actions occur as a result. **Purpose:** We investigated the behavioral and neural basis responsible for hypersexual ICD in PD using an erotic stop-signal task inside an MRI scanner. **Methods:** Male PD+ICD (n=13; age= 64.3) and PD-ICD patients (n=15; age= 65.1) performed the task while on and off medicated and compared to healthy male controls (n=12; age=58.9). The erotic stop-signal task presented participants either an erotic or non-erotic image (1s), followed by a go signal sometimes replaced with a stop signal (33%). Event-related fMRI (3T Siemens) acquired brain signals during task performance. **Results:** Behaviorally, PD +ICD patients were slower to inhibit actions that followed an erotic image as compared to PD-ICD patients and controls. Erotic stimuli produced a BOLD increment in ICD+ as compared to PD-ICD group (on medication) in the globus pallidum pars externa (main effect; $z = 3.32$, $p < .01$). When stopping was successful in the erotic condition, PD-ICD and controls activated anterior putamen and caudate while such activity was absent in the PD+ICD patients. However, in unsuccessful stop, an enlarged activity over supplementary motor area and globus pallidus external was detected in PD+ICD patients ($z=2.42$, $p < .01$). **Conclusions:** These findings provide an aberrant cortico-subcortical interaction during stopping sexual desire in

hypersexual ICD patients. The study thus represents the initial step towards defining optimal targets for neuromodulation approaches in PD+ICD treatment.

Disclosures: **I. Obeso:** A. Employment/Salary (full or part-time):; Fundación HM Hospitales. 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.; Instituto de Salud Carlos III, Contrato PostDoctoral Sara Borrell. **J. Pineda-Pardo:** None. **J. Molina:** None. **L. Vela:** None. **F. Alonso:** None. **J. Obeso:** None.

Poster

255. Cognitive Control in a Clinical Population

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 255.11/TT47

Topic: H.02. Human Cognition and Behavior

Support: NIH R01 DA03889

NIH T32 DA007209

NIH 403 DA042336

Title: Effects of the classic hallucinogen psilocybin and the dissociative hallucinogen dextromethorphan on cognition

Authors: *F. S. BARRETT[1,2], T. M. CARBONARO[2], M. W. JOHNSON[2], R. R. GRIFFITHS[2,3]
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Abstract: Classic hallucinogens (serotonin 2A receptor agonists) and dissociative hallucinogens (NMDA receptor antagonists) have a wide range of neuropsychological effects. Drugs of both classes are being pursued as novel treatments for mood disorders. While classic and dissociative hallucinogens have different pharmacologic mechanisms of action, they may have similar subjective and neuropsychological effects. The objective of this double-blind, placebo controlled crossover study was to compare the neuropsychological effects of multiple doses of the classic hallucinogen psilocybin (10, 20, and 30 mg/70 kg doses) with the effects of a single high dose of the dissociative hallucinogen dextromethorphan (DXM; 400 mg/70 kg). Twenty hallucinogen users (11F, 9M) completed five drug administration sessions during which computerized neuropsychological tasks were assessed. Overall cognitive impairment, as assessed with the Mini-Mental State Examination, was not observed with psilocybin or DXM. Orderly and dose-dependent effects of psilocybin were observed, and consisted of impairments of psychomotor performance, working memory, episodic memory, associative learning, and visual perception.

Effects of a high dose of DXM were observed, and consisted of impairments of psychomotor performance, working memory, visual perception, and associative learning that were in the range of effects of a moderate to high dose (20 to 30 mg/70 kg) of psilocybin. Psilocybin had greater effects than DXM on measures of working memory. DXM had greater effects than all doses of psilocybin on measures of word recognition sensitivity, response inhibition, and executive control. The selective impairing effects of DXM on word recognition sensitivity, response inhibition, and executive control may indicate less desirability of dissociative hallucinogens compared to classic psychedelics when considering these compounds as novel treatments for mood disorders.

Disclosures: F.S. Barrett: None. **T.M. Carbonaro:** None. **M.W. Johnson:** None. **R.R. Griffiths:** Other; Heffter Research Institute.

Poster

255. Cognitive Control in a Clinical Population

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 255.12/TT48

Topic: H.02. Human Cognition and Behavior

Support: Ministry of Health and Welfare, Republic of Korea (HM14C2578)

Title: Abnormal gray matter volume and executive control in young adults with internet gaming disorder

Authors: D. LEE, *Y.-C. JUNG
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Abstract: Objectives: Internet gaming disorder (IGD) is defined as the excessive and compulsive internet gaming behavior despite negative psychosocial consequences. IGD is characterized by impairments for the executive control. We hypothesized that individuals with IGD would show structural alterations in brain regions which involve executive control. We involved young adults with IGD who continued excessive internet gaming over long periods of time beginning early adolescence. Their long-standing maladaptive online gaming despite adverse consequences established presence of pathological addictive processes. **Methods:** To investigate the gray matter abnormalities in IGD, the voxel-based morphometry(VBM) analysis with the diffeomorphic anatomical registration using an exponentiated Lie algebra algorithm(DARTEL) was performed in 31 young male adults with IGD and 30 age-matched male healthy controls. We also perform scales for impulsiveness to reflect difficulties in executive control. Then, we investigated the relationships between structural brain differences and impulsivity in IGD. **Results:** IGD subjects showed smaller gray matter volume(GMV) in brain regions implicated in executive control such as the anterior cingulate cortex(ACC) and the

right supplementary motor area(SMA). The GMV in the ACC and the SMA was negatively correlated with self-reporting scales reflecting impulsiveness. IGD subjects also exhibited smaller GMV in top-down attentional control-related brain regions involving the left inferior parietal lobule(IPL) and the left anterior temporal lobe(ATL) when compared to healthy controls. **Conclusion:** We found that young adults with IGD showed gray matter abnormalities in brain regions which involve executive control and top-down attentional processes. The alterations of gray matter in the anterior cingulate cortex and the supplementary motor area were significantly correlated with impulsivity. Our findings suggest that grey matter abnormalities for executive control-related regions play an essential role in pathophysiology of IGD.

Disclosures: D. Lee: None. **Y. Jung:** None.

Poster

255. Cognitive Control in a Clinical Population

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 255.13/TT49

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant R01 NR014810

Title: Functional connectivity changes in the brain following orthopedic surgery

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Abstract: Cognitive decline can occur after major surgeries. Understanding neural correlates that might be associated with surgery-related cognitive decline is a key step toward the development of predictive biomarkers and therapeutic interventions. As part of an ongoing investigation studying neuroimaging biomarkers of post-operative cognitive decline, we recorded resting-state fMRI pre-surgery and post-surgery in patients who elected to undergo total knee replacement surgery, and age- and sex-matched controls. Graph theoretic analysis was conducted to examine pre- and post-surgery changes in brain functional connectivity. 44 controls (average age: 69.3, male: 20, female: 24) and 47 patients (average age: 67.5, male: 19, female: 28) enrolled in the study. Resting state functional MRI scans were acquired pre-surgery and post-surgery (48 to 72 hours post). A standard mask comprised of 234 brain regions was used to parcellate the brain images for each participant. The Brain Connectivity Toolbox was used to construct the weighted networks of brain connectivity. Measures including network resilience and node degree were calculated to assess the impact of surgery on functional connectivity before and after surgery. Network resilience analyses suggested functional brain networks became more disorganized by exhibiting increased randomness following surgery. For the controls no difference in network resilience was found between the first (“before”) and second

("after") scans. Node degree analyses revealed (1) the connectivity between the temporal lobe structures and the rest of the brain was lower following surgery and (2) the connectivity between frontoparietal executive control structures and the rest of the brain was higher following surgery. No such differences were observed in controls. These results show that orthopedic surgery has a significant impact on brain functional network organization in older adults electing total knee replacement surgery. Although there is clear evidence of neural injury to key brain regions supporting mnemonic functions, there is also evidence for frontal compensation, possibly to offset the adverse influences of such injury. Further analyses are underway to determine the long-term outcome of these changes in brain network activity, the role these changes might play in postoperative cognitive decline, and identify factors that mitigate surgery-related neural injury. This study was supported by NIH grant R01 NR014810.

Disclosures: H. Huang: None. **J. Tanner:** None. **C. Price:** None. **M. Ding:** None.

Poster

255. Cognitive Control in a Clinical Population

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 255.14/TT50

Topic: H.02. Human Cognition and Behavior

Support: CIHR Grant MOP-FDN-148418

Title: Using an emotional saccade task to establish behavioural biomarkers in attention-deficit hyperactivity disorder and bipolar disorder

Authors: *R. YEP[1], D. C. BRIEN[1], B. C. COE[1], A. MARIN[2], D. P. MUNOZ[1]
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Abstract: Despite distinct differences in age of onset and core symptoms, attention-deficit hyperactivity disorder (ADHD) and bipolar disorder (BD) share cognitive and emotional processing deficits that can make differential diagnoses difficult. In order to better characterize these two disorders, we compared the performance of adult ADHD and BD groups on a saccade paradigm designed to probe both executive functioning and emotional processing. Performance on this task may identify subtle differences between ADHD and BD that traditional clinical assessments are not sensitive enough to capture. We hypothesize that patient groups will be differentiated from controls on the basis of executive functioning performance, and patient groups will be further differentiated from one another on the basis of emotional processing performance. Healthy control, ADHD, and BD participants performed an interleaved pro/antisaccade task (look towards vs. look away from a visual target, respectively) in which the gender of emotional faces (happy, sad, fearful, angry, neutral) acted as the directional cue to

perform either the pro or antisaccade. Saccade behavior, including saccadic reaction time and direction error percentage, was compared between pro/antisaccade trials, face stimuli, and participant groups. Saccadic reaction time and direction error performance was significantly worse on antisaccade trials compared to prosaccade trials, with ADHD and BD groups making more direction errors than controls on antisaccade trials. The presentation of emotional face stimuli, particularly negatively valenced and neutral faces, differentially affected the behavioural performance of ADHD and BD groups. The findings presented here suggest that executive dysfunction is a key deficit in both patient groups, and that it is differentially impaired when recruitment of emotional processing systems is also required. Further characterization of how these processing systems interact in ADHD and BD could be used to develop psychiatric endophenotypes to help improve diagnostic accuracy.

Disclosures: R. Yep: None. **D.C. Brien:** None. **B.C. Coe:** None. **A. Marin:** None. **D.P. Munoz:** None.

Poster

255. Cognitive Control in a Clinical Population

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 255.15/TT51

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant K23 MH081175

Title: Neuroanatomical correlates of cognitive function in type 2 diabetes and major depression

Authors: H. DENG[1], M. LAMAR[3], M. JEAN[1], S. YANG[1], A. KUMAR[2], *O. A. AJILORE[1]
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Abstract: The objective of this study was to investigate whether major depression and type 2 diabetes each independently produce cognitive deficits and whether severity of depression or diabetes are correlated with cognitive measures. This study will also examine the relationship of orbitofrontal (OFC) and anterior cingulate (ACC) volumes/thickness with executive functioning and attention/processing speed. Fifty-eight type 2 diabetics with depression, 74 non-depressed type 2 diabetics, 93 non-diabetics with major depression, and 94 controls without diabetes or depression were compared. A two-way ANOVA did not find a significant effect of diabetes or depression status on either cognitive domain. A follow-up ANOVA did not find a main effect of group on either cognitive domain. Using brain magnetic resonance imaging, volumetric measures of the prefrontal cortex were studied in relation to the two cognitive domains of interest. There were no group differences in OFC or ACC volumes or thickness. Partial correlations revealed a cross-diagnostic effect. HbA1c had a large, negative relationship with executive function in the depressed only group while depression severity had a moderate,

negative relationship with attention/processing speed in the diabetes only group. Further analyses identified the right rostral ACC to be associated with the relationship between HbA1c and executive function while the total OFC thickness was found to be associated with the correlation between depression severity and attention/processing speed.

Disclosures: H. Deng: None. **M. Lamar:** None. **M. Jean:** None. **S. Yang:** None. **A. Kumar:** None. **O.A. Ajilore:** None.

Poster

255. Cognitive Control in a Clinical Population

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 255.16/TT52

Topic: H.02. Human Cognition and Behavior

Support: NIMH R01MH084812

NIMH R01MH074457

NIMH R56MH097870

NIDA K01DA037819

Title: Combined impact of HIV and cannabis use on insular functional connectivity

Authors: *M. RIEDEL[1], J. S. FLANNERY[2], R. GONZALEZ[2], A. R. LAIRD[1], M. T. SUTHERLAND[2]
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Abstract: Neurocognitive alterations have been independently documented among individuals with human immunodeficiency virus (HIV) and those who regularly use cannabis (CB), but the combined impact on functional connectivity (FC) has yet to be considered. Given the neurocognitive deficits caused by HIV (Heaton et al., 2011) and the suggested brain metabolic alterations in frontal white matter pathways from HIV and cannabis (Chang et al., 2006), we delineated alterations in FC of various insular (INS) regions presumably subserving cognitive functions among HIV and CB-using participants.73 individuals (21 HIV+/CB+; 19 HIV+/CB-; 21 HIV-CB+; 12 HIV-CB-) underwent resting-state fMRI. Resting-state FC analyses were performed using bilateral anterior (a), middle (m), and posterior (p) INS seeds. To investigate the independent and combined impact of HIV and CB, whole-brain connectivity maps were generated for each ROI and compared across groups (threshold: p-voxel<0.001; p-cluster: p<0.05).Among HIV+ participants (main effect) the left aINS demonstrated reduced FC with the anterior and posterior cingulate, the right aINS showed reduced FC with the bilateral dorsomedial prefrontal cortex and striatum, and the right mINS showed reduced FC with the left

insula and striatum. The right pINS showed an HIV x CB interaction with the left inferior parietal lobule/supramarginal gyrus (IPL; Figure 1 inset). Specifically, among HIV- participants pINS-IPL FC was reduced in CB users, however, among HIV+ individuals such FC was increased among CB users (Figure 1).We identified alterations in INS FC associated with HIV in frontal, striatal, and cingulate regions. These outcomes are consistent with HIV-related fronto-striatal dysfunction and associated cognitive impairment (Plessis et al., 2014). Interestingly, CB use among HIV+ individuals appeared to normalize insula-parietal lobe FC. INS FC alterations may mediate some aspects of cognitive dysfunction associated with HIV infection and/or CB use.

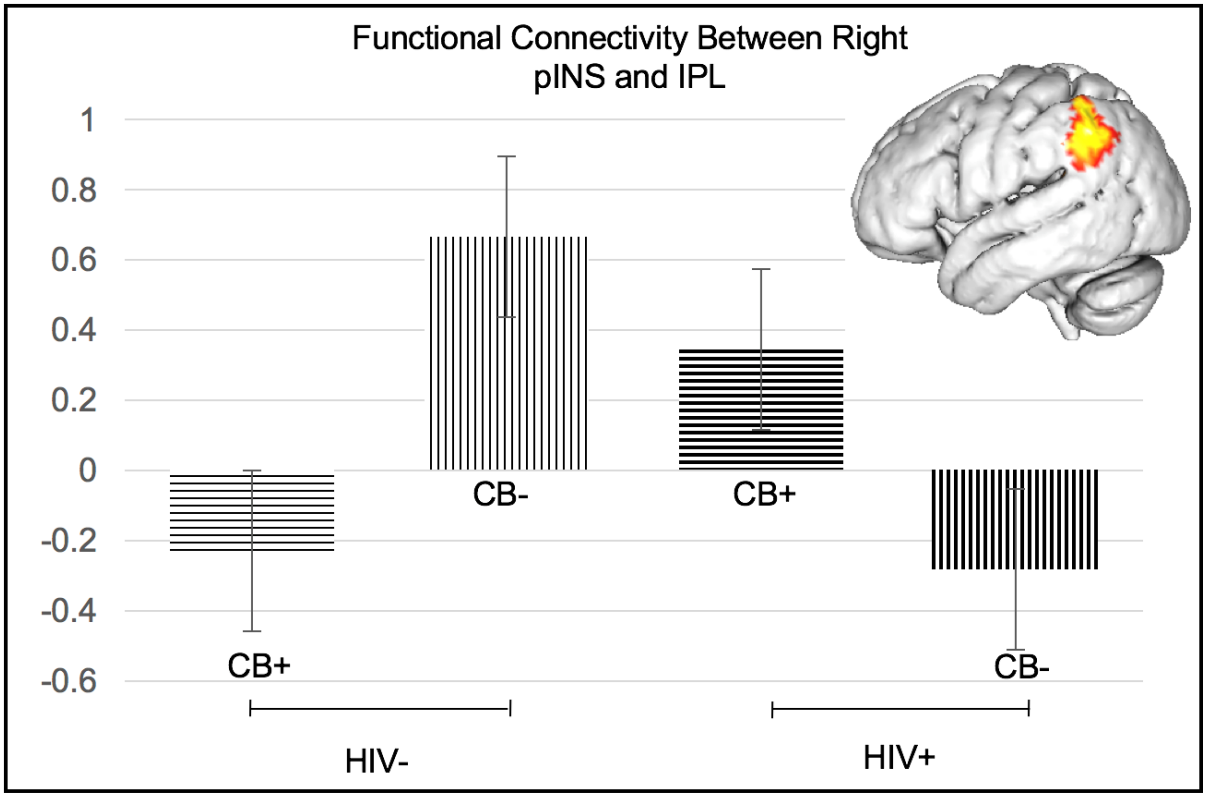

Figure 1. Functional Connectivity Estimates Between Right Posterior Insula Seed and Left Inferior Parietal Lobule. Average correlation coefficients in IPL (inset) ROI resulting from interaction between HIV and CB. Among HIV- individuals, CB users showed reduced FC, yet among HIV+ individuals CB users showed increased FC to the IPL.

Disclosures: M. Riedel: None. **J.S. Flannery:** None. **R. Gonzalez:** None. **A.R. Laird:** None. **M.T. Sutherland:** None.

Poster

255. Cognitive Control in a Clinical Population

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 255.17/TT53

Topic: H.02. Human Cognition and Behavior

Support: CONACyT CB-2012#178811

Title: Inhibitory control task performance in patients with substance abuse is not associated with adherence to residential treatment

Authors: *S. E. MORALES MONDRAGÓN[1], O. INOZEMTSEVA[2], J. JUAREZ[3], E. MATUTE-VILLASEÑOR[4]
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Abstract: One of the most effective methods of addiction rehabilitation is residential treatment. However, in this method the patients frecuently show lack of adherence to the treatment and the factors involved are not clear. One of the possible factors related to lack of adherence to treatment is an inhibitory control (IC) deficit. IC is a cognitive process that regulates different motor, behavioral, and cognitive responses and each one of them has been associated with a specific type of IC and with a particular task. There are few studies in the literature related with IC and adherence to treatment and the findings are contradictory. Therefore, the purpose of the present study was to detect which type of IC is closely related to adherence to treatment. Thus, approximately two weeks after admission in a rehabilitation center, we evaluated sixty-four patients who were dependent on different substances, had a high severity of consumption, and met the DSM-V substance dependence criteria. The sample demographic characteristics were a mean age of 32.58 years, mean CI of 96.86, and mean educational level of 11.22 years. The inpatients were categorized into two groups according to treatment adherence: 26 patients (40.6%) belonged to the dropped out of treatment group (DOG) and 38 (59.4%) to the remained internal group (RIG). The Stroop color and word interference test was administered to evaluate the ability to inhibit a prepotent learned response; a flanker paradigm to evaluate the ability to inhibit a prepotent perceptual response; and a go/no-go task to evaluate the ability to inhibit a prepotent motor response. The Iowa Gambling Task was used to detect the ability to delay immediate gratification. All participants completed the Impulsivity State Scale in order to assess levels of behavioral impulsivity and the Behavior Rating Inventory of Executive Function (BRIEF-A) to Asses the ability to exert executive control over behavior. When comparing the DOG and the RIG we did not observe differences regarding age, education level, IQ, or gender. Neither did we find significant group differences in any of the inhibitory tasks that were

administered. However, we did find differences in the BRIEF-A, specifically in the inhibition scale, self-regulation scale, emotional control scale and in the Behavioral Regulation Index. The DOG had worse scale scores than the RIG . According to our results, inhibitory control task performance is not directly related with treatment adherence. It seems that executive functions, such as control and self-regulation, are factors that are more likely involved.

Disclosures: S.E. Morales Mondragón: None. **O. Inozemtseva:** None. **J. Juarez:** None. **E. Matute-Villaseñor:** None.

Poster

256. Rhythm and Timing

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 256.01/TT54

Topic: H.02. Human Cognition and Behavior

Title: Perceptual priors on musical rhythm revealed by iterated reproduction

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Abstract: Probability distributions over external states (priors) are essential to the interpretation of sensory signals. Priors for cultural artifacts such as music and language remain largely uncharacterized, but critically constrain cultural transmission, because only those signals with high probability under the prior can be reliably reproduced and communicated. Extending previous research on concept learning and language (Bartlett 1932, Griffiths and Kalish 2005, Xu & Griffiths 2010), we developed a method to estimate priors for simple rhythms via iterated reproduction of random temporal sequences. Listeners were asked to reproduce random “seed” rhythms; their reproductions were fed back as the stimulus, and over time became dominated by internal biases, such that the prior could be estimated by applying the procedure multiple times. Our method can be applied irrespective of the participant’s musical or cultural background, and is hypothesis-neutral, allowing any possible pattern of results to be detected.
We measured listeners’ priors over the entire space of two- and three-interval rhythms, examining Westerners with different level of musical expertise as well as members of the Tsimane, a native Amazonian society with very limited exposure to Western music. We found that priors in Westerners showed peaks at rhythms with simple integer ratios, but only those that are prevalent in Western music. Priors were similar for musicians and nonmusicians, suggesting that they are shaped primarily by passive exposure to the music of a culture. Priors in a native Amazonian society also exhibited modes at integer ratios, but were otherwise qualitatively different from priors in Westerners, in ways that are consistent with the structures prevalent in their music. The results were similar for several different modes of reproduction (for example,

finger tapping versus rhythmic vocalization of a repeated syllable), but did not extend to the reproduction of spoken phrases, indicating that integer ratio priors are at least somewhat specific to music. Our results are consistent with biological constraints that favor integer ratios, but indicate that any such constraints are strongly modulated by experience. Our method holds promise for characterizing of priors for a range of other auditory domains including phonetics, speech rhythms, and musical melodies.

Disclosures: N. Jacoby: None. **J. McDermott:** None.

Poster

256. Rhythm and Timing

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 256.02/TT55

Topic: H.02. Human Cognition and Behavior

Support: NSF BCS-146063

Title: Beta-band response synchronizes and predicts rhythmic flashing visual stimuli

Authors: *D. COMSTOCK, R. BALASUBRAMANIAM
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Abstract: In auditory rhythm processing, phase-locked gamma-band activity corresponds with the onset of tones, while non phase-locked gamma-band activity corresponds with the expected onset of tones. The non phase-locked response is considered predictive, since this occurs even when an expected tone is omitted. Previous research suggests that this gamma-band activity represents allocation of attention to rhythmic auditory sequences in service of the perception of the timing element of the rhythm. Whether such a similar pattern of activity is seen in the case of rhythmic visual stimuli remains unexplored. In the present study, participants attended to a series of rhythmic visual flashes while we recorded 32 channels of scalp EEG. We analyzed the neural time-frequency activity elicited from rhythmic flashing stimuli. Our data show non-phase-locked beta-band activity that was predictive of the onset of a flash, as this activity persisted even in the absence of the flash. On the contrary, phase-locked theta, alpha, and low-beta-band oscillations were seen corresponding to the timing of the rhythmic visual stimulus. These findings implicate the existence of an attentional oscillation mechanism for the visual system similar to that seen in the auditory system, but spread across different bands of neural activity.

Disclosures: D. Comstock: None. **R. Balasubramaniam:** None.

Poster

256. Rhythm and Timing

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 256.03/TT56

Topic: H.02. Human Cognition and Behavior

Support: NSF 1553895

NEI EY021252

Title: Perceptual discrimination of temporal duration based on ongoing motor behavior

Authors: W. ZHOU[1], A. DANIEL[1], *W. M. JOINER[2], M. WIENER[3]
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Abstract: A critical aspect of behavior is that mobile organisms must be able to precisely determine *where* and *when* to move. A better understanding of the mechanisms underlying precise movement timing and action planning is therefore crucial to understanding how we interact with the world around us. Recent theories of timing suggest that our experience of time is directly and intrinsically computed within the motor system, consistent with the theory of embodied cognition. Indeed, a variety of studies have recently demonstrated that concurrent movement impacts the estimate of a temporal duration, such that the perception of time is shifted towards the duration of movement. In order to investigate the role of the motor system, we tested human subjects on a novel task combining reaching and time perception. In this task, subjects were required to move a robotic manipulandum to one of two physical locations to categorize a concurrently timed supra-second auditory stimulus (1-4seconds, log-spaced) as “long” or “short”, relative to a running standard interval, yielding a rich set of data that allows us to investigate timing and motor behavior at a granular level. Critically, subjects were divided into two groups: one in which movement during the interval was unrestricted, and so subjects could move freely to their choice, and one in which they were restricted from moving until the stimulus interval has elapsed. Our results revealed a similar degree of accuracy between the two groups, yet with a higher degree of precision for subjects in the free-moving group. By further decomposing choice and response time data with a drift diffusion model of decision making, we identified the source of this change to a shift in the response threshold (a) for free-moving subjects, indicating a change in the decision-layer. This finding was further supported by examination of the response trajectories of both groups; subjects in the hold group exhibited substantial changes-of-mind (Resulaj, et al. 2009), in which movement to one response shifted mid-trajectory, indicating uncertainty in the response. Additionally, in both groups, we observed that the eventual choice could be determined by movement parameters (e.g. trajectory, force) before the response was made, and even before the interval had elapsed. These findings suggest

that perceptual timing may be instantiated within the motor system as an ongoing readout of timing judgment and confidence.

Disclosures: W. Zhou: None. **A. Daniel:** None. **W.M. Joiner:** None. **M. Wiener:** None.

Poster

256. Rhythm and Timing

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 256.04/TT57

Topic: H.02. Human Cognition and Behavior

Support: Irish Research Council RPG2013-1

Title: Distinct temporal processing schemes for speech and music

Authors: *N. ZUK[1], J. MURPHY[2], E. LALOR[1]
[1]Dept. of Biomed. Engin., Univ. of Rochester, Rochester, NY; [2]Trinity Col. Ctr. for Bioengineering, Trinity Col., Dublin, Ireland

Abstract: Speech and music share similar temporal attributes such as rhythm and phrasing, but we perceive these attributes differently. Yet it is still unclear how temporal processing in the brain contributes to the differences in perception for speech and music. One key issue is that typical research techniques using simplistic and repetitive stimuli may show results that are hard to extend into a naturalistic context. Here, we used electroencephalography (EEG) to examine temporal properties of neural activity that reflect the neural processing of long continuous streams of real speech and music. We focused on the time-varying EEG signals with the largest variability, and we used a modeling approach to identify temporal properties of the EEG that could best reconstruct the envelopes of the stimuli. By decomposing the EEG signals into their fine-structure, envelope, and time-varying mean we were able to separately examine neural activity associated with time-varying phase and power fluctuations, both of which have been found to reflect speech and music processing in previous studies. We show that the slow, second-long fluctuations from the time-varying mean of the EEG signal are dominant in reconstructing the envelope of speech. In contrast, the faster fluctuations in the time-varying fine structure and envelope of the EEG signals are more useful for reconstructing the envelope of music. And unlike the reconstruction for speech, including the time-varying fine structure and envelope of the EEG improves the reconstruction accuracy of music more than using the raw EEG alone. Our results identify distinct temporal processing schemes for speech and music that reflect the different ways in which the brain parses these two stimuli.

Disclosures: N. Zuk: None. **J. Murphy:** None. **E. Lalor:** None.

Poster

256. Rhythm and Timing

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 256.05/TT58

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant 409670

Title: Feeling the beat engages auditory dorsal stream in early blind and sighted

Authors: *J. PHILLIPS-SILVER[1], J. W. VANMETER[2], J. R. RAUSCHECKER[3]
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Abstract: Abilities that rely on the auditory dorsal stream for timing and anticipation, including spatial localization and beat asynchrony detection (i.e., when a beat is 'out of time' in a temporal sequence), are spared or even enhanced in the early blind (Renier et al., Neuron, 2010; Lerens et al., Perception, 2014). We propose that 'feeling the beat' in music relies on the auditory dorsal stream (Rauschecker & Scott, 2009), basal ganglia and cerebellum (Merchant et al., Phil Trans R Soc B, 2014), and that this auditory-motor rhythm ability is preserved in the early blind. To test this hypothesis, early blind and sighted participants were trained to interpret an ambiguous 6-beat rhythm by bouncing on either every second or every third beat of the rhythm. Immediately after, they entered the MRI scanner for functional imaging and tapped along to the beat of the same ambiguous rhythm according to their training. They then performed an experimental task of Beat Recognition, in which they identified acoustically-accented versions of the rhythm, played across a variety of percussion instruments, that corresponded to the way they had moved (i.e., with accents on every second or third beat). Results show that beat recognition based on body movement engages key auditory dorsal stream areas including posterior superior temporal gyrus, inferior parietal lobe, premotor cortex and supplementary motor area, as well as anterior and posterior insula, basal ganglia and cerebellum. The early blind group additionally recruits visual cortex, reflecting cortical reorganization for the musical rhythm task. These findings suggest that "feeling the beat" of music, consistent with its auditory-motor nature, is primarily a dorsal-stream ability, and that it is preserved in early blindness.

Disclosures: J. Phillips-Silver: None. **J.W. VanMeter:** None. **J.R. Rauschecker:** None.

Poster

256. Rhythm and Timing

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 256.06/TT59

Topic: H.02. Human Cognition and Behavior

Support: Sports Research Grant from Yamaha Motor Foundation for Sports

Title: Accented metronome stabilizes auditory-motor coordination of whole-body rhythmic movement

Authors: *T. ETANI[1], A. MIURA[3], M. OKANO[4], H. TANOSAKI[5], M. SHINYA[6], K. KUDO[2]
[1]Grad. Sch. of Arts and Sci., [2]Grad. Sch. of Interdisciplinary Information Studies, The Univ. of Tokyo, Tokyo, Japan; [3]Fac. of Sports Sci., Waseda Univ., Tokyo, Japan; [4]Col. of Sport and Hlth. Sci., Ritsumeikan Univ., Shiga, Japan; [5]The Unviersity of Tokyo, Tokyo, Japan; [6]The Grad. Sch. of Integrated Arts and Sci., Hiroshima Univ., Hiroshima, Japan

Abstract: Humans are capable of synchronizing their movement with environmental information such as auditory rhythm. The performance of coordination is affected not only by the physical characteristics of the effector (e.g., eigenfrequency) but also by the perceptual information. The present study investigated the effect of perceptual information induced by metronome accent on the performance of auditory-motor coordination of whole-body rhythmic movement.
Fourteen healthy adults synchronized their dance-like knee-bending movement with metronome (one beat with flexion movement, and one beat with extension movement), which accelerated log-arithmetically from 60 to 240 bpm. Synchronization performance was compared between six conditions combining three sound-movement combinations and two starting conditions. Three sound-movement combinations were as follows: (1) combining flexion movement with loud sound and extension movement with quiet sound (LF-QE condition), (2) combining flexion movement with quiet sound and extension movement with loud sound (QF-LE condition), and (3) combining both movements with loud sound (Control condition). Two starting conditions were as follows: (1) starting with flexion movement (Flexion condition), and starting with extension movement (Extension condition). During the task, the knee angle was recorded by using a goniometer with a 1000-Hz sampling frequency.
Firstly, the angular velocity was calculated by differentiating the knee angle. Then, the variance of phase angle defined as $\phi = \arctan(\omega/\theta)$, where ω is the angular velocity and θ is the knee angle, was calculated for each condition as an index of synchronization performance.
The result of the ANOVA and the multiple comparison showed that the variance of LF-QE condition was significantly smaller than the other two combinations, and the variance of Control condition was significantly larger than the other two conditions ($ps < .05$). In addition, the variance for Flexion condition was significantly smaller than that for Extension condition ($p <$.

05). These results suggest that (1) accent stabilizes auditory-motor coordination of whole-body rhythmic movement, (2) combining accented sound with flexion movement stabilizes the coordination, and (3) the initial movement condition affects the coordination performance. These results indicate that there are preferred combinations of accented sound and movement as well as preferred initial movement condition, which stabilize the synchronization performance.

Disclosures: T. Etani: None. **A. Miura:** None. **M. Okano:** None. **H. Tanosaki:** None. **M. Shinya:** None. **K. Kudo:** None.

Poster

256. Rhythm and Timing

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 256.07/TT60

Topic: H.02. Human Cognition and Behavior

Title: Drum-playing modulates the post-auricular muscle response

Authors: Z. E. SWANN, *P. A. SIMEN
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Abstract: The post auricular muscle, located behind the ear above the mastoid bone, is known to produce a brief, involuntary reflex roughly 10 milliseconds after high-frequency sounds in many (but not all) human participants. The electrical signature of this vestigial response, the post-auricular muscle response (PAMR), is a muscle action potential observable in electrodes placed above the mastoids. We found that the PAMR was bilaterally modulated by task goal for equivalent sound stimuli (snare drum sounds). We sought to investigate the brain basis of inter-beat interval timing in rhythmic behavior. We used electroencephalography (EEG) to monitor neural and muscular signals while human participants actively produced sequences of drumbeats, with passive listening and non-rhythmic drumming tasks as control conditions. In each condition, participants produced or listened to rhythmic or non-rhythmic patterns of snare drumbeats at 70-100 beats per minute for two minutes. Resulting PAMR amplitudes, surprisingly, ranged from 5-200 microvolts (μV) in active drumming, versus 3-70 μV in passive listening. Within participants, active drumming produced a dramatically larger average PAMR than passive listening, and rhythmic drumming/listening produced larger average PAMRs than corresponding non-rhythmic conditions. We further observed a distinct latency difference relative to stimulus time between active and passive trials, with active responses occurring approximately 8 milliseconds (ms) after the snare sound, and passive responses at approximately 12 ms after the sound. The latency of the PAMR suggests it is mediated by only a few synaptic connections between cochlea and motor neurons. Modulation by task goal suggests a top-down effect in which attention to rhythmic production can functionally enhance this connectivity. However, we observed no correlation between PAMR magnitude and inter-beat interval duration, nor any

obvious, beat-by-beat basis for PAMR modulation. We are conducting further research to identify whether PAMR modulation is purely attentional in nature, using a third task condition in which an oddball bass drum sound is randomly generated instead of a snare. Participants respond when they detect this oddball timbre-change. Results should help determine whether PAMR-reduction results because participants ignore sounds during passive listening, or whether the PAMR reflects motor planning/performance monitoring in the auditory system. If the latter, then PAMR magnitude and latency may serve as useful tools for investigating the brain basis of timed, rhythmic behavior.

Disclosures: Z.E. Swann: None. **P.A. Simen:** None.

Poster

256. Rhythm and Timing

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 256.08/TT61

Topic: H.02. Human Cognition and Behavior

Support: Vanier Canada Graduate Scholarship

Canadian Institutes of Health Research

Title: Neural oscillatory activities for processing dynamic auditory information: From intrapersonal to interpersonal entrainment

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Abstract: Humans must process highly dynamic information, such as in speech and music, in order to decode meaning and react in real time. Prior studies showed that sensory systems proactively predict upcoming information to optimize perceptual and sensorimotor processing. Predictive processing may be represented by neuronal oscillations. In particular, the power of induced beta oscillations (15 - 25 Hz) in auditory and motor areas entrains to the rate of a presented isochronous tone sequence (e.g. Fujioka et al., 2012, JN), with reductions in beta power following sound event onsets, and with the slope of the rebound predicting the onset of the next sound event. However, it remains unclear whether beta entrainment facilitates perceptual performance intrapersonally, and whether complex interpersonal cooperative activities such as group musical performance can be represented by oscillatory entrainment between individuals. In the first study, we investigated how oscillatory neural activity intrapersonally entrains to an external auditory sequence, and how it relates to perceptual processing. By combining EEG and psychophysical techniques, we presented identical tones in rhythmic versus arrhythmic sequences; occasionally, one tone was replaced by a target tone with

modified pitch, and participants were instructed to discriminate whether target pitches (presented louder) were higher or lower than the standard pitch. We investigated how pre-target oscillatory neural activity predictively determines post-target perceptual performance. The results showed 1) pitch discrimination sensitivity was higher when target tones were embedded in rhythmic than arrhythmic sequences, 2) pre-target beta power entrained to the temporal regularity of the sequence, and 3) trial-by-trial analyses found that the size of pre-target beta entrainment positively predicted pitch discriminative sensitivity. These results indicate that beta entrainment improves perceptual processing for dynamic auditory information. In the second study, we investigated dynamic sensorimotor processing in a real-world interpersonal interaction, using professional string quartets as a model for interpersonal coordination. We experimentally manipulated leadership roles during performances, and employed Granger causality to investigate the directional coupling among musicians. Analyses on body movements revealed that directional coupling followed assigned leadership (Chang et al., in press, PNAS), as predicted. Ongoing analyses are examining EEG dynamics, especially in beta band, to investigate oscillatory synchronization and information flow between brains.

Disclosures: **A. Chang:** None. **D.J. Bosnyak:** None. **L.J. Trainor:** None.

Poster

256. Rhythm and Timing

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 256.09/TT62

Topic: H.02. Human Cognition and Behavior

Support: CIHR MOP 115043

NSERC

James S. McDonnell Foundation

Title: Live music increases intersubject synchronization of audience members' brain rhythms

Authors: ***M. J. HENRY**[1], D. J. CAMERON[1], D. SWARBRICK[2], D. BOSNYAK[2], L. J. TRAINOR[2], J. A. GRAHN[1]
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Abstract: Attending concerts is enjoyable for a number of reasons: watching performers make live music affords a qualitatively different experience than listening to a recording. Moreover, an important contributor to the enjoyment of a concert—at least anecdotally—is forming a bond with others who are enjoying the same musical experience. The current study considered the possibility that a live musical experience, i.e., the presence of live performers as well as an audience, might change the way brain rhythms synchronize across audience members, thereby

changing audience members' musical and affiliative experiences. We collected electroencephalography (EEG) data in three different social contexts. First, EEG was measured simultaneously from 20 audience members (in a larger crowd of approximately 80 people) while they observed a live musical performance. Second, EEG was measured simultaneously from 20 audience members (in a larger crowd of approximately 80 people) while they watched the recording of the first concert on a large movie screen and with audio identical to the live concert. Finally, EEG was measured from 20 participants in small groups of 2 participants seated apart (tested in 10 separate sessions) while they observed the recorded musical performance. Thus, we manipulated the presence of the performers while keeping audience context fixed, and we manipulated the presence of other audience members while keeping the recorded performance fixed. We analyzed the data in terms of intersubject synchronization (ISS), which quantifies the degree to which brain rhythms are synchronized across groups of individuals. ISS was calculated for individual frequencies ranging between 0.1 Hz ("infra-slow" oscillations) to 60 Hz (gamma-band oscillations) for each social context condition. We observed differences in the delta (2-4.5 Hz) and low-beta (13-16 Hz) bands depending on the presence of the performers—that is, audience members' brain waves were more synchronized with each other when the performers were present. The delta band corresponds roughly to the range of rates in which a musical beat would be felt, and beta band brain rhythms, in addition to having strong associations with movement and motor system, critically have been linked to timing and temporal prediction in rhythmic sequences. ISS was similar across conditions that involved watching a recorded performance, whether other audience members were present or not. Thus, the presence of live performers at a concert leads to increased synchronization of audience members' brain rhythms selectively in frequency bands that are associated with feeling and moving along with a musical beat.

Disclosures: M.J. Henry: None. **D.J. Cameron:** None. **D. Swarbrick:** None. **D. Bosnyak:** None. **L.J. Trainor:** None. **J.A. Grahn:** None.

Poster

256. Rhythm and Timing

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 256.10/TT63

Topic: H.02. Human Cognition and Behavior

Support: 985 Grant from Tsinghua University (X.W.)

Title: Subjective time estimation of music, noise, and pure tone sequences

Authors: *J. HUANG
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Abstract: Temporal information is one of the most important characteristics of auditory stimuli. Auditory timing perception plays a critical role in the processing of auditory sequential events. It has been suggested that the timing mechanism is programed internally in the brain or coded by a state-dependent neural network that is influenced by sensory inputs. In this study, we examined the factors that influence subjective time estimation of different acoustic sequences. Subjects were asked to first listen to a sequence of sounds and then wait for a time period equivalent to the estimated duration of the sequence before pressing a button to indicate its completion. The testing stimuli included music note sequences, randomized music notes, amplitude-modulated noises or pure tones. Results show that the accuracy of the timing estimate was largely determined by the overall duration of acoustic events, regardless of the temporal pattern or the spectral contents of the sequences. The error of the time estimation varied as a function of the duration of acoustic sequences, from overestimate to underestimate as the sequence duration increased beyond 7-8 seconds. Our findings provide evidence to support the idea that timing is internally programed. Furthermore, the dependency of the time estimation error on the duration of acoustic stimuli suggests the co-existence of expansion and compression mechanisms in auditory temporal processing.

Disclosures: J. Huang: None.

Poster

256. Rhythm and Timing

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 256.11/TT64

Topic: H.02. Human Cognition and Behavior

Support: KAKENHI Grant JP15H02718

AIST

Title: Uncertainty of subjective temporal order without subjective simultaneity

Authors: *S. YAMAMOTO
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Abstract: There has been intense debate over whether “subjective temporal order” and “subjective simultaneity” share common mechanisms. The brain can judge which stimulus was first when two stimuli are presented with a sufficiently long interval. Conversely, judging the temporal order becomes difficult and perceiving the stimuli as simultaneous is more likely when the interval is short. This raises a question: does the uncertainty of subjective temporal order lead to subjective simultaneity? To answer this question, we examined subjective temporal perception using two visual stimuli. Participants were seated in front of two red light-emitting diodes

(LEDs) that were placed horizontally and separated by a distance of 1 cm. Two LEDs flashed successively; the stimulus onset asynchronies (SOAs) were randomly sampled from -150 (left first) to 150 ms (right first) in 15-ms steps (mean = 0 ms). The duration of each LED flash was 50 ms (short) or 250 ms (long). There were four total duration combination conditions of the right and left flashes: short/short, short/long, long/short, and long/long. The participants were required to judge the temporal relationship of the two stimuli by choosing from four choices ("right first," "left first," "simultaneous," "not simultaneous, but unsure of order"). In the conditions where the duration of the two stimuli was the same (i.e., short/short or long/long), the participants tended to choose "simultaneous" for the short SOAs (<50 ms) while they chose "right first" or "left first" for the longer SOAs (>50 ms). The participants rarely chose "not simultaneous, but unsure of order". On the other hand, in the conditions where the duration of two stimuli was different (i.e., short/long or long/short), the participants mostly chose "right first" or "left first" but rarely chose "simultaneous" or "not simultaneous, but unsure of order". The probabilities of "right first" and "left first" were around 50% when the long stimulus was presented ~30 ms earlier, which is known as the P-centered effect. Therefore, the participants experienced an uncertain temporal order of two visual stimuli at the SOA around +30 and -30 ms in the short/long and long/short conditions, respectively, but they did not perceive them as simultaneous. The data clearly showed that temporal order uncertainty is independent of subjective simultaneity, suggesting that the subjective temporal order and the subjective simultaneity are processed by different mechanisms in the brain.

Disclosures: S. Yamamoto: None.

Poster

256. Rhythm and Timing

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 256.12/TT65

Topic: H.02. Human Cognition and Behavior

Title: The mechanisms of timing: An integrative theoretical approach

Authors: *L. N. PANTLIN[1], M. PRINCE[2], D. DAVALOS[3]
[1]Psychology - Cognitive Neurosci., Colorado State Univ., Fort Collins, CO; [2]Colorado State Univ., fort collins, CO; [3]Psychology, Colorado State Univ., Fort Collins, CO

Abstract: Accurate timing allows individuals to perform functions central to societal demands, such as creating and maintaining schedules, understanding chronological sequences, and executing basic functions: motor and speech timing, responding to environmental warning signs, and planning. Since timing impacts various functions, it has been considered a cognitive primitive; however, research often examines only one modality at a time, providing a disjointed, myopic view of the mechanisms that comprise timing. This study extends prior work by

integrating and explaining the relationship between two commonly examined timing modalities, physiological and behavioral, and relating these lower-level processing indices of timing to upper-level processing or social-cognitive timing abilities (SCTA). The hypothesis was that those with better physiological timing would be associated with better SCTA and this relationship would be mediated by increased behavioral time accuracy. Participants (N = 36) were screened for select psychopathologies often associated with timing deficits (i.e. psychosis, TBI, substance-use), underwent EEG recordings of duration-based mismatch negativity to measure physiology, performed two behavioral timing tasks, and three measures of SCTA (sequential processing, two time management surveys). The direction of the relationship between physiology, behavioral accuracy and SCTA was tested with two mediation models, with SCTA as a latent variable. Model 1 (CFI=1.00, SRMR=.06) tested behavioral accuracy as a mediator of the c-path, physiology underlying SCTA. Model 2 (CFI=1.00, SRMR=.05) tested the reverse c-path of SCTA underlying physiology and had better model fit. Although sample size is small (N =36) and data collection is still underway, Model 2 demonstrated a significant relationship of SCTA predicting physiology (b=-.58, p=.04). All other pathways were nonsignificant, but in the expected direction. Participants who were more accurate on behavioral tasks also demonstrate better SCTA and more negative mismatch negativity amplitudes, thus, better physiological processing of time. SCTA play a key role in determining physiological timing abilities; therefore, tactics to increase time accuracy should target this realm. These findings are promising, and the hierarchical relationship between each level of temporal processing should be explored to help determine if timing is a singular, yet multifaceted domain, or if timing is composed of separate entities.

Disclosures: L.N. Pantlin: None. **M. Prince:** None. **D. Davalos:** None.

Poster

256. Rhythm and Timing

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 256.13/TT66

Topic: H.02. Human Cognition and Behavior

Title: Causal role of beta oscillations in time estimation

Authors: *M. WIENER[1], A. PARIKH[2], A. KRAKOW[3], H. B. COSLETT[4]
[1]Dept. of Psychology, George Mason Univ., George Mason Univ., Fairfax, VA; [2]Univ. of Pennsylvania, Philadelphia, PA; [3]Johns Hopkins Univ., Baltimore, MD; [4]Hosp. of Univ. PA., Philadelphia, PA

Abstract: The neural mechanisms underlying time perception are of vital importance to a comprehensive understanding of behavior and cognition. Recent work has pointed to a supramodal role for beta oscillations in coordinating endogenous timing mechanisms for the

purpose of measuring temporal intervals (Merchant & Yarrow, 2016). However, the majority of this work has employed paradigms relying on timed motor responses, which are confounded by beta's established role in motor movement (Baker, 2007). Further, no study to date has tested if the alteration of beta oscillations subsequently impacts time perception. Here, we address these concerns and demonstrate for the first time a causal connection between beta oscillations and timing. To accomplish this, we first re-analyzed two, separate EEG datasets from psychophysical experiments (Wiener, et al. 2012; 2015) demonstrating that beta oscillations are associated with the retention and comparison of a memory standard for duration, and that transcranial magnetic stimulation (TMS) of the right supramarginal gyrus leads to an increase in midline beta power during the encoding of a temporal interval, corresponding with a longer perceived interval of time. Next, we conducted a study of 25 healthy human participants using transcranial alternating current stimulation (tACS), over frontrocentral cortex, at alpha (10Hz) and beta (20Hz) frequencies, during a visual temporal bisection task, demonstrating that beta stimulation exclusively shifts the perception of time such that stimuli are reported as longer in length, while preserving precision. Finally, we decomposed trial-by-trial choice data with a drift diffusion model of decision making and temporal encoding that reveals the shift in timing is caused by a change in the starting point of accumulation, rather than the drift rate or threshold. Our results provide causal evidence of beta's involvement in the perception of time, and point to a specific role for beta oscillations in the encoding and retention of memory for temporal intervals.

Disclosures: **M. Wiener:** None. **A. Parikh:** None. **A. Krakow:** None. **H.B. Coslett:** None.

Poster

256. Rhythm and Timing

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 256.14/UU1

Topic: H.02. Human Cognition and Behavior

Title: Cognitive functions of the brain: A perspective based on the time-dimension entanglement with information processing in neural circuits

Authors: *D. S. GUPTA[1], S. TEIXEIRA[2]
[1]Biol., Camden County Col., Blackwood, NJ; [2]Federal Univ. of Piauí (UFPI), Parnaíba, Brazil

Abstract: A distributed modular clock model was proposed earlier to explain the timing functions of the brain (Gupta 2014). According to this model, neural temporal units serve as an important basis for processing time-intervals during perceptual, sensory and motor tasks. Neural temporal unit is represented by the periodic activity of endogenous neural oscillators, participating in the CNS networks subserving perceptual, sensory or motor tasks. The summation of neural temporal units, processes time-intervals associated with various cognitive functions. Thus, for example, if the neural temporal unit, represented by neural oscillator in the network for

a subjective timing task, is smaller on physical-time scale, then the subjective time reported in the task will be greater than the elapsed physical time and the vice versa. Neural temporal units are calibrated in this model via feedback processes during the brain's interaction of the external four-dimensional physical environment. The calibration of neural temporal units is critically important for the information processing that allows organism to exist in its external physical environment. However, the information processing underlying the summation of neural temporal units to process various time-intervals is not clear. In this poster, the author will present evidence to discuss how information processing - underlying cognitive functions - is intertwined with time-dimension, as well as how the representation of space-time in neural circuits is important for the timing during cognitive functions of the brain. The role of cortical-basal ganglia-thalamic-cortical loops, which was proposed to serve as circuits for feedback processes calibrating neural temporal units in cognitive tasks (Gupta (2014)), will be examined, with an emphasis on the role of the supplementary motor area in this loop.

Disclosures: D.S. Gupta: None. **S. Teixeira:** None.

Poster

256. Rhythm and Timing

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 256.15/UU2

Topic: H.02. Human Cognition and Behavior

Support: IMN Grant W81XWH-11-2-0145

National Center for Responsible Gaming

Title: Increasing cortical dopamine tone improves time perception in humans

Authors: J. MITCHELL[1], T. VEGA[1], D. WEINSTEIN[1], *A. S. KAYSER[2]
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Abstract: Time perception is a fundamental cognitive function that contributes to motivated behaviors in rodents and humans. In keeping with this role, time perception is thought to depend upon dopaminergic circuits involving the cortex and striatum. However, the influence of cortical dopamine tone on such circuits is unclear. We hypothesized that tolcapone, a catechol-O-methyltransferase inhibitor, would differentially augment cortical dopamine tone and thereby increase the fidelity of temporal duration estimation in human subjects. To test this hypothesis, we recruited 66 subjects to participate in a randomized, double-blind, within-subject crossover study of tolcapone's influence on time perception. Subjects completed a task in which they estimated time intervals of 5, 15, 30, and 60 seconds on both tolcapone and placebo in two

counterbalanced sessions at least one week apart; a subset of 40 subjects also underwent resting state functional MRI. Our data demonstrate that subjects' estimates of duration across all intervals increase, and become more accurate, on tolcapone versus placebo (linear mixed effects model: $T(524) = 2.04$, $p = 0.04$). The degree of this improvement positively correlated with subjective measures of stress, depression, and alcohol consumption, and was most robust in carriers of the COMT val158 allele, who have previously been shown to have hypodopaminergic tone in frontal cortex (Slifstein et al., 2008). Moreover, using two seed regions, the right inferior frontal gyrus (R IFG) and supplementary motor area (SMA), defined by a recent meta-analysis of time perception (Wiener et al, Neuroimage, 2010), we show not only that a connection from R IFG to the right putamen decreases in strength on tolcapone versus placebo across all subjects ($p < 0.05$, corrected), but also that the strength of this decrease correlates inversely with the increase in duration estimation on tolcapone versus placebo ($r = -0.37$, $p = 0.02$). Together these data indicate that cortical dopamine tone causally influences time perception in humans. We anticipate these data will serve as a starting point in determining whether COMT inhibitors could be therapeutically effective in treating decision-making disorders and addictive behaviors.

Disclosures: **J. Mitchell:** None. **T. Vega:** None. **D. Weinstein:** None. **A.S. Kayser:** None.

Poster

257. Timing, Rhythm, and Sequencing

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 257.01/UU3

Topic: H.02. Human Cognition and Behavior

Support: NSF BCS143 9267

Title: Item-item and item-position strategy use in a cross-species sequence memory task

Authors: *A. GUDMUNDSON[1], S. M. STARK[3], C. E. STARK[2]
[1]Neurobio. and Behavior of Learning and Memory, [2]Univ. of California Irvine, Irvine, CA; [3]Neurobio. & Behavior, Univ. of California, Irvine, Irvine, CA

Abstract: A fundamental part of memory for events is the ability to organize and order events in time. Our lab has collaborated in the development of a cross-species, non-spatial memory task that would allow us to investigate the neurobiological basis of sequence memory using an integrative approach that capitalizes on the strengths of simultaneous human and animal model research. In the task, participants are shown a sequence of trials (4 odors for rats and 6 fractal images for humans) and must indicate on each trial whether an item is "in sequence" or "out of sequence" by releasing or continuing to hold a response key. Previous work demonstrated that rats and humans performed similarly for both in sequence and a variety of out of sequence probe trials, suggesting that there are likely to be comparable cognitive processes and underlying neural

mechanisms between the species (Allen et al., 2014). Likewise, in both species, we have observed evidence for hippocampal and prefrontal contributions and interactions in the task (Allen et al., 2016; Elias et al. 2016; Boucquey et al., under review). Here, we sought to augment this neurobiological work with a behavioral investigation into what strategies are being used to solve the task. Specifically, we sought to determine the degree to which participants engage in an item-item sequential association strategy (A leads to B, B to C, etc.) versus an item-in-position association strategy (A is in the 1st position, B the 2nd, etc.). In a series of behavioral experiments in humans, we augmented the existing probe types extensively to better measure the use of these two strategies and altered the structure of the sequence to bias the use of one or the other of the two strategies. Across these experiments, results show that subjects can engage in either strategy depending on task demands, but that both are typically present. By being able both to assess the strategy with more precision and bias participants towards one strategy or the other, we can better investigate neural mechanisms underlying each.

Disclosures: A. Gudmundson: None. **S.M. Stark:** None. **C.E. Stark:** None.

Poster

257. Timing, Rhythm, and Sequencing

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 257.02/UU4

Topic: H.02. Human Cognition and Behavior

Support: Mitacs Globalink (Canada)

Title: Comparing human and nonhuman primate brain responses to auditory sequences using EEG

Authors: *D. CAMERON[1], L. PRADO[2], J. A. GRAHN[3], H. MERCHANT[2]
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Abstract: Humans have the ability to perceive and move to the ‘beat’ in musical rhythms. This complex behaviour may be unique among primates, and involves extracting regularities from complex, non-isochronous auditory sequences and synchronizing movements to those regularities. To characterize cross-species differences in neural processing of rhythm and beat perception, we compared brain responses in humans and a macaque monkey using electroencephalography (EEG). EEG was recorded while participants listened passively to auditory sequences that consisted of white noise bursts (65ms) separated by intervals. Intervals were structured to create 5 types of sequences: i) isochronous (at three rates), ii) random, iii) strongly beat-based, iv) weakly beat-based, or v) non-beat-based. We compared the two species’ evoked and induced responses in EEG, at various frequency bands (e.g., beta and gamma) to

isochronous and random sequences, and compared neural entrainment at low-frequency (1-5 Hz) regularities in the structures of non-isochronous sequences (iii-v). Similarities and differences between species' brain responses reveal common and distinct aspects of neural processing of auditory sequences.

Disclosures: D. Cameron: None. **L. Prado:** None. **J.A. Grahn:** None. **H. Merchant:** None.

Poster

257. Timing, Rhythm, and Sequencing

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 257.03/UU5

Topic: H.02. Human Cognition and Behavior

Support: NIGMS of NIH under Award R01-GM103894

Title: Propofol sedation impedes stream of consciousness by prolonging temporal autocorrelation of intrinsic brain activity

Authors: *Z. HUANG[1], X. LIU[2], A. G. HUDETZ[1]
[1]Dept. of Anesthesiol., Univ. of Michigan Med. Sch., Ann Arbor, MI; [2]Dept. of Radiology, Med. Col. of Wisconsin, Milwaukee, WI

Abstract: Background. The stream of consciousness consists of subjective experiences that occur in a temporal continuum. Real-world events on multiple timescales are perceived via a hierarchical organization of temporal receptive windows (TRWs) of the brain [1,2]. The state-dependent mechanisms of receptive temporal organization can be probed by anesthesia combined with functional neuroimaging. During sedation, the flow of conscious experience becomes slow, sparse and fragmented with dream-like stories. Accordingly, we hypothesize that sedation is accompanied by a prolongation of the brain's intrinsic functional timescales or TRWs.
Methods. Resting-state fMRI BOLD signals were acquired in healthy volunteers with 15-min scans in wakefulness, propofol-induced light and deep sedation (1-2 ug plasma concentration), emergence, and recovery. Sliding window analysis was used to delineate state transitions as a function of drug effect. TRWs were measured by the first order temporal autocorrelation (AC1) and the fractional standard deviation (fSD) of low-frequency BOLD fluctuations [2]. Global functional connectivity (GFC) and topographical similarity (TS) across different stages of propofol sedation were assessed. TS quantifies the divergence of spatial configuration of graph node degrees from baseline over time [3].
Results. AC1 and fSD increased gradually from wakefulness to deep sedation, decreased during transition and reached complete recovery. GFC and TS decreased during sedation, which was reversed during transition and recovery. Analysis of two independent datasets with high-dose

propofol anesthesia (4 μg/ml) and patients with disorders of consciousness (DOC) yielded consistent results.
Conclusions. The results suggest that propofol sedation extends the brain's temporal receptive windows of information processing. This effect may be related to a decrease in large-scale information exchange, as suggested by the breakdown of global functional connectivity and its departure from the optimal spatial configuration. A mismatch between the brain's intrinsic temporal receptive windows and the timescale of external world events during sedation could reduce the bandwidth of sensory information processing with an extension of psychological time perception and could impede information integration over longer timescales leading to temporal fragmentation of the stream of consciousness.
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[1] Hasson U, J. et al, Neuroscience, 2008, 28(10): 2539-2550.
[2] Honey C J, et al, Neuron, 2012, 76(2): 423-434.
[3] Tagliazucchi E, et al. Journal Roy Soc Interface, 2016, 13(114): 20151027.

Disclosures: Z. Huang: None. **X. Liu:** None. **A.G. Hudetz:** None.

Poster

257. Timing, Rhythm, and Sequencing

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 257.04/UU6

Topic: H.02. Human Cognition and Behavior

Support: National Natural Science Foundation of China (31371129)

Title: Temporal recalibration in the visual modality requires spatial grouping

Authors: *L. GU, Y. HUANG, X. WU
Psychology Dept., Sun Yat-Sen Univ., Guangdong, China

Abstract: Multi-modality sensory inputs often occur in asynchrony and the brain is capable of adjusting the sense of relative timing to reduce the perceived asynchrony, which is referred to as temporal recalibration. Whereas cross-modal temporal recalibration has long been demonstrated for various combinations of sensory inputs (especially for audio-visual stimuli), it is a matter of debate whether temporal recalibration occurs in the visual modality. In the present study, an isochronous visual sequence composed of the collision of an orange bouncing ball on a bar and an isochronous visual sequence consisting of the flash of a green ball were exposed to the subjects for 3 minutes, simultaneously or with a constant relative timing (+233ms or -233ms). The ball collision and the ball flash were either spatially separated (separate condition) or overlapped (grouping condition). After that, the subjects were instructed to judge the simultaneity of each pair of ball collision and ball flash with a lag randomly chosen from 13

values between –415 and +415 ms. The results showed a shift of the point of subjective simultaneity toward the leading stimulus in the grouping condition but not in the separate condition. The present finding suggests that for motion and color that are supposed to be independently processed in different visual areas, temporal recalibration requires spatial grouping.

Disclosures: L. Gu: None. **Y. Huang:** None. **X. Wu:** None.

Poster

257. Timing, Rhythm, and Sequencing

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 257.05/UU7

Topic: H.02. Human Cognition and Behavior

Title: Relative hemispheric alpha power during a temporal bisection task

Authors: A. CRUZ[1], *M. I. LEON[2]
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Abstract: We measured Alpha (8-13 Hz) power from scalp electrodes positioned over the left and right posterior parietal cortex of subjects performing a Go/No-Go temporal bisection task. During practice trials, subjects categorized the duration (0.57 sec or 1.74 sec) of a visual test cue. A trial began by prompting the question, “Is it short?” or “Is it long?” At the termination of each visual cue, subjects decided “Yes” by making a right-arm reach to depress a choice button, or “No” by remaining still. Experimental sessions included seven additional cues of intermediate duration. All nine durations were randomly interleaved across trials. During the test cue, we observed a gradual increase in the relative (left vs. right) power as time elapsed. As the cue duration approached the subjects’ bisection points, where Yes and No decisions were equally likely, the relative power came to be clearly modulated by the question that subjects were evaluating. When subjects were subsequently tested with a longer set of durations (1.15 sec - 3.48 sec), the plots of relative power underwent a rightward shift in time, in correspondence with the shift in subjects’ temporal judgements.

Disclosures: A. Cruz: None. **M.I. Leon:** None.

Poster

257. Timing, Rhythm, and Sequencing

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 257.06/UU8

Topic: H.02. Human Cognition and Behavior

Support: "AGETIME" EFRE/ESF

Title: Integrating space, time and numerosity in a navigational context: An fMRI study

Authors: *M. RIEMER[1,2,3], E. KÜHN[1], J. SHINE[1], T. WOLBERS[1,3]
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Abstract: The compelling interdependency between the perception of space, time and numerosity is especially evident in the domain of spatial navigation, because moving in space requires time and is usually associated with a higher amount of encountered events. Knowledge about the length of a covered distance contains valuable information about the corresponding travel time and vice versa.
We used fMRI to identify the overlapping and diverging neuronal networks underlying the processing of traveled distance, travel time and numerosity. Twenty-five healthy, young participants were tested in a virtual environment, walking along a straight path, while their attention was directed either to travel time, to the distance covered, or to the amount of blinking dots appearing on the surface of the path. An adaptive testing strategy was employed to ensure equal difficulty between the conditions, which could be verified by behavioral performance parameters.
Analyses of repetition suppression effects across space, time and numerosity trials revealed distinct regions specifically recruited when attention was directed to each dimension. We further used multivariate pattern analysis (MVPA) to decode neuronal pattern containing dimension-specific information. In general, our results reveal characteristic as well as overlapping activation patterns for integration processes relating to spatial distance, temporal duration and numerosity. The results are discussed with respect to the concept of a generalized magnitude system to represent cross-dimensional quantities and provide new insights into the interrelations between the neuronal processing of space, time and numerosity in the context of spatial navigation.

Disclosures: **M. Riemer:** A. Employment/Salary (full or part-time):; Medical Faculty (FME), Otto-von-Guericke University, Magdeburg, Germany. **E. Kühn:** None. **J. Shine:** None. **T. Wolbers:** None.

Poster

257. Timing, Rhythm, and Sequencing

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 257.07/UU9

Topic: H.02. Human Cognition and Behavior

Title: The time-dependent effects of cardiovascular exercise on associative memory

Authors: *A. R. PAHWA, J. B. CAPLAN, D. F. COLLINS
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Abstract: Abstract
A single bout of cardiovascular exercise can improve performance on memory tasks. To date, this has been shown only when exercise is performed within an hour of the encoding or retrieval phases of memory tasks. Here we characterize the time-dependence of the effects of exercise on associative memory when both encoding and retrieval occur at 2, 5, and 8 hours after exercise. We hypothesized that performance on a paired-associate learning [PAL], a test of associative memory, would be improved for at least 8 hours after exercise. Baseline PAL performance was assessed, then participants either ran on a treadmill (exercise group, n=18), or solved Sudoku puzzles (control group, n=18). Each group was subdivided into 3 subgroups, returning either 2, 5, or 8 hours later to perform a second round of PAL study and test, on different pairs than the baseline test. Two hours after exercise, scores on the second PAL task were 9% higher than scores for the same participants at baseline, and 11% higher than comparable data from the control group. PAL scores were not different 5 hours after exercise compared to appropriate baseline or control data. Eight hours after exercise, PAL scores fell below baseline (by 15%) and control (by 14%) data. PAL scores in the control group did not change over time. These data show that a single bout of exercise initially enhances, but later, diminishes, associative memory. This time-dependent effect of exercise on associative memory may reflect a combination of exercise-induced neurochemical and neurovascular changes that influence cognitive processing that are independent of current theories of consolidation. These results have broad implications for the timing of exercise programs to maximize, and not hinder, learning.

Disclosures: A.R. Pahwa: None. **J.B. Caplan:** None. **D.F. Collins:** None.

Poster

257. Timing, Rhythm, and Sequencing

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 257.08/UU10

Topic: H.02. Human Cognition and Behavior

Support: Yale-NUS Internal Grant IG15-B052

Yale-NUS Start-up Grant R-607-264-057-121

Title: An exploration of time perception in early-stage romantic relationships

Authors: *J. C. LIU, N. M. Y. KUEK
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Abstract: Prior research suggests that the early stage of romantic love is characterized by passion, with high levels of physiological arousal and dopaminergic activity. In turn, these characteristics have been found to influence time perception, such that individuals who experience arousal-inducing events or who have received dopamine agonists overestimate time durations. Bringing these findings together, we hypothesized that an individual in a romantic relationship would experience the dilation of time in the presence of their romantic partner.
To test our hypothesis, we recruited 80 healthy young adults (40 couples) who entered a heterosexual romantic relationship in the 3 months prior to study enrolment. All participants completed a portfolio of 3 time perception tasks which varied in terms of experimental control and ecological validity. First, in the temporal bisection task, participants were shown photographs that were presented for durations ranging from 400-1600ms and were asked to judge whether these were of 'short' (close to 400ms) or 'long' durations (close to 1600ms). Photographs were either of their partner, an attractive opposite-gendered stranger, or an average-looking opposite-gendered stranger, with the order of photograph presentation counter-balanced across participants. In the second task, the temporal reproduction task, participants again viewed photographs of their partner, an attractive stranger, or an average stranger (in counter-balanced order). These were shown for 2-6s, with participants reproducing the duration of photograph presentation using a keypress. Finally, in a second reproduction task, participants used their non-dominant hand to hold either their partner's hand or a stress ball (in counter-balanced order across participants). They were exposed to 300Hz auditory tones that were presented for 2-6s, and were asked to reproduce these durations using a keypress.
We found significant partner effects in the two duration reproduction tasks. Namely, early stage romantic couples were found to overestimate time intervals in the presence of their partner, as compared to attractive and average controls (Task 2) or a neutral stress ball (Task 3). (For Task 1, a reduced number of trials per photograph type led to excessive miscategorisation of the anchors (400ms and 1600ms) and we were unable to evaluate the partner effect.)

Taken together, our findings support the old adage that time stands still or slows down when one is in love. These results inform ongoing debates between current models of interval timing, and add to the growing literature of everyday experiences that modulate our perception of time.

Disclosures: J.C. Liu: None. **N.M.Y. Kuek:** None.

Poster

257. Timing, Rhythm, and Sequencing

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 257.09/UU11

Topic: H.02. Human Cognition and Behavior

Title: A fast recognition memory system: The temporal dynamics of perirhinal and hippocampal structures in visual recognition memory

Authors: *E. DESPOUY[1], *E. DESPOUY[1], J. CUROT[1,2], M. DEUDON[1], L. VALTON[1,2], J.-C. SOL[2], J.-A. LOTTERIE[2], M. DENUELLE[2], E. BARBEAU[1]
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Abstract: Recognition memory refers to the ability to know that an item has previously been encountered. It relies on two processes: a fast one (familiarity) and a slower one (recollection). It involves the medial temporal lobes, especially the perirhinal cortex and the hippocampus. There is an ongoing debate regarding the respective role of these structures in recognition memory, especially about the way they interact with each other and with other brain areas. There are some arguments in favor of the idea that the hippocampus is not necessary in patients with isolated lesions of this structure but it has never been explored in normal subjects. As normal subjects probably use both the perirhinal cortex and the hippocampus under normal circumstances, we chose a speeded task that can presumably dissociate the role of these structures. Our hypothesis was that fast responses obtained during a speeded recognition memory task would depend on the perirhinal cortex and not on the hippocampus. We used intracerebral recordings in epileptic patients (n=13) while they performed the SAB (Speed and Accuracy Boosting procedure), a task based on high-speed constraints. Based on a classical go/no-go task, the SAB relies on a response deadline (600-800 ms) and audio feed-backs to constrain subjects to answer both very fast and accurately. Stimuli (natural and man-made objects) consist of targets that had to be recognized among distractors. We focused our analyses on hits and correct rejection using different EEG analyses. Evoked potentials analyses enabled us to highlight an earlier activation but also an earlier differential activity between old and new pictures in the perirhinal cortex, at least 100 ms before the hippocampus. A whole brain analysis revealed a three-stage model of spatio-temporal dynamics, involving first the right perirhinal cortex, then the co-activation of a set of brain areas including regions in the parietal and frontal lobes followed lastly by the

hippocampus. A multivariate pattern analysis allowed us to show that perirhinal cortex activity was related to recognition memory at latencies compatible with the earliest reaction times, which was not the case of the hippocampus. In conclusion, our results demonstrate that the perirhinal cortex shows the earliest activity related to recognition memory, on time to be related to the earliest reaction time; that the hippocampus is too slow to be involved in these fastest reaction times and importantly that a set of brain areas in the parietal and frontal lobes are activated right after the perirhinal cortex, but before the hippocampus, suggesting there exists a network of brain areas involved in fast recognition memory.

Disclosures: E. Despouy: None. **J. Curot:** None. **M. Deudon:** None. **L. Valton:** None. **J. Sol:** None. **J. Lotterie:** None. **M. Denuelle:** None. **E. Barbeau:** None.

Poster

257. Timing, Rhythm, and Sequencing

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 257.10/UU12

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant NS092079

NIH Grant NS097480

Title: Distinct role of the cerebellum in behavioral and neural expressions of rhythm-based and interval-based temporal predictions

Authors: *A. BRESKA, K. T. DUBERG, R. B. IVRY
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Abstract: Humans routinely use temporal regularities in the world to predict the timing of upcoming events and to prepare for them by shifting attention in time. Recent studies indicate that in rhythmic contexts, temporal prediction may be mediated by oscillatory entrainment, independent of dedicated timing circuits. The cerebellum is thought to play a key role in timing based on evidence from various tasks such as repetitive tapping and duration perception, but its role in temporal prediction is unknown. Moreover, the cerebellum was found to be especially important for precise timing of discrete events but less so for timing in more cyclical or continuous contexts, suggesting that it might be differentially involved in temporal prediction of different sources. To directly test these questions, we examined the performance and EEG activity of individuals with cerebellar degeneration (CD) in temporal prediction tasks. Participants provided speeded responses to a visual target (green circle) that followed a warning signal (white circle, WS). Temporal predictions were cued by having the WS and target extend a rhythmic visual stream, or by presenting the WS-target interval in the beginning of the trial using

two visual stimuli, but such that the whole stream was aperiodic. In each condition, the target appeared at the non-cued interval in a small number of trials (invalid), to test the costs of prediction relative to validly cued targets. The CD group had faster reaction times for valid versus invalid trials in both conditions, confirming the formation of temporal predictions, with the effect stronger in the rhythm condition. The EEG analysis showed that expecting a target at a short vs long interval led to faster buildup of the contingent negative variation (CNV), a slow potential related to preparation, and this effect was stronger in the rhythm condition. Predictive timing is best viewed in the absence of a stimulus, on short trials in which the target is omitted. Here, beta-band activity (15-25 Hz) over motor areas was suppressed at the expected target time, and the CNV reversed its trajectory immediately after target omission, in the rhythm condition only. In contrast, temporal adjustment of alpha-band activity (8-13 Hz) over occipital electrodes was only observed in the Interval condition. Finally, latency shortening of the P3 potential for temporally valid targets, previously observed for both types of predictions, was absent in both conditions in the CD group. As a whole, our findings extend the role of the cerebellum in timing of discrete intervals to temporal prediction, and isolate the neural stages of temporal prediction that depend on or are independent of the cerebellum.

Disclosures: **A. Breska:** None. **K.T. Duberg:** None. **R.B. Ivry:** None.

Poster

257. Timing, Rhythm, and Sequencing

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 257.11/UU13

Topic: H.02. Human Cognition and Behavior

Support: NARSAD Distinguished Investigator

Brain Health Institute, Rutgers

Title: Does sexual violence in the past alter temporal perspective in the present?

Authors: *E. M. MILLON, H. M. CHANG, K. N. SCHRODER, T. J. SHORS
Behavioral and Systems Neuroscience, Dept. of Psychology, Rutgers Univ., Piscataway, NJ

Abstract: Sexual violence (SV) affects over 25% of women worldwide (WHO, 2013). Most experiences occur from age 16-19 (DOJ, 1997), and one in five report SV during college (Cantor et al., 2015). Women who experience SV in their lifetime ruminate more and remember the event with greater vividness, along with significant increases in trauma-related symptoms (e.g., Shors and Millon, 2016; Millon et al., under review). Because most ruminations are about the past, we hypothesized that women with sexual violence in the past would express a disruption in temporal processing and perspective (i.e., how one processes time in the present). To test this hypothesis,

we provided the temporal bisection task to women with and with SV history. During the task, participants made temporal judgments of stimulus durations ranging from 400ms-1600ms, presented as a red circle on the computer screen. Women with SV history underestimated the duration of temporal stimuli compared to women without SV history, particularly at the 800ms duration ($p < 0.05$). There were no group differences in time sensitivity (i.e. accuracy; $p > 0.05$). Women with sexual violence history also reported significantly more ruminative thoughts and remembered a past stressful event with greater vividness ($p's < 0.01$). Overall, these temporal processing data suggest women with a history of sexual violence may process time differently and these changes are potentially related to the rumination of autobiographical memories.

Disclosures: E.M. Millon: None. **H.M. Chang:** None. **K.N. Schroder:** None. **T.J. Shors:** None.

Poster

257. Timing, Rhythm, and Sequencing

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 257.12/UU14

Topic: H.02. Human Cognition and Behavior

Support: NIH grants R01-HL102119

NIH grants R01-MH107571

NIH grants P30-NS045839

the PENN IOA Pilot Project

the program for professors of special appointment (Eastern Scholar) at Shanghai Institutions of Higher Learning

Title: Randomized response-stimulus intervals implicitly encoded as temporal probabilities in the human brain

Authors: *F. N. YANG[1], S. XU[3], T. LIU[4], H. RAO[2]
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Abstract: Introduction: The psychomotor Vigilance Test (PVT) is a well validated stimulus-response task to evaluate the ability to sustain attention and respond in a timely manner to salient signals. During this test, participants are asked to monitor for the appearance of a millisecond counter in screen and stop the counter as quickly as possible with a button press. Previous studies

have revealed a significant effect of faster response times (RT) after longer response-stimulus intervals (RSI) during the PVT. However, the underlying neural mechanism of this RSI effect remains unclear. We hypothesized that participants may implicitly use the temporal probabilities of RSIs to facilitate their response and test this hypothesis with computational modeling of both behavioral and neuroimaging data. **Method:** Twenty-eight participants completed a 20 min PVT in a Siemens 3T MRI scanner. The response-stimulus intervals (RSI) of the PVT were randomly drawn from a continuous uniform distribution on the interval [2000, 8000] milliseconds. For behavioral data modeling, a simple rise-to-threshold model was used to analyze the grouped RT data. For neuroimaging data modeling, temporal probabilities of RSIs were calculated using the hazard function (i.e., the likelihood that the next stimulus is about to appear, given it has not occurred yet) and entered the voxel-wise GLM analysis of imaging data. **Results:** RT monotonically decreases as RSI increases. This pattern is well captured by the rise-to-threshold model, which attributes it to changes in perceptual sensitivity rather than threshold adjustment. Robust parametric modulation of temporal probabilities is observed not only in the sensory areas including the primary visual cortex and the supplementary motor area, but also in the parietal cortex and basal ganglia, which are known to be involved in time expectation. **Conclusion:** These findings are consistent with previous studies on expected visual events and suggest that randomized RSIs may be implicitly encoded as temporal probabilities to facilitate perceptual decision making. Although participants were not instructed to pay attention to the RSI differences during the PVT, their brain might be sensitive to the temporal probabilities of upcoming stimulus.

Disclosures: **F.N. Yang:** None. **S. Xu:** None. **T. Liu:** None. **H. Rao:** None.

Poster

257. Timing, Rhythm, and Sequencing

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 257.13/UU15

Topic: H.01. Animal Cognition and Behavior

Support: McGovern Institute

NIH NINDS-NS078127

Klingenstein Foundation

Simons Foundation

Sloan Foundation

Title: A thalamocortical substrate for flexible motor timing

Authors: *J. WANG[1], M. JAZAYERI[1,2]
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Abstract: Cognitive flexibility is central to adaptive behavior. A fundamental component of such flexibility is the ability to recruit relevant circuits and dynamics in the brain. We trained monkeys to use a contextual cue to flexibly produce either 800 ms or 1500 ms by a self-initiated saccade. We found that flexible switching between the two contexts was accompanied by an adjustment of the speed with which population activity in the medial prefrontal cortex (MFC) evolved over time. Analysis of a recurrent neural network model of the task as well as a simpler two neuron model revealed that such speed control could result from interactions between an external drive and the nonlinearities of cortical circuits. This motivated us to ask where such external input may originate from. We hypothesized that thalamocortical projections supply this flexibly-controlled input. To test this hypothesis, we first used antidromic stimulation to identify a region of the thalamus where neurons monosynaptically project to MFC. We verified the importance of this pathway by reversible inactivation, which had a profound impact on MFC signals and caused a significant impairment in the animals' timing behavior in both contexts. We then characterized the relationship between thalamocortical activity and timing behavior. Many MFC-projecting neurons had sustained activity with firing rates that increased or decreased systematically in relation to the context-dependent produced interval. This feature was also evident in the principal components of population activity suggesting that flexible adjustment of sustained firing rates was an important contributor and could be the key input that adjusts speed in cortical dynamics. These findings reveal the crucial role of thalamocortical sustained activity in supplying flexible context-dependent drive for the temporal control of movement initiation. More generally, our work demonstrates a potential mechanism for controlling cortical dynamics that confers temporal flexibility to sensorimotor and cognitive functions.

Disclosures: J. Wang: None. **M. Jazayeri:** None.

Poster

258. Schizophrenia: Developmental Models

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 258.01/UU16

Topic: H.03. Schizophrenia

Support: NIH R01 MH097803

NSERC

OMHF

Title: Hippocampal morphology of mice lacking Egr3

Authors: *A. L. GALLITANO[1,3], S. J. BRUNWASSER[4], M. CHARBEL[3], N. MICKS[5], K. MARBALLI[3], J. MEDEIROS[5], D. F. MARRONE[5,2]
[1]Basic Med. Sci., Univ. of Arizona, Phoenix, AZ; [2]Univ. of Arizona, McKnight Brain Institute, AZ; [3]Univ. of Arizona Col. of Med. - Phoenix, Phoenix, AZ; [4]Washington Univ. Sch. of Med., Saint Louis, MO; [5]Wilfrid Laurier Univ., Waterloo, ON, Canada

Abstract: Early growth response 3 (*Egr3*) is an immediate-early gene implicated in normal hippocampal development (e.g., Roberts et al., 2006), synaptic plasticity (e.g., Gallitano-Mendel et al., 2007, Li et al., 2007; Cheval et al., 2012), as well as hippocampus-dependent learning (Cheval et al., 2012). Consistent with these data, we have shown that mice lacking *Egr3*, a key regulator of neural plasticity, show both deficits in hippocampus-dependent learning (e.g., Gallitano-Mendel et al., 2007) and alterations of behaviorally-induced gene expression (e.g., Maple et al., 2017). The current investigation addresses whether there are structural changes in the hippocampus of these mice that may underlie the physiological changes previously observed. Analysis of $Egr3^{-/-}$ mice, as well as wild-type littermates, was conducted using quantitative morphometry of Nissl-stained sections, as well as cells stained using the Golgi-Cox method. Preliminary data show no significant changes in granule cell number or morphology in the absence of *Egr3*. Further analyses will characterize changes among the pyramidal cell layers of these mice. Collectively, these data will help elucidate the role of *Egr3* in hippocampal development, as well as the mechanism for the behavioral and physiological deficits seen in these mice.

Disclosures: A.L. Gallitano: None. **S.J. Brunwasser:** None. **M. Charbel:** None. **N. Micks:** None. **K. Marballi:** None. **J. Medeiros:** None. **D.F. Marrone:** None.

Poster

258. Schizophrenia: Developmental Models

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 258.02/UU17

Topic: H.03. Schizophrenia

Support: CONACyT Grant 575264

CONACyT Grant 252808

Title: Alterations in dendritic spines morphology of corticolimbic neurons in rats after neonatal ventral hippocampus lesion

Authors: *H. TENDILLA[1,2], A. J. VÁZQUEZ-HERNÁNDEZ[1], R. A. VÁZQUEZ-ROQUE[1], L. GARCÉS-RAMÍREZ[2], G. FLORES[1]

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Abstract: Neonatal ventral hippocampus lesion (NVHL) in the rat is considered a schizophrenia-related neurodevelopmental model since it leads to several behavioral, anatomical-functional and biochemical alterations at the postpubertal age, therefore the mechanisms involved in the NVHL can be associated with the psychopathology of the disease. Previous reports of our group have demonstrated that behavioral and neurochemical alterations induced by the NVHL correlates with neural hypotrophy in corticolimbic areas, included the lack of dendritic spines, suggesting synaptogenesis modifications. Dendritic spines are specialized post-synaptic structures whose shape and density change neuronal activity. Despite dendritic spines are very dynamic structures they are commonly classified into three types: thin, mushroom and stubby according to its head and neck characteristics, and the specific morphology of the spines are related to its function. In this study, we aimed to evaluate the effects of the excitotoxic hippocampal lesion on the seventh postnatal day in the rat on the spine density and spines morphology at the adult age of pyramidal neurons of the prefrontal cortex layers 3 and 5, the basolateral amygdala and medium spiny neurons of the nucleus accumbens by the Golgi-Cox stain method. Our results confirm that corticolimbic neurons have a minor spine density due the NVHL, but also we found decreased number of mushroom-like spines in animals with the excitotoxic lesion, suggesting that the dendritic spines dynamics also underlies the abnormalities caused by the NVHL.

Disclosures: H. Tendilla: None. **A.J. Vázquez-Hernández:** None. **R.A. Vázquez-Roque:** None. **L. Garcés-Ramírez:** None. **G. Flores:** None.

Poster

258. Schizophrenia: Developmental Models

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 258.03/UU18

Topic: H.03. Schizophrenia

Support: R01MH110681

Title: Blunted prefrontal dopamine release in a NMDA receptor hypofunction mouse model

Authors: *K. NAKAO[1], Y. FUJITA[3], K. JAUNARAJS[2], K. HASHIMOTO[3], K. NAKAZAWA[1]
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Abstract: In vivo PET imaging demonstrates an increase in psychostimulant-induced dopamine (DA) release in the striatum of patients with schizophrenia. A recent PET study also showed a deficit in amphetamine-induced DA release in PFC in schizophrenia. Such dysfunction of DA

system in schizophrenia may be following to a deficit in NMDA receptor (NMDAR) function. We investigated the impact of NMDAR blockade on amphetamine-induced DA release in PFC and striatum in an NMDAR hypofunction mouse models, where NMDAR subunit GluN1 deletion occurs in a subset of GABA neurons in postnatal development or in adulthood (Belforte et al, 2010). Notably, over 80 % of parvalbumin (PV)-positive GABA neurons in the mPFC are GluN1-deleted, while less than 5% of PV local neurons are affected in the ventral striatum or VTA. We also used a PV-cre or somatostatin-cre mediated GluN1 KO mouse strain. We measured psychostimulant-induced locomotor activity, the basal levels of tissue DA and its metabolites by HPLC, and extracellular DA levels from accumbens (NAc, lateral shell) and mPFC before and after amphetamine (2.5 mg/kg, i.p.) by in vivo microdialysis technique. Postnatal GluN1 KO mutant mice showed much higher stimulant-induced locomotor activity compared to the controls. Almost no genotypic difference was detected in tissue DA and HVA levels by HPLC. In vivo brain microdialysis showed no differences in the baseline DA levels in mPFC and NAc before the treatment. Amphetamine injection evoked 21.6-fold DA release from the baseline in the NAc of the postnatal KO mice, whereas only 5-fold increase in the control mice ($F(1, 10) = 9.4$, $p=1.9E-05$, repeated ANOVA). In a separate cohort, no amphetamine-induced DA increase was detected in mutant mPFC, whereas 3-fold increase was observed in the control mPFC ($F(1, 15) =7.1$, $p=9.3E-05$, repeated ANOVA). A similar blunted DA release in mPFC was observed in PV- GluN1 KO mutants, while the DA behavior of adult GluN1 KO mutant mice or somatostatin-cre/GluN1 KO mutant mice was similar to that in control mice. In conclusion, postnatal NMDAR hypofunction in GABA neurons, in particular in PV neurons, confers mPFC hypo-DA and striatal hyper-DA levels, further suggesting a role of PV neuron-NMDAR hypofunction in schizophrenia pathophysiology.

Disclosures: K. Nakao: None. **Y. Fujita:** None. **K. Jaunarajs:** None. **K. Hashimoto:** None. **K. Nakazawa:** None.

Poster

258. Schizophrenia: Developmental Models

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 258.04/UU19

Topic: H.03. Schizophrenia

Support: NIH-NIMH MH071533-11

Title: Synaptic remodeling of small dendritic spines over adolescent auditory cortex development

Authors: *E. M. PARKER[1], C. E. MOYER[3], J. T. NEWMAN[1], Z. P. WILLS[1], M. L. MACDONALD[2], R. A. SWEET[4]
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Biol., Univ. of California Santa Cruz, Santa Cruz, CA; [4]Dept Psychiatry, Univ. of Pittsburgh Dept. of Psychiatry, Pittsburgh, PA

Abstract: Dendritic spines are motile, postsynaptic structures at excitatory synapses. Following synaptic remodeling of excitatory circuits during adolescence in normal development, dendritic spine density is reduced in cortical areas including primary auditory cortex (A1) in adulthood. Excess synaptic remodeling during adolescence is thought to occur in schizophrenia (Sz), resulting in excessive loss of dendritic spines. Reduced dendritic spine density has been observed in multiple brain regions in Sz in adulthood, including in A1. We recently reported that the dendritic spine density reduction in Sz in A1 is limited to dendritic spines of smaller volumes, which are presumed to be predominantly transient. Further, we found that increased levels of a peptide shared among $Ca_V\beta$ isoforms was associated with reduced density of small, but not large dendritic spines in A1. Overexpressing *CACNB4,* which encodes the $Ca_V\beta$ isoform $Ca_V\beta4$ and is associated with Sz risk, led to reduced density of small dendritic spines in primary neuronal culture. For the current study, we hypothesized that previous observations of reduced A1 dendritic spine density during adolescent development is driven by and selective for small dendritic spine loss. We measured dendritic spine density over A1 adolescent development using stereological and quantitative confocal fluorescence microscopy techniques and found that mean density of small dendritic spines was significantly reduced in adult (P84) as compared to early adolescent (P28) mouse A1 ($p<.001$). The density of large dendritic spines was not altered. These findings suggest that the smallest and likely transient dendritic spines are targeted during synaptic remodeling in A1 during adolescent development. We will report findings from experiments that characterize $Ca_V\beta$ isoform levels over normal A1 mouse development to determine if elevated *CACNB4* levels are associated with dendritic spine density reduction during adolescent development in mouse A1.

Disclosures: E.M. Parker: None. **C.E. Moyer:** None. **J.T. Newman:** None. **Z.P. Wills:** None. **M.L. MacDonald:** None. **R.A. Sweet:** None.

Poster

258. Schizophrenia: Developmental Models

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 258.05/UU20

Topic: H.03. Schizophrenia

Support: MH071533 (RAS)

Title: A schizophrenia-associated missense mutation in kalirin converges on multiple RhoA-dependent pathways involved in cytoskeletal morphology

Authors: *M. J. GRUBISHA[1], G. E. HOMANICS[2], P. PENZES[3], R. A. SWEET[4]
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Abstract: Study: Kalirin (KAL) is a Rho GEF that is highly involved in regulation of cytoskeletal morphology within dendrites. There are several isoforms of the protein that arise from differential splicing. A missense mutation (P2255T, KAL9-PT) in the KAL9 isoform has been associated with schizophrenia. PTKAL9 demonstrates increased RhoA activation in an *in vitro* overexpression system. We hypothesized that the increased RhoA activity arising from the PT mutation contributes to a disease associated phenotype in pyramidal cells.
Methods: A humanized mouse model of the KAL9-PT mutation was created using CRISPR/Cas9 genome editing. Frontal pole homogenate was collected from wild-type (KAL9-WT) and KAL9-PT mice and RNAseq was performed on an Illumina HiSeq platform. Differential gene expression was calculated and pathway analysis was performed using BaseSpace Correlation engine. *In vitro* morphological studies were performed on DIV8 neurons grown from dissociated cortical cultures derived from KAL9-WT and KAL9-PT P0 mouse pups.
Results:. Frontal pole cortex from KAL9-PT CRISPR/Cas9 mice shows differential expression of multiple genes which are enriched in neuron development pathways using gene ontology classifications. Of these differentially regulated genes, multiple RhoA-dependent signaling pathways which are involved in cytoskeleton dynamics were identified. *In vitro* morphological data will be presented.
Conclusion: The increased RhoA activity arising from the PT mutation results in perturbation of multiple convergent pathways involved in signaling to the cytoskeleton in a RhoA-dependent manner. These signaling pathway perturbations may underlie some of the observed functional impairments seen in pyramidal cells in schizophrenia.
Significance: Using a disease-associated mutation to model convergent pathway perturbations involved in cytoskeleton remodeling may aid the development of novel pharmacotherapeutics for schizophrenia.
Funding Source: MH071533 (RAS)

Disclosures: M.J. Grubisha: None. **G.E. Homanics:** None. **P. Penzes:** None. **R.A. Sweet:** None.

Poster

258. Schizophrenia: Developmental Models

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 258.06/UU21

Topic: H.03. Schizophrenia

Support: NIMH Grant MH097997

JJ Peters VA MIRECC

Title: Dominant expression of human mutant DISC1 in oligodendrocyte progenitors increases their proliferation by altering neuregulin signaling

Authors: *P. L. KATSEL[1], P. FAM[1], W. TAN[1], S. KHAN[1], Y. JOUROUKHIN[2], S. RUDCHENKO[3], M. PLETNIKOV[2], V. HAROUTUNIAN[1,4]
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Abstract: Strong evidence corroborates involvement of oligodendrocyte (OLG) dysfunction in the pathophysiology of schizophrenia (SZ). Expression of mutant human DISC1 (hDISC1) in neural progenitors exerts a significant influence on oligodendrogenesis during early development. Neuregulins regulate brain development and their abnormal signaling detected in SZ. We examined gene expression of receptors and downstream effectors of neuregulin signaling in isolated OLG ($NG2^+$) and non-OLG ($NG2^-$) progenitors from mutant hDISC1 and control mice during embryonic of development (E15). Gene expression changes were measured by a 24-plex QuantiGene assay. Expression values were normalized to housekeeping genes. We found that RNA levels of mutant hDISC1 in forebrain OLG progenitors were almost 2 fold higher than in forebrain $NG2^-$ cells and 4.6 fold higher than in hindbrain OLG progenitors in mutant embryos, while similar ratio for $NG2^-$ cells were only 2.6 fold. OLG progenitors were characterized by high expression of their specific markers: Sox10, NG2, PDGFRA, and Nkx2-2, which were depleted in $NG2^-$ cells. Endogenous mouse Disc1 levels were significantly decreased ($p=0.002$) only in the forebrain OLG progenitors, but were unchanged in both forebrain and hindbrain $NG2^-$ cells. Evaluation of the neuregulin signaling pathway in OLG progenitors from forebrain and hindbrain regions of control embryos showed no significant changes, while forebrain OLG progenitors isolated from mutant mice show aberrant changes for the levels of neuregulin 1 and negative regulators of AKT signaling and changes indicative of activation of Ras-Raf-ERK signaling implicated in enhanced proliferation. Evaluation of neuregulin signaling pathway in $NG2^-$ cells isolated from forebrain regions show noticeable activation of PI3K-AKT-mTOR signaling cascade compare to the same cells isolated from hindbrain with no apparent difference between mutant and control groups. Activation of the PI3K-AKT-mTOR signaling cascade is suggestive of increased differentiation and cell growth. Flow cytometry analysis shows expansion of ($Nkx2\text{-}2^+$) OLG progenitors in the forebrain of hDISC1 embryos corroborating changes in neuregulin signaling in forebrain OLG progenitors indicative of increased proliferation. Thus, anomalous developmental positioning and proliferation of OLG identity cells impacts cortical organization which may have long-term effect on development and beyond. Our results provide new clues for how genetic risk factors could contribute to the developmental mechanisms of OLG dysfunction in SZ.

Disclosures: **P.L. Katsel:** None. **P. Fam:** None. **W. Tan:** None. **S. Khan:** None. **Y. Jouroukhin:** None. **S. Rudchenko:** None. **M. Pletnikov:** None. **V. Haroutunian:** None.

Poster

258. Schizophrenia: Developmental Models

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 258.07/UU22

Topic: H.03. Schizophrenia

Support: Institutional Support: USF Department of Molecular Medicine

Title: Altered sensorimotor gating, associative learning, and neurogenesis in a novel schizophrenia model using DISC1 and Reelin gene mutations

Authors: *H. L. MAHONEY[1], C. MORRIS[1], B. M. CAPRARO[1], A. YUNUS[4], C. CARDONA[1], E. J. PETERSON[1], H. S. JUSTIN[1], K. STEVANOVIC[5], A. L. LUSSIER[6], J. GAMSBY[1], E. J. WEEBER[2], D. GULICK[3]
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Abstract: This study evaluates behavior and neurogenesis in a novel genetic mouse model of schizophrenia (SCZ) in which two putative SCZ susceptibility genes, Disrupted-in-schizophrenia-1 (DISC1) and Reelin, have been disrupted. Reelin is essential for proper brain lamination during development, and is a key regulator of neurogenesis and synaptic plasticity in the adult. In patients with SCZ, Reelin expression is lowered by ~50% in postmortem brain tissue. Reelin is reduced to a similar magnitude in the heterozygous reeler mouse, which demonstrate some schizophrenia phenotypes. Disruption of DISC1 has also been linked to SCZ. DISC1 is involved in multiple cellular processes, including adult neurogenesis and dendritogenesis, and it acts upstream of Reelin to regulate its processing by proteolytic cleavage. We hypothesized that combined disruption of DISC1 and Reelin would generate a more severe SCZ-like phenotype than either mutation alone, including behavioral and learning deficits and altered neurogenesis.
Heterozygous reeler mice were bred with mice expressing dominant-negative c-terminal truncated human DISC1 to produce offspring with both mutations. These double transgenic mice were subjected to a battery of SCZ-relevant behavioral tests to evaluate sensorimotor gating, social behavior, learning and memory, and affect. Neurogenesis and neuronal maturation were assessed using doublecortin immunohistochemistry and stereological estimation. Results were compared to the performance of mice with only one of the two mutations and wild type mice. Double transgenic mice had a robust deficit in pre-pulse inhibition, indicating a sensorimotor gating deficit, and spent less time socially interacting. Interestingly, these mice also exhibited higher freezing than controls in contextual FC, but also in the pre-CS control test, indicating increased anxiety. Exploratory behavior was normal in the double mutant mice, although mutant

DISC1 mice spent more time in the open arms of the elevated plus maze. Maturation of adult-born neurons was also altered in double transgenic mice: while they had no difference in the total number doublecortin positive cells, more of these cells were in immature stages of development. To our knowledge, this is the first study to combine mutant DISC1 insertion with Reelin haploinsufficiency. This novel model recapitulates some hallmark behavioral changes observed in other SCZ models, and marked alterations in neuronal maturation. Following characterization, this model will be used to investigate gene-environment interactions that may lead to SCZ susceptibility.

Disclosures: H.L. Mahoney: None. **C. Morris:** None. **B.M. Capraro:** None. **A. Yunus:** None. **C. Cardona:** None. **E.J. Peterson:** None. **H.S. Justin:** None. **K. Stevanovic:** None. **A.L. Lussier:** None. **J. Gamsby:** None. **E.J. Weeber:** None. **D. Gulick:** None.

Poster

258. Schizophrenia: Developmental Models

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 258.08/UU23

Topic: H.03. Schizophrenia

Support: NIH Grant T32 GM007507

University of Wisconsin, Madison Start-up Fund

Title: A novel Disc1 rat model of schizophrenia-like deficits

Authors: *B. R. BARNETT[1,2], E. A. SAWIN[3], C. D. RUBENSTEIN[4], V. P. BAKSHI[2,5], J.-P. YU[2,6]
[2]Neurosci. Training Program, [3]Sch. of Med. and Publ. Hlth., [4]Translational Genomics Facility, [5]Psychiatry, [6]Radiology, [1]Univ. of Wisconsin, Madison, Madison, WI

Abstract: Schizophrenia is a chronic and debilitating mental illness affecting perception, cognition, behavior, and social functioning and affects up to 1% of the worldwide population. *Disc1* is a well-known genetic variant of large effect in the neuropathogenesis of schizophrenia first identified in a unique Scottish pedigree segregating with schizophrenia and influences neuronal migration and patterning in early neurodevelopment as well as corticogenesis *in vivo*. To further understand the contribution of *Disc1* in the both the neurodevelopment and neuropathogenesis of schizophrenia, we have generated a novel biallelic CRISPR/Cas9 *Disc1* rat knockout model. Using CRISPR/Cas9, the second coding exon of *Disc1* was targeted for genome editing through the generation of nonsynonymous mutations. An *in vitro* transcription template was generated and microinjected into Sprague Dawley embryos, and subsequently implanted into pseudopregnant female Sprague Dawley recipients. Genotyping of potential

founders indicated the successful excision of the target, and genotyping of the resultant pups from the F1 generation identified two ideal loss-of-function alleles: *Disc1*[860] and *Disc1*[874]. To the best of our knowledge, our model represents the first biallelic knockout model of *Disc1*, as well as the first *Disc1* knockout in rat, making it a useful entry point to explore important systems-level functional markers of schizophrenia. We will explore the gene-specific contribution of *Disc1* in the modulation of core behavioral endophenotypes and establish a novel platform for further exploration into the molecular, behavioral, and neuroimaging features of this novel animal model of schizophrenia.

Disclosures: B.R. Barnett: None. **E.A. Sawin:** None. **C.D. Rubenstein:** None. **V.P. Bakshi:** None. **J. Yu:** None.

Poster

258. Schizophrenia: Developmental Models

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 258.09/UU24

Topic: H.03. Schizophrenia

Support: NIGMS/NIH P20GM0103423

Title: Longitudinal evaluation of prepulse inhibition in DISC1 knockout rats reveals sexually dimorphic patterns of impairment across development

Authors: *S. S. DESROCHERS[1], M. J. GLENN[2], E. L. BAINBRIDGE[2]
[1]Biol., [2]Psychology, Colby Col., Waterville, ME

Abstract: Schizophrenia is a chronic disorder characterized by three symptom categories: positive (hallucinations, delusions), negative (anhedonia, anxiety), and cognitive (sensory processing and memory deficits). Our understanding of the biological bases of schizophrenia is facilitated by the use of animal models and advances in genetic tools have spurred the development of several etiological models. We work with a genetic model using a biallelic deletion of the disrupted-in-schizophrenia-1 (DISC1) gene in Sprague-Dawley rats. Mutations of DISC1 are associated with a higher prevalence of mental illness, especially schizophrenia. Adult DISC1 knockout, compared to wildtype, rats consistently display features of schizophrenia-like outcomes in rodent models: hyperactivity, anxiety, and impaired memory. They also display deficits in prepulse inhibition (PPI), a sensory gating phenomenon that is also absent in humans with schizophrenia. The present study investigated the progression of this cognitive symptom using a longitudinal design. Also under examination was the extent to which the emergence and severity of PPI deficits were sexually dimorphic; schizophrenia onset and symptoms can be sexually dimorphic but there is mixed evidence in the human and animal literature about the extent to which females display PPI deficits. Cohorts of DISC1 and wildtype female and male

rats were bred on site and PPI was assessed at postnatal days 17 (preweaning), 26 (prepubertal), 39 (adolescent), and 67 (adult). Cohorts of untested rats from each condition were sacrificed at each timepoint to investigate neural correlates, including markers of hippocampal function and dopaminergic activity. The findings were that no rats exhibited significant PPI at preweaning. Following that, male DISC1 knockout rats were significantly impaired at the prepubertal and adult timepoints; but not in adolescence. This pattern points to a need to examine PPI more extensively through the adolescent period. Females exhibited little evidence of PPI deficits. PPI is sensitive to females' hormonal cycles and this may have contributed to our findings. Neuronal assays, which are ongoing, may aid our understanding of these patterns. Nonetheless, these findings highlight the importance of including females in the study of schizophrenia. Additionally, as cognitive symptoms in schizophrenia are difficult to treat, these results may point to windows of opportunity for intervention.

Disclosures: S.S. Desrochers: None. **M.J. Glenn:** None. **E.L. Bainbridge:** None.

Poster

258. Schizophrenia: Developmental Models

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 258.10/UU25

Topic: H.03. Schizophrenia

Support: NIH Grant MH103775

Title: The cognitive function of adolescent and adult male and female rats in the MAM animal model of schizophrenia

Authors: *M. GHASEMZADEH, R. DIDOMINICIS, C. ALBRECHT, L. KELBLE, D. KRAVTSOV
Dept. of Biomed. Sci., Marquette Univ., Milwaukee, WI

Abstract: Schizophrenia is a neurodevelopmental mental disorder with distinct abnormal behaviors and cognitive deficits. Since the MAM neurodevelopmental animal model (E17 gestational methylazoxymethanol acetate administration) displays many of the anatomical and neurochemical deficits associated with schizophrenia, we examined the performance of the MAM-treated animals (Sprague-Dawley rats) in behavioral cognitive tasks to evaluate the extent and nature of the deficits in this model. Rats were bred on site and MAM (22 mg/kg, ip) or saline (1 ml/kg, ip) was administered on gestation day 17. Male and female offspring were housed 3-4 per cage and were provided with enrichment. All efforts were made to eliminate sources of stress in these animals during development and behavioral testing. We examined the male and female rats both during adolescence (PND 35-45) and adult (PND> 90) ages. The adolescent MAM rats (male and female) responded with higher locomotor activity in a novel environment, which

continued through adulthood. In an open field arena, adolescent and adult MAM-treated rats (male and female) spent more time in the center of the arena compared to the saline-treated animals. In addition, adolescent and adult MAM-treated animals (male and female) spent more time on the open arm of the elevated plus maze compare to saline-treated rats. We also examined the sensory information processing in adult saline and MAM rats (male and female) using the prepulse inhibition of startle response task. Our results suggest that adult male MAM rats perform better in prepulse inhibition of startle response while the adult female MAM rats displayed deficits in sensory processing. Similarly, adult male MAM rats engaged in higher levels of social interaction, whereas adult female MAM rats were not different from saline-treated animals. Both adult MAM genders performed similar to the saline-treated rats in novel object recognition. The overall pattern of behaviors displayed by the MAM animal model is suggestive of a decrease in behavioral inhibition. Some aspects of the schizophrenia symptoms also suffer from the loss of behavioral inhibition. The data suggest that the MAM animal model may be useful in examining the neuronal basis of behavioral inhibition.

Disclosures: **M. Ghasemzadeh:** None. **R. DiDominicis:** None. **C. Albrecht:** None. **L. Kelble:** None. **D. Kravtsov:** None.

Poster

258. Schizophrenia: Developmental Models

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 258.11/UU26

Topic: H.03. Schizophrenia

Support: NHMRC grant #1020981

NHMRC Principal Research Fellowship #1117079

Title: Raloxifene alters the effect of testosterone-removal on truncated tropomyosin receptor kinase B isoform gene expression in prefrontal cortex of adult male rats

Authors: *T. RAHMAN[1,2], T. D. PURVES-TYSON[1,2], C. SHANNON WEICKERT[1,2]
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Abstract: People with schizophrenia suffer from deficits in executive function that involves dysregulated prefrontal cortex. Men with schizophrenia generally have low circulating testosterone, and in a clinical study we found that this correlated with worse executive function. These same men exhibited improved working memory and attention after treatment with selective estrogen receptor modulator, raloxifene. Understanding how raloxifene works in the mammalian cortex can help uncover new and better treatments for this disorder. People with

schizophrenia have increased truncated isoforms of tropomyosin receptor kinase B (TrkB) in prefrontal cortex that may contribute to their deficits in cognition. Previously, we found that testosterone-removal during adolescence via gonadectomy increases the gene expression of truncated TrkB isoform, T2, messenger ribonucleic acid (mRNA) in prefrontal cortex of young adult rats. Here, we investigated if these changes also occur later in adulthood, and we investigated the effect of estrogen receptor modulation on TrkB gene expression. We predicted that raloxifene treatment at adulthood would alter the effect of gonadectomy at adolescence on TrkB isoform gene expression in prefrontal cortex of rats. Early adolescent [postnatal day (P) 45] male Sprague-Dawley rats were sham-operated (SB) or gonadectomised and given blank implants (GB). These rats were then treated with either vehicle (V) or raloxifene (R, 5 mg/kg) for four weeks from young adulthood (P59) to sacrifice (P88). This produced four groups (n=12-15 each): SBV, GBV, SBR, GBR. TrkB [full length, truncated (T1, T2)] mRNA transcripts were quantified in prefrontal cortex via quantitative polymerase chain reaction, and normalised to the geomean of four housekeeper mRNAs. Raloxifene treatment reduced TrkB-T1 mRNA by ~25% in intact rats (SBV-SBR, $p<0.05$) and did not alter full length or truncated TrkB mRNAs in gonadectomised rats (GBV-GBR, $p>0.05$). In vehicle treated rats, gonadectomy did not alter full length or truncated TrkB mRNAs (SBV-GBV, $p>0.05$). However, in raloxifene treated rats, gonadectomy increased TrkB-T1 mRNA by ~49% and TrkB-T2 mRNA by ~156% (SBR-GBR, $p<0.05$). These results indicate that estrogen receptor modulation by raloxifene may increase neurotrophic support in intact rats and decrease neurotrophic support in gonadectomised rats. Our results suggest that raloxifene may have distinct actions on cortical TrkB isoform gene expression in males based on whether they have low or normative circulating testosterone.

Disclosures: **T. Rahman:** None. **T.D. Purves-Tyson:** None. **C. Shannon Weickert:** F. Consulting Fees (e.g., advisory boards); Member of an Advisory Board for Lundbeck Australia Pty Ltd.

Poster

258. Schizophrenia: Developmental Models

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 258.12/UU27

Topic: H.03. Schizophrenia

Support: Lewis Biophotonics Fellowship

NIH Grant AG047669

Title: The role of neuregulin 1 and basal forebrain cholinergic neurons in cognitive functions and behaviors

Authors: *C.-T. LEE[1], L. SERVILIO[1], B. DOMINGUEZ[1], F. DE WINTER[2], K.-F. LEE[1]
[1]Salk Inst., LA Jolla, CA; [2]Lab. for Neuroregeneration, Netherlands Inst. for Neurosci., Amsterdam, Netherlands

Abstract: Neuromodulation is fundamental for regulating neural circuits underlying behaviors. Cholinergic neurons (CNs) play essential neuromodulatory roles in a variety of neural behaviors, including attention, cognition, consciousness and maintenance of the integrity of thought. For example, basal forebrain CNs (BFCNs) have recently been shown to elicit fast and precisely timed feedback behavioral responses. Furthermore, cholinergic deficits in BF have been commonly reported in schizophrenia and Alzheimer's Disease. Neuregulin 1 (NRG1) is highly expressed in both central CNs and non-CNs. In addition, many polymorphisms in the NRG1 gene have been associated with increased risk for schizophrenia. However, how BFCNs modulate cognitive functions and behaviors and how dysfunctions of CNs or NRG1 result in schizophrenia still remain unknown. Here we combined mouse genetics, anatomical, molecular, electrophysiological and optogenetics approaches and behavioral tests to elucidate molecular and circuit mechanisms underlying cognitive and behavioral deficits in mice lacking NRG1 in central CNs. We crossed ChAT knock-in Cre mice with floxed Nrg1 mice to conditionally knock out Nrg1 in CNs. The conditional knock-out (CKO) mice showed impaired sensorimotor gating (prepulse inhibition), enhanced vocalization, and tremor. We found altered electrophysiological properties of BFCNs in these CKO mice, which may result in abnormal activities in BFCNs. Immunostaining showed eliminated NRG1 also accompanied with decreased muscarinic acetylcholine receptor clusters in BFCNs of CKO mice. We also examined the synaptic connections and spontaneous inputs in layer V pyramidal neurons and GABAergic interneurons in the prefrontal cortex, which is one of main downstream targets of BFCNs related to high cognitive functions. Finally, we manipulated the neuronal activities of prefrontal cortical projecting BFCNs by using in vivo optogenetics to examine their roles in cognitive functions such as sensorimotor gating in Nrg1 CKO mice.

Disclosures: C. Lee: None. **L. Servilio:** None. **B. Dominguez:** None. **F. De Winter:** None. **K. Lee:** None.

Poster

258. Schizophrenia: Developmental Models

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 258.13/UU28

Topic: H.03. Schizophrenia

Support: Grant-in-Aid for Scientific Research on Innovative Areas (Micro-endophenotypes) No. 24116010

JSPS Grant-in-Aid for Basic Scientific Research B No. 25290004

JSPS Grant-in-Aid for Basic Scientific Research B No. 17H04030

Title: Abnormal development of nigral dopamine activities in a cytokine-induced schizophrenia model; implication for its postpubertal onset

Authors: *H. NAMBA, K. TOMIYAMA, H. NAWA
Mol. Neurobiol., Brain Res. Inst., Niigata Univ., Niigata, Japan

Abstract: Schizophrenia typically develops during and after human adolescent stage. However, it remains to be understood how the disease onset is limited to the post-pubertal stage. To address this question, we employed one of animal models for schizophrenia, in which behavioral and cognitive abnormalities emerge at the post-pubertal stage. The animal model was made by subcutaneously administering a cytokine, epidermal growth factor (EGF), to rat or mouse pups and displayed various behavioral abnormalities in prepulse inhibition, social interaction, latent inhibition of fear learning, etc. We analyzed the spontaneous activity and channel properties of developing nigral dopamine neurons and compared these indices between the schizophrenia model and control animals. *In vivo* spontaneous activity was monitored in an anesthetic condition and electrophysiological properties were analyzed by slice patch-clamp recording. At the peri-adolescence stage of postnatal 6 week, the burst ratio of *in vivo* spontaneous activities of EGF pre-treated animals was significantly lower than that of controls. After the adolescence stage of postnatal week 12, however, the relative relation became opposite; the burst ratio of firing activities of EGF pre-treated animals became higher than that of controls. In parallel with the developmental alteration of the spike activity, the amplitudes of spike after-hyperpolarization and apamin-sensitive Ca^{2+}-activated K^+ current were decreased in EGF-pretreated mice. The neonatal EGF treatment also decreased hyperpolarization-activated currents, I_h, which plays a role in the regulation of their pacemaker-like firing. Thus, the EGF-triggered alterations in the channel properties of dopamine neurons presumably contributed to the post-pubertal elevation of their burst firing. These electrophysiological studies on the EGF model for schizophrenia suggest the possibility that the aberrant post-pubertal hyperactivity of midbrain dopaminergic neurons determines the temporal specificity of the disease onset.

Disclosures: H. Namba: None. **K. Tomiyama:** None. **H. Nawa:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Higeta Shoyu Co., Ltd.

Poster

258. Schizophrenia: Developmental Models

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 258.14/UU29

Topic: H.03. Schizophrenia

Support: MH092740

MH083911

Title: NL-2 R215H mutant mouse model display GABAergic deficits and schizophrenia like behaviors

Authors: *D. JIANG
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Abstract: Abstract
Schizophrenia disorder (SCZD) is a chronic neurodevelopment disorder characterized by psychosis and cognitive deficits. GABAergic neural transmission deficits have long been proposed to play important roles in the pathophysiology of schizophrenia. Recently our group found that a small number of SCZ patients carry mutations in the gene encoding neuroligin 2 (NL-2), a cell adhesion molecule located at postsynaptic sites of inhibitory synapses. Our previous study showed that among the mutations, the Arg^{215} □ His^{215} (R215H) substitution of NL2 is a loss of function mutation that results in the failure of GABAergic synapse formation. Based on this exciting finding, we generated a NL2 R215H single point mutation knock-in mouse model by introducing the R215H mutation into mouse genome. We found that R215H mutant mice have dramatic reduction of NL2 protein expression, impaired GABAergic synapse transmission, and display schizophrenia-like behaviors partially recapitulate human patients' symptom. These results indicate that R215H KI mouse model may be a useful experiment system for further study of schizophrenia disorder.

Disclosures: D. Jiang: None.

Poster

258. Schizophrenia: Developmental Models

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 258.15/UU30

Topic: H.03. Schizophrenia

Support: JSPS KAKENHI Grant Number 25290004

MEXT KAKENHI Grant Number 24116010

Grant for Promotion of Niigata University Research Projects

Title: Neonatal exposure to epidermal growth factor leads to abnormal auditory responses in rats: Their implication in schizophrenia modeling

Authors: *H. INABA[1], ***H. INABA**[1], I. NARIHARA[1], R. KAI[1,2], H. NAMBA[1], F. NIN[3], H. HIBINO[3], H. NAWA[1]

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Abstract: Individuals with schizophrenia show neuropathological deficits in sensory processing such as auditory hallucination. Epidermal growth factor (EGF) is one of the ErbB receptor ligands which are implicated in schizophrenia neuropathology and genetics. We have shown that rats neonatally treated with this cytokine later exhibit several neurobehavioral abnormalities relevant to schizophrenia, including impaired acoustic prepulse inhibition and abnormal social interaction. With the given large behavioral differences between humans and rodents, however, it remains to be tested whether this animal model exhibits the schizophrenia-like auditory neuropathology as seen in human patients. To explore such deficits in auditory processing, we monitored auditory evoked responses of this EGF model with electrocorticography (ECoG). Auditory ON and OFF (i.e. offset) responses were triggered with tone bursts (75 dB, 2 or 20 kHz; 1, 3, or 10 sec duration), and recorded from the primary auditory cortex under urethane anesthesia. In general, the peak amplitude of OFF responses tended to increase following longer tone stimuli. In EGF-treated rats, the mean peak amplitude of ON responses was significantly reduced in 20 kHz but not 2 kHz stimuli. The peak amplitude and their latency of OFF responses were reduced and delayed, respectively, in both frequencies with the reduced inter-trial coherence of OFF responses. Subchronic treatment with an atypical antipsychotic drug (risperidone) ameliorated the deficits in peak amplitude of ON responses as well as in peak latencies of OFF responses. Our preliminary experiments revealed that mean auditory brainstem responses (ABR) of EGF-treated rats to high frequency (16, 24, and 32 kHz) stimuli exhibited non-significant treads to be decreased, but the individual ABR of EGF-treated rats were still within the normal range of control ABR distribution. These observations indicate that perinatal exposure to EGF later results in an impairment of auditory evoked ON and OFF responses and presumably hampers auditory cognition of this animal model, which might associate with the auditory hallucination of patients with schizophrenia.

Disclosures: H. Inaba: None. **I. Narihara:** None. **R. Kai:** None. **H. Namba:** None. **F. Nin:** None. **H. Hibino:** None. **H. Nawa:** None.

Poster

258. Schizophrenia: Developmental Models

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 258.16/UU31

Topic: H.03. Schizophrenia

Title: Neuregulin 1 type III overexpressing mice possess an altered hippocampal transcriptome that implicates the Igf and PI3K pathways: A microarray study

Authors: *J. C. OLAYA[1], *J. C. OLAYA[1], M. A. KONDO[1], D. SINCLAIR[2], M. M. MATSUMOTO[3], T. KARL[4], C. SHANNON WEICKERT[1]
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Abstract: Schizophrenia patients carrying Neuregulin 1 (NRG1) HapICE risk alleles appear to overproduce the NRG1 type III (III) isoform in their brain. In order to assess the impact of NRG1 III overexpression on the mammalian brain, we previously generated a mouse that overexpresses Nrg1 III in CamKII+ neurons. This transgenic mouse (Nrg1 III tg) exhibits several schizophrenia-like behavioural deficits including impaired fear conditioning, a task that requires intact hippocampal functioning. Given this finding, we sought to assess potential mechanisms by which Nrg1 III overexpression may perturb biological functioning in the hippocampus. To achieve this, we performed a transcriptomic microarray (Affymetrix GeneChip Mouse Gene 2.0 ST) of the hippocampus of 8 Nrg1 III tg and 10 WT mice. Using the Benjamini-Hochberg correction and a threshold criteria of a fold change of $> \pm 1.2$ and a false discovery rate of < 0.2, we found 187 transcripts to be significantly altered across genotype. Interestingly, several of these downregulated transcripts including 5-hydroxytryptamine (serotonin) receptor 2C and angiotensin converting enzyme are implicated in hippocampal function and are altered in people with schizophrenia. Additionally, several transcripts involved in the insulin-like growth factor (Igf) pathway (including Igf2, Igf binding protein 2 and Igf binding protein 7) are also downregulated and were confirmed via qPCR ($p < 0.5$). Abnormal Igf signaling may be of interest as downstream Igf1/Igf receptor 1 signaling may converge on downstream Nrg1 signaling via the PI3K kinase pathway (a pathway which mediates numerous crucial biological processes including cell survival, apoptosis and proliferation). Supplementing this, we found several more transcripts that mediate the PI3K pathway to be altered including phosphoinositide-3-kinase, class 2, beta polypeptide, Growth arrest-specific 6 (upregulated), and Serine Peptidase Inhibitor, Kunitz Type 2 (downregulated). In sum, microarray analysis has uncovered several potentially relevant pathological processes in the hippocampus that may be driven by Nrg1 III overexpression. In particular, the role of Nrg1 on Igf signaling in the brain is completely unknown and thus this work provides the first insight into the possible juncture between these two crucial biological pathways within the context of Nrg1 III overexpression in schizophrenia.

Disclosures: J.C. Olaya: None. **M.A. Kondo:** None. **D. Sinclair:** None. **M.M. Matsumoto:** None. **T. Karl:** None. **C. Shannon Weickert:** None.

Poster

258. Schizophrenia: Developmental Models

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 258.17/UU32

Topic: H.03. Schizophrenia

Support: Mississippi State University Office of Research

NIH 5T35OD010432

Title: Juvenile Toxoplasma gondii infection in mice exacerbates spatial learning deficits and reduces anxiety related behavior

Authors: *J. B. EELLS, S. X. GUO-ROSS, C. SMITH, S. MIDDLEBROOKS, A. VARELA-STOKES
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Abstract: *Toxoplasma gondii* is an obligate intracellular protozoan that infects approximately 20% of the population in the United States, with around 8% of children infected. *T. gondii* infection is associated with an increased risk and severity of schizophrenia, an increased risk of obsessive compulsive disorder, attempted suicide and addiction, and cognitive deficits in children and young adults. Currently, the mechanisms through which *T. gondii* infection alters behaviors and contributes to mental illness in humans is unclear and even less is known of how early life infection with *T. gondii* alters brain development and function. In order to better understand these effects, the current study compared the behavioral effects of juvenile and adult *T. gondii* infection in mice. Additionally, we investigated the effect of the Nurr1-null heterozygous (+/-) genotype with *T. gondii* infection as previous data has found these mice are more susceptible to the behavioral effects of *T. gondii* infection. Mice were infected at either 30 d or 90 d of age then tested beginning at 130 d of age for activity in an open field, avoidance of bobcat urine, episodic memory of a novel object, sensorimotor gating using prepulse inhibition of the acoustic startle response, spatial memory in the Barnes maze, anxiety in zero maze, spontaneous alternation in the Y-maze, and depressive behavior in the tail suspension test. *T. gondii* infection, both adult and juvenile, and the Nurr1 +/- genotype significantly reduced body weight to very similar levels. Behavioral data indicates that juvenile infection significantly decreased anxiety as compared to control mice and adult infected mice based on time in the open portion of the zero maze. Both *T. gondii* infection and the Nurr1 +/- genotype were associated with impaired spatial learning in the Barnes maze while juvenile infection exacerbated deficits in spatial learning in the Barnes maze as an indicated by an increase time to find and enter the escape compartment across all trials. *T. gondii* infection also attenuated spontaneous alternation in the Y maze and increased time immobile in the tail suspension test. These data indicate that *T. gondii* infection in juveniles can exacerbate the behavioral consequences of infection. As humans are commonly infected with *T. gondii*, infection in a child may be a greater risk factor for learning and memory deficits as well as future mental illnesses. Investigating how *T. gondii* infection alters learning and memory and behavior in mice will help determine the mechanisms responsible for these effects, which could be used to mitigate the risk for cognitive deficits and mental illnesses in infected individuals.

Disclosures: J.B. Eells: None. **S.X. Guo-Ross:** None. **C. Smith:** None. **S. Middlebrooks:** None. **A. Varela-Stokes:** None.

Poster

258. Schizophrenia: Developmental Models

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 258.18/UU33

Topic: H.03. Schizophrenia

Support: Ontario Mental Health Fundation

Title: PTP1B effects on synaptic function in a mouse model of schizophrenia induced by maternal immune activation

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Abstract: Schizophrenia (SZ) is a severe heterogeneous mental disorder that affects 0.7% of the population and does not discriminate against race or sex. The variety of symptoms have been classified into three categories: positive (hallucinations, delusions), negative (flat affect, social withdrawal, and lack of speech, motivation and pleasure), and cognitive symptoms (executive function deficits affecting working memory and attention control). SZ is highly sensible to environmental factors. Infection during gestation is estimated to be the cause of 14-21% of cases. In mice, we can inject poly(I:C) in pregnant dams to mimic viral infection and observe an array of SZ-like phenotypes (anxiety, working memory, sensory-motor gating and sociability deficits) due to an elevation of IL-6 during a crucial period of fetal brain development, known as maternal immune activation (MIA).
Independently emerging evidence involves metabotropic glutamate receptors (mGluR5) and endocannabinoid (eCB) signalling in SZ. mGluR5 facilitates eCB signalling via the PLCβ-DGLα pathway. Protein Tyrosine Phosphatase 1B (PTP1B), a target gene of IL-6, can disrupt endocannabinoid signalling in the basolateral amygdala by dephosphorylating metabotropic glutamate receptors. In our study, pregnant C57BL6 dams are injected with 5mg/kg poly(I:C) i.v. at gestational day 9.5 or equal volume saline solution. Neuronal PTP1B knock out (KO) or wildtype (WT) offspring then undergo a behavioral test battery at 3 months: Beam break test (locomotion), elevated plus maze and open field tests (anxiety), Y-maze test (working memory), social interaction test (sociability), and prepulse inhibition to acoustic startle response (sensory-motor gating). Offspring of vehicle treated control mice have not shown differences across the genetic model. Only limited offspring of poly(I:C) treated mice have been observed presently. Going forward, offspring of Poly(I:C) dams will be assessed. We expect WT SZ model mice to show deficits while KO mice to be protected. Electrophysiology signatures of endocannabinoid signalling, depolarization induced suppression of inhibition and induced inhibitory long term depression, will be studied. DHPG and AM251 will be used to manipulate mGluR5 and CB1R

activity respectively and determine pathway. Since SZ in humans likely has multiple aetiologies, and current targeting of the dopaminergic system is ineffective at treating negative symptoms, the validation of PTP1B as a therapeutic target of schizophrenia with a preclinical model, i.e. MIA, would provide further incentive for future clinical trials.

Disclosures: P. Couture: None. **Z.T. Qin:** None. **H. Chen:** None.

Poster

258. Schizophrenia: Developmental Models

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 258.19/UU34

Topic: H.03. Schizophrenia

Support: K12 HD43489-14

P50 MH103222

Title: Prenatal kynurenine elevation in rats: Sleep disturbances and hippocampal-prefrontal mediated learning impairments

Authors: *A. BARATTA[1], *A. BARATTA[1], S. A. BUCK[1], J. A. MONG[2], A. POCIVAVSEK[1]
[1]Maryland Psychiatric Res. Ctr., [2]Pharmacol., Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: Distinct abnormalities in kynurenine pathway metabolism have been reported in various psychiatric disorders, including schizophrenia (SZ). Kynurenic acid (KYNA) is an endogenous antagonist of α7 nicotinic acetylcholine (α7nACh) and NMDA receptors, and increases in brain KYNA have been implicated in the pathology of SZ. Based on the neurodevelopmental hypothesis of SZ etiology, wehave developed a model to study the KYNA hypothesis of SZ (Pocivavsek et al., Psychopharmacology, 2014).The bioprecursor to KYNA, kynurenine (100 mg/day),is fed to pregnant Wistardams from embryonic day (ED) 15 to ED 22 (control: ECon; kyn-treated: EKyn). Tissue KYNA levels remain increased in the hippocampus and prefrontal cortex of adult EKyn animals and EKyn offspring display learning and memory impairments,similar to cognitive dysfunctions that are core to SZ psychopathology. Asdisturbances in sleep can oftenaggravate illness severity for SZ patients and plausible hypotheses suggest that cognitive deficits and abnormal sleep may be connected, in the present study we investigated the sleep-wake behavior of adult EKyn offspring.Adult (postnatal day 56-85) ECon and EKyn offspring were implanted with telemetric devices to acquire polysomnographic recordings that combine electroencephalogram (EEG) and electromyogram (EMG)(N = 7 per group). Analyses of vigilance state-related parameters categorized as wake, rapid eye movement (REM) and non-REM (NREM) were assessed for 24 h. EKyn offspring had significantly reduced REM duration (-21%, $P < 0.01$) and average duration of each REM bout (-

13%, P < 0.05). No significant changes in NREM or wake architecture were found. In separate animals, we assessed spatial learning and memory in the Barnes maze (N = 22 - 25 per group). EKyn offspring displayed significant impairments, evidenced as increased latency to find the escape box, during the acquisition trials (P < 0.05). After training, the location of the Barnes maze escape box was moved to engage prefrontal-hippocampal circuitry during the reversal trial. EKyn offspring were significantly impaired, taking longer to find the new escape box (P < 0.05), making more errors (P < 0.01), and also entering the previous escape box location more frequently than ECon offspring (P < 0.01). Taken together, our data demonstrate a striking REM sleep deficit and an impairment in hippocampal-prefrontal mediated learning and memory in offspring that were exposed to elevated kynurenine during a vulnerable period in early brain development. We are continuing to elucidate the possible role of the kynurenine pathway, and KYNA in particular, in mediating the interplay between REM sleep and cognitive function.

Disclosures: **A. Baratta:** None. **S.A. Buck:** None. **J.A. Mong:** None. **A. Pocivavsek:** None.

Poster

258. Schizophrenia: Developmental Models

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 258.20/UU35

Topic: H.03. Schizophrenia

Title: Abnormalities in cortical parvalbumin-positive interneuron density and distribution and auditory evoked potentials in a mouse model of 22q11.2 Deletion Syndrome

Authors: F. A. ZINNAMON[1,2], F. G. HARRISON[2], *K. H. WANG[1], J. F. LINDEN[2]
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Abstract: 22q11.2 Deletion Syndrome (22q11DS) is the strongest known genetic risk factor for the development of schizophrenia (SCZ). The Df1/+ mouse model of 22q11DS recapitulates many features of human 22q11DS and schizophrenia, including cognitive impairment and frequent otitis media, a middle ear disease that can cause conductive hearing loss. Both hearing loss and SCZ risk factors have been associated with abnormalities in parvalbumin-positive (PV+) inhibitory interneuron circuitry in the cortex. Additionally, impairments in auditory evoked potentials (AEPs) serve as endophenotypic markers of SCZ. However, the relationship between hearing loss, genetic risk of SCZ, AEPs, and PV+ interneuron circuitry remains poorly understood. We explored this relationship through immunohistochemical and electrophysiological studies of auditory and frontal cortices in wildtype (WT) mice and Df1/+ mice with and without hearing loss. We tested hearing thresholds using auditory brainstem response measurements. During the same session, we also recorded AEPs to explore how hearing loss and genotype affect auditory cortical activity. PV+ immunohistochemistry on coronal sections through the auditory and frontal cortices of the mice indicated significant

reductions in PV+ interneuron cell counts and densities in Df1/+ mice within the primary auditory cortex (A1) but not the secondary motor cortex (M2). Quantifications of PV+ interneuron density across cortical layers showed that PV+ cell distributions were abnormal in both A1 and M2. Additionally, Df1/+ mice with hearing loss displayed altered AEPs suggestive of increased central auditory gain compensating for reduced input. Results indicate that genetic risk of schizophrenia and developmental hearing loss interact to produce cumulative abnormalities in PV+ interneuron networks with functional physiological sequelae.

Disclosures: F.A. Zinnamon: None. **F.G. Harrison:** None. **K.H. Wang:** None. **J.F. Linden:** None.

Poster

258. Schizophrenia: Developmental Models

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 258.21/UU36

Topic: H.03. Schizophrenia

Support: NIMH 1R01MH101130

NARSAD Young Investigator Grant

PhRMA Research Starter Grant in Pharmacology/Toxicology

University of South Carolina ASPIRE I Grant

University of South Carolina School of Medicine Research Development Fund Grant

Title: The role of PDE11A4 in isolation-induced neuroinflammation and social deficits

Authors: K. PILARZYK[1], *M. P. KELLY[2]
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Abstract: Phosphodiesterase 11A (PDE11A) is an enzyme that degrades cyclic nucleotides (cAMP and cGMP) and is the only PDE whose mRNA expression is restricted to the hippocampal formation. Previously, we showed that PDE11A4 is required for intact social behaviors—both for the formation of social memories and for social approach behaviors. We seek here to determine how isolation impairs social behaviors by decreasing PDE11A4 signaling and, subsequently, upregulating neuroinflammatory processes. When compared to group housing, one month of chronic social isolation decreased expression of PDE11A4 specifically within the membrane compartment of the ventral hippocampus (VHIPP). This decrease in PDE11A4 was also found acutely, after only one hour of social isolation. This PDE11A4 loss in the membrane compartment is specific, as there were no changes in the cytosolic or nuclear

compartments. In contrast to PDE11A4, PDE2A and PDE10A do not change with social isolation, suggesting that the effect on PDE11 is specific. Isolation-induced decreases in PDE11A4 expression appear functional as measured by changes in relevant signal transduction cascades and impairments in social behavior that occur in a PDE11A genotype-dependent manner. Interestingly, when looking at known markers of inflammation, we found that social isolation does increase proinflammatory cytokine interleukin-6 (IL-6) expression in the cytosol of the VHIPP, and deletion of PDE11A is sufficient to upregulate IL-6 expression specifically in the cytosol. In addition, we found that deletion of PDE11A is sufficient to increase the infiltration and the activation of microglia within the VHIPP. Together these data suggest that PDE11A4 is not only a key regulator of social behavior, but isolation-induced decreases in PDE11A4 are sufficient to impair subsequent social behavior and may account for the increases in neuroinflammation that are seen with social isolation.

Disclosures: K. Pilarzyk: None. **M.P. Kelly:** None.

Poster

258. Schizophrenia: Developmental Models

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 258.22/UU37

Topic: H.03. Schizophrenia

Support: NIH IRTA Fellowship

Intramural Research Program NIMH

Title: Neuronal avalanche dynamics in a developmental NMDAR hypofunction model of schizophrenia in mouse

Authors: *K. O. GOEL, S. SESHADRI, D. PLENZ
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Abstract: Cognitive impairment in schizophrenia (SZ) is thought to be rooted in excitatory-inhibitory imbalance, which results from NMDA receptor hypofunction during early neurodevelopment, and may be facilitated by Parvalbumin-positive interneuron (PVin) dysfunction. However, recent discoveries have questioned whether PVins are the main link between NMDAR hypofunction, abnormal dynamical states, and cognitive impairment in SZ. For example, mature PVins show weak NMDAR expression and currents and, in fact, a PVin-specific NMDAR knockout does not prevent the induction of SZ-associated phenotypes by NMDAR antagonists, but instead potentiates it. Additionally, power deficits observed for gamma frequency in SZ also exist in other frequency bands (including alpha and theta), which are relevant for cognition but not directly related to PVin dysfunction. This suggests a need for

alternate dynamic profiles as well as exploration into the effect of other interneuron types. Here we used the neonatal phencyclidine (PCP, an NMDAR antagonist) model, which is based on the NMDAR hypofunction theory of SZ, and reproduces several phenotypes observed in SZ patients, ranging from neuroanatomical to behavioral. The main advantage of this model over acute or subchronic PCP models is its resemblance to the human disease course of SZ, in which insults during neurodevelopment produce disease onset at adolescence. After performing PCP injections during development in mice (n = 5), preliminary results demonstrated cognitive impairment using the novel object recognition test (NORT) of visual working memory, where PCP-treated animals showed reduced preference for exploration of a novel object compared to non-PCP-treated littermates. Using 2-photon imaging of layer 2/3 pyramidal neurons in sensorimotor cortex of PCP-treated mouse during awake resting activity suggests an increase in repeat ROI firing, increase in sigma values, and a decrease in the burst length distribution slope when compared to non-PCP-treated littermates. We are currently using the PCP model in transgenic mouse lines, which will enable us to dissect interneuron dysfunction linked to this novel dynamical phenotype in the context of an NMDAR hypofunction model of schizophrenia.

Disclosures: **K.O. Goel:** None. **S. Seshadri:** None. **D. Plenz:** None.

Poster

258. Schizophrenia: Developmental Models

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 258.23/UU38

Topic: H.03. Schizophrenia

Support: Linden Fund

Title: Pairing of neonatal phencyclidine and adolescent stress as a model of schizophrenia

Authors: *A. MOGHADAM, L. R. VOSE, O. MIRY, P. K. STANTON
New York Med. Col., Valhalla, NY

Abstract: Schizophrenia is a debilitating mental disorder that has a lifetime prevalence of ~1%. The mainstay in treatment is antipsychotic medication, used primarily to ameliorate the positive symptoms (e.g. hallucinations) of the disease. However, this has not improved the functional independence of individuals with schizophrenia, likely because of the lack of therapies acting on other aspects of the disease, specifically the cognitive (e.g. learning and memory deficits) and negative (e.g. impaired sociability) components, the severity and type of which are strong predictors of disease prognosis. To further elucidate pathological mechanisms responsible for the disease, identify novel biological targets, and screen for therapeutic agents, we have established a new animal model of schizophrenia, one that addresses both cognitive and negative components. Our paradigm models a “two-hit” hypothesis of schizophrenia, which focuses on multiple

contributing factors and theorizes that individuals who are predisposed to develop the disease do so in response to triggering stressors. The “first hit” disrupts the central nervous system and promotes a persistent vulnerability, while a stressor later in life (the “second hit”) induces the disease state in susceptible individuals. We have applied this theory to a rat model by administering the N-methyl-D-aspartate glutamate receptor antagonist phencyclidine (PCP) during neonatal life (the “first hit”), followed by the “second hit” during early adolescence, a 2 hour restraint stress followed by a 20 minute forced swim stress. This protocol revealed that neonatal PCP, in combination with adolescent stress, resulted in persistent cognitive deficits that depend on both hits. Furthermore, these animals also exhibit marked reductions in long-term potentiation (LTP) of synaptic strength at Schaffer collateral-CA1 synapses in *in vitro* hippocampal slices, a biological substrate of learning and memory which correlated with the cognitive deficits observed. This model will be further developed by addressing three aims: 1) examination of known behavioral phenotypes in schizophrenia, including cognitive, sensorimotor, and social ability; 2) measurement of markers of synaptic function in both hippocampus and prefrontal cortex, including activity-dependent long-term synaptic plasticity and changes in dendritic spine shape and function; and 3) assessment of known biochemical correlates of schizophrenia, like dopaminergic hyperactivity in the mesolimbic system. Optimization of this two-hit model has the potential to better mimic human disease, speeding the development of novel therapies for schizophrenia.

Disclosures: A. Moghadam: None. **L.R. Vose:** None. **O. Miry:** None. **P.K. Stanton:** None.

Poster

258. Schizophrenia: Developmental Models

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 258.24/UU39

Topic: H.03. Schizophrenia

Support: NIH MH57440

Title: The impact of stress during adolescence or adulthood is dependent on critical-period-like stress sensitivity

Authors: *X. ZHU, F. V. GOMES, A. MADDE, A. A. GRACE
Neurosci., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Early-life external stressors, when interact with intrinsic genetic predisposition, are known to contribute to the pathogenesis of schizophrenia. However, the impact of stress can vary depending on the timing and the length of exposure. Adolescence, as a developmental period of heightened plasticity, is proposed to be particularly sensitive to environmental insults, as opposed to adulthood. In the current study, we aimed to 1) determine if adolescent stress

exposure could produce long-term circuit deficits that resemble schizophrenia, and 2) evaluate if regaining neural plasticity in adulthood could recapitulate adolescent stress sensitivity. Male Sprague-Dawley rats were submitted to a 10-day combined footshock (FS) and restraint stress (RS) during adolescence (PD31-40) or adulthood (PD65 -74). Using *in vivo* electrophysiology, the dopamine (DA) system activity in the ventral tegmental area (VTA) was evaluated 1-2 weeks (short-term effect) or 5-6 week (long-term effect) post-stress. Changes in the locomotor response to amphetamine were also evaluated. Our data suggest that adolescent stress induced both short- and long-term schizophrenia-like changes in the VTA DA system, as indicated by the increased VTA DA neuron population activity and the augmented locomotor response to amphetamine. In contrast, adult stress only produced short-term changes consistent with models of depression, as indicated by the decreased DA neuron population activity, which failed to persist after 5-6 weeks. However, when the stressors were applied concurrently with sodium valproate (VPA; 300mg/kg i.p.), a putative "critical period" re-opener that increases neural plasticity through inhibition of histone deacetylase, adult stress increased VTA DA neuron population activity similar to that occurring with adolescent stress. These results suggest that 1) timing of stress is a critical determinant of the circuit pathology in adult, 2) adolescent stress may be a precipitating factor for the transition to psychosis, and 3) re-opening the sensitive period in the adult recreated an adolescent phenotype of restored vulnerability to stress-induced pathology of schizophrenia.

Disclosures: X. Zhu: None. **F.V. Gomes:** None. **A. Madde:** None. **A.A. Grace:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Johnson & Johnson, Lundbeck, Pfizer, GSK, Merck, Takeda, Dainippon Sumitomo, Otsuka, Lilly, Roche, Asubio, Abbott, Autofony, Janssen, Alkermes.

Poster

258. Schizophrenia: Developmental Models

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 258.25/UU40

Topic: H.03. Schizophrenia

Support: NIH Grant MH057440

NIH Grant MH104320

Title: Pomaglumetad methionil normalizes increased DA neuron activity in the VTA in the methylazoxymethanol acetate developmental disruption model of schizophrenia

Authors: *S. SONNENSCHEIN, A. A. GRACE
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Abstract: Our previous studies show that withdrawal from prior D2 antagonist treatment interferes with the ability of novel target compounds to reverse the hyperresponsive state of the DA system in the methylazoxymethanol acetate (MAM) rat model of schizophrenia, suggesting that such compounds may have shown efficacy if tested in the appropriate patient population. For this reason, we tested whether pomaglumetad methionil, which showed promise as a novel antipsychotic in preclinical research but failed to show efficacy in clinical trials, could impact the hyperdopaminergic state thought to underlie psychosis. MAM and SAL rats were treated with pomaglumetad methionil (1, 3, 10mg/kg, i.p) or 1 mg/kg saline 30 minutes prior to anesthetized in vivo electrophysiological recordings. The population activity of VTA DA neurons was measured by passing an electrode in a preset pattern, counting the number of spontaneously firing DA neurons, and analyzing their firing rate and bursting activity. Pomaglumetad methionil dose-dependently reduced the number of spontaneously active DA neurons in the VTA of MAM rats to control levels without affecting DA firing in SAL rats. As in the MAM rats, DA neuron population activity can be increased in a hippocampal-dependent manner via acute restraint stress. Administration of 3 mg/kg pomaglumetad methionil prior to 2h restraint stress prevented the restraint-induced increase in DA neuron activity. Thus, the ability of pomaglumetad methionil to reduce the hyperdopaminergic activity in both MAM rats and in normal rats following restraint stress suggests that it can indirectly regulate DA neuron activity, which may contribute to its potential therapeutic effects.

Disclosures: S. Sonnenschein: None. **A.A. Grace:** None.

Poster

258. Schizophrenia: Developmental Models

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 258.26/UU41

Topic: H.03. Schizophrenia

Support: ERC Consolidator Grant 681577 “Psychocell”

Title: Glutamatergic dysfunction within neonatal prefrontal circuitry in a gene-environmental model of mental disorders

Authors: *M. CHINI, C. LINDEMANN, J. A. PÖPPLAU, X. XU, J. AHLBECK, S. H. BITZENHOFER, I. L. HANGANU-OPATZ
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Abstract: Over the last decades, psychiatric diseases have emerged as one of the biggest burdens for health care systems. The devastating symptoms are firstly detectable in adulthood, yet they seem to result from abnormal brain maturation. While advancement has been made in the treatment of certain categories of symptoms, a comprehensive mechanistic understanding of the

progression of these disorders throughout life is still lacking. To address this knowledge gap, mouse models mimicking both the genetic (mutation of Disrupted-In-Schizophrenia 1 (DISC1) gene) and environmental (maternal immune activation) risk factors of mental disease (dual-hit GE mice) are instrumental. We previously showed that impaired maturation of functional communication within prefrontal-hippocampal networks of these mice may represent a mechanism underlying the ontogeny of such disorders. However, the cellular substrate of these alterations and the pathophysiology that leads to them are still unknown. Here, we combine in vitro and in vivo electrophysiology, optogenetics, pharmacology, and morphological investigation of pyramidal neurons in the prefontal cortex (PFC) and report layer-specific glutamatergic dysfunction of prefrontal networks in dual-hit GE mice. Deficits in spiking and oscillatory network activity are confined to layers II/III and beta-low gamma rhythms. Light-activation of this same neuronal population in GE mice, transfected with highly-efficient channelrhodopsins, induces broad frequency network activation and not, as in control mice, a specific entrainment in beta-low gamma rhythms. Whole-cell patch-clamp recordings from pyramidal neurons in vitro confirm the layer and frequency-specific alterations. Confocal microscopy-based morphometric analysis identifies severe reduction in the dendritic branching complexity and spine density restricted to pyramidal neurons in prefrontal layers II/III. The observed deficits can be partially rescued by inhibition of microglial cells that have an activated phenotype in neonatal GE mice. These data give first insights into the cellular mechanisms of abnormal network wiring during the neonatal development, and into possible strategies for the prevention of the resulting disease-related cognitive dysfunctions.

Disclosures: M. Chini: None. **C. Lindemann:** None. **J.A. Pöpplau:** None. **X. Xu:** None. **J. Ahlbeck:** None. **S.H. Bitzenhofer:** None. **I.L. Hanganu-Opatz:** None.

Poster

259. Mouse Connectomics

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 259.01/UU42

Topic: I.03. Anatomical Methods

Support: U01MH105971

Title: Mouse brain light sheet atlas with iDISCO+ in CCF space

Authors: K. UMADEVI VENKATARAJU[1], J. COLLINS[2], Z. KHAKU[2], K. JOSEPH[2], N. CAIN[3], *P. OSTEN[1]
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Abstract: Brain template images and annotation atlases are key to accurately analyzing the expression data in whole brain microscopy images. We have developed a brain template for iDISCO+ clearing protocol and light sheet fluorescence microscopy (LSFM). iDISCO+ clearing protocol uses methanol and dichloromethane instead of tetrahydrofuran to maintain tissue morphology and the size of cleared samples. In the 488-nm wavelength the major structures are intrinsically highlighted, providing a counterstain without the need for immunolabeling with antibodies. Since the contrast between regions is different from our previous serial two-photon tomography (STPT) based brain template, we developed a new template brain based on the LSFM images.
We used 96 wild type C57BL6 mice, 8 - 10 weeks old to create a new light sheet template. They were imaged with a .63 magnification sagittally. The entire field was captured from the olfactory bulbs to the cerebellum (CCF-iDISCO+488) using the 488-nm channel. The atlas was created in the same coordinate space as the Common Coordinate Framework STPT atlas (CCF-STPT) hosted by the Allen Mouse Brain Atlas. It is available at same resolutions as the CCF-STPT atlas (10 micron, 25 microns, 50 microns and 100 micron resolutions), hence it is compatible with the ontology and annotation volumes provided by the Allen Brain Institute. We additionally provide the annotation labels for the same volume from our previous work, that has 800+ labels registered from the Allen Nissl atlas. The CCF-iDISCO+488 atlas was created by registering the 25-micron resolution downsized image onto the CCF-STPT atlas. These registration parameters were used to register the 10 micron images to the 10-micron space to create a 96-brain average template brain. This template brain provides better contrast in regions where the ventricles and fiber tracts lie close to each other, thus inherently providing more robustness in registration of iDISCO+ images compared to that of the CCF-STPT.

Disclosures: K. Umadevi Venkataraju: None. **J. Collins:** None. **Z. Khaku:** None. **K. Joseph:** None. **N. Cain:** None. **P. Osten:** None.

Poster

259. Mouse Connectomics

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 259.02/UU43

Topic: I.03. Anatomical Methods

Support: EY023173

MH105982

U01MH105982

BBP in EPFL

Title: Whole-brain reconstruction and classification of spiny claustrum neurons of mice

Authors: *Y. WANG[1], H. GONG[2], Y. LI[3], X. KUANG[3], T. L. DAIGLE[4], L. MADISEN[6], H. GU[1], M. MILLS[1], L. GRAY[1], B. TASIC[5], A. LI[8], J. A. HARRIS[4], Q. LUO[9], C. KOCH[6], H. ZENG[7]
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Abstract: The claustrum is a thin, irregular, sheet-like neuronal structure hidden beneath the inner surface of neocortex, which both receives input from and projects back to almost all regions of cortex. Although the specific long-range inputs and outputs of the claustrum have been described in detail for the mouse, the morphologies and projections of individual claustrum neurons are not yet known. To describe and classify claustrum neuron types based on their morphologies, we manually reconstructed the full extent of 26 single spiny claustrum neurons using Neurolucida 360 software from a whole brain image stack (composed of more than 10K images, resolution XYZ: 0.3 x 0.3 x 1 μm) acquired with a two-photon fluorescence micro-optical sectioning tomography system (*2p*-fMOST). We sparsely labeled claustrum neurons using a specific tamoxifen-inducible Cre driver line (Gnb4-CreERT2) crossed to a bright GFP reporter (Ai139, Ai140). Based on the projections of fully reconstructed axons, spiny claustrum neurons were preliminarily classified into 2 types, with 2 subtypes each: (1) ***Midline projecting neurons (MPN)***: axonal clusters predominantly target cortical areas at or near the midline; ***subtype_A (MPN_A)*** with axonal projections only in ipsilateral hemisphere, and ***subtype_B (MPN_B)*** with axonal projections to both ipsilateral and contralateral hemispheres. (2) ***Lateral projecting neurons (LPN)***: axonal clusters target lateral cortical regions, ***subtype_A (LPN_A)*** with axonal projections only in ipsilateral hemisphere and ***subtype_B (LPN_B)*** with axonal projections in both ipsilateral and contralateral hemispheres. These neurons of different types branch extensively throughout the cortex, connecting to most of cortical regions. Remarkably, individual axons of single ***MPN_A*** cells were found to wrap around the entire ipsilateral cortex, and hence named “crown of thorns” neurons. The morphological features of fully reconstructed spiny claustrum neurons support the hypothesis that these neurons take in information from across cortex and widely disperse this information across cortex, somewhat reminiscent of neuromodulatory systems.**Key Words:** Brain Initiative, claustrum neurons, whole-brain reconstruction.

Disclosures: **Y. Wang:** None. **H. Gong:** None. **Y. Li:** None. **X. Kuang:** None. **T.L. Daigle:** None. **L. Madisen:** None. **H. Gu:** None. **M. Mills:** None. **L. Gray:** None. **B. Tasic:** None. **A. Li:** None. **J.A. Harris:** None. **Q. Luo:** None. **C. Koch:** None. **H. Zeng:** None.

Poster

259. Mouse Connectomics

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 259.03/UU44

Topic: I.03. Anatomical Methods

Title: The Allen Mouse Common Coordinate Framework: Providing spatial integration of data and knowledge on cells, circuits and function

Authors: D. FENG, Q. WANG, S.-L. DING, N. S. GRADDIS, P. LESNAR, Y. LI, J. ROYALL, S. M. SUNKIN, W. WAKEMAN, H. ZENG, C. KOCH, *J. A. HARRIS, L. NG
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Abstract: The Allen Mouse Common Coordinate Framework (CCF) is a fully annotated 3-D mouse brain atlas that serves as an essential tool to study the structure and function of the brain of the young adult C57BL/6J laboratory mouse at molecular, cellular, system and behavioral levels. It has been successfully used over the past 12 years for large-scale data mapping, quantification, presentation, visualization and analyses, evolving over multiple versions. Here, we present a newly completed version (CCFv3), a significantly improved 3-D reference space for data integration and analyses. CCF version 1 (CCFv1, 2005), created to support the Allen Mouse Brain Atlas, was based on the 2-D Allen Reference Atlas (ARA) which used 528 Nissl-stained sections of a near complete brain for areal delineations. Approximately 200 structures were extracted from the 2-D drawings to create 3-D annotations. Tissue damage, individual section deformations and the lack of 3-D ground truth limited the accuracy of this 2-D to 3-D conversion. A second CCF version (CCFv2, in 2011) was constructed to support the Allen Mouse Brain Connectivity Atlas. In CCFv2, flaws in the 3-D reconstructions were corrected and the volume was mirrored across the mid-line to create a symmetric reference space which included 860 structures. In CCFv3 (2016), we introduced the first set of annotations drawn in 3-D using a 10μm isotropic, highly anatomically detailed population average (template) of 1675 mouse brain specimens. In its first release, CCFv3 contained ~200 newly drawn structures in 3-D visible on the template (~ 50% of areas in mouse brain), merged with CCFv2 to create an interim map containing structures not yet completed in 3-D. Now, our CCFv3 consists of more than 500 gray matter structures, cortical layers, ~80 white matter fiber tracts, and ventricles drawn in 3-D using the anatomical template and other data types registered to this template, including gene expression, connectivity, and histochemistry, to enable precise structure annotation. CCFv3 is now in use as the spatial framework to integrate and ultimately compare data collected across multiple large-scale projects, including the Allen Cell Types, Allen Brain Observatory, and Allen Mouse Connectivity resources, as well as across the larger mouse brain community.

Disclosures: **D. Feng:** None. **Q. Wang:** None. **S. Ding:** None. **N.S. Graddis:** None. **P. Lesnar:** None. **Y. Li:** None. **J. Royall:** None. **S.M. Sunkin:** None. **W. Wakeman:** None. **H. Zeng:** None. **C. Koch:** None. **J.A. Harris:** None. **L. Ng:** None.

Poster

259. Mouse Connectomics

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 259.04/UU45

Topic: I.03. Anatomical Methods

Support: Allen Institute for Brain Science

Title: Anterograde tracing and anatomical template based brain-wide mapping of white matter fiber tracts in a 3-D common coordinate framework of mouse brain

Authors: *S.-L. DING, J. ROYALL, P. LESNAR, Q. WANG, K. HIROKAWA, Y. LI, A. HO, C. KOCH, S. SUNKIN, H. ZENG, L. NG, J. A. HARRIS
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Abstract: There is rapid growth in the availability of MRI-based white matter fiber tract atlases of both human and nonhuman brains that have a wide range of uses. These include the measurement and comparison of *in vitro*, *ex vivo*, and *in vivo* brain-wide functional connectivity in normal and abnormal conditions, as well as guidance of stereotaxic operation and anatomical targeting such as deep brain stimulation. While several brain atlases are available in the mouse, these have limited annotation of white matter tracts, often without boundary outlines to indicate the extent of their trajectories. There is a recent emergence in DTI-based white matter tract atlases of the mouse brain. However, these are not based on real fiber tracing techniques, and their use as a common framework needs re-evaluation. In the present study, we aim to map brain-wide white matter fiber tracts in a 3-D mouse brain common coordinate framework (CCF), utilizing anterograde tracing datasets such as Allen Mouse Brain Connectivity Atlas (Oh et al., 2014) and an average anatomical template generated from serial 2P block-face images acquired from 1675 adult C57BL/6J mice. Approximately 80 fiber tracts were fully reconstructed with a 3-D drawing tool, ITK-SNAP. These reconstructions mainly include roots of cranial nerves, commissural fibers linking both hemispheres, ascending and descending projecting tracts and their decussations, and converging zones such as the internal capsule and cerebral peduncle. The component of each white matter tract is variable. Some fiber tracts originate mainly from single projections such as commissural branch of stria terminalis, mammillo-thalamic tract and mammillo-tegmental tract. Others contain bidirectional fibers such as stria medullaris of thalamus, which consists of fibers from both habenula and hypothalamus. Some are also composed of fibers originating from many sources. Stria terminalis, for example, contains portions originating from amygdaloid nuclei, bed nucleus of stria terminalis, hypothalamus,

thalamus, dorsal raphe nucleus, parabrachial nucleus and prosubiculum. Some white matter fiber tracts were annotated for the first time, including medial corticohypothalamic tract, uncinate fasciculus, optic and auditory radiations and supracallosal white matter (a distinct region immediately above the corpus callosum consisting of association fibers ascending to and descending from cerebral cortex). In summary, we have generated detailed mapping of brain-wide white matter fiber tracts in a 3-D CCF of mouse brain. This tool will facilitate the measurement, comparison and localization of anatomical and functional networks across the mouse brain.

Disclosures: S. Ding: None. **J. Royall:** None. **P. Lesnar:** None. **Q. Wang:** None. **K. Hirokawa:** None. **Y. Li:** None. **A. Ho:** None. **C. Koch:** None. **S. Sunkin:** None. **H. Zeng:** None. **L. Ng:** None. **J.A. Harris:** None.

Poster

259. Mouse Connectomics

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 259.05/UU46

Topic: I.03. Anatomical Methods

Support: NIH Grant U01MH105982

Eunice Kennedy Shriver National Institute Of Child Health & Human Development

Title: The Allen mouse common coordinate framework: A 3D delineation of the mouse gray matter with multi-modality references

Authors: *Q. WANG[1], J. ROYALL[2], P. LESNAR[2], S.-L. DING[2], K. HIROKAWA[2], Y. LI[3], A. HO[4], W. WAKEMAN[3], N. GRADDIS[3], S. SUNKIN[5], C. KOCH[1], L. NG[3], H. ZENG[6], J. A. HARRIS[2]
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Abstract: Large-scale data generation, such as mapping gene expression patterns (Lein et al., 2007), circuits (Oh et al., 2014) and cell types in whole mouse brain accelerates our understanding of the basic organization of the mouse brain. It remains a big challenge to quantitatively analyze data from different experiments, visualize them and integrate multimodal data sets. To that end we have produced the Allen Mouse Common Coordinate Framework (CCF), a digital 3D mouse brain atlas manually delineated in 3D space based on a unified analysis of various registered reference data with the 3D drawing tool ITK-SNAP. We began by creating an average template from the background autofluorescence in serial 2P block-face images acquired from 1675 adult laboratory mice. At high resolution (10 micron isotropic),

native contrast features within the template itself allowed us to observe many brain structures. For delineation of cortical and subcortical gray matter structures, we employed the following: 1) five histochemical reference data sets, 2) connectivity data from the Allen Mouse Brain Connectivity Atlas (http://connectivity.brain-map.org), and, 3) block-face 2P scanned brain images from 56 Cre driver mouse lines crossed to a fluorescent reporter line, and registered with the average template through local and global alignment. With aid of these data sets, a total of 43 cortical areas and subdivisions were delineated from surface views using a curved cortical coordinate system in the CCF, including ten visual areas with unique shapes and sizes. This delineation shows three and six more visual areas in the CCF compared to the parcellation of the visual cortex in the Allen Reference Atlas (ARA) (Dong, 2007) and the Paxinos and Franklin's mouse atlas (2001), respectively. Outside of the cortex, more than 270 structures were delineated. Some were not previously annotated in the ARA or Paxinos and Franklin mouse atlases, such as the prosubiculum and area postriata. Others were further divided, such as the lateral geniculate nucleus, now sub-divided to its shell, core and ipsilateral retina projection zones, and the medial mammillary body delineated now to 5 subdivisions instead of the 2 or 3 annotated in the two atlases. In some cases, structures were drawn differently. For example, CA2 was delineated in our 3D atlas all the way to the anterior pole of the hippocampus and completely separated CA1 and CA3 compared to the two atlases, which designated this region CA3. With accurately reconstructed cortical and subcortical gray matter structures in 3D space, our CCF provides a foundation for integrating, analyzing, visualizing and modeling multi-modal large-scale data sets.

Disclosures: **Q. Wang:** A. Employment/Salary (full or part-time):; Allen Institute for Brain Science. **J. Royall:** A. Employment/Salary (full or part-time):; Allen Institute for Brain Science. **P. Lesnar:** A. Employment/Salary (full or part-time):; Allen Institute for Brain Science. **S. Ding:** A. Employment/Salary (full or part-time):; Allen Institute for Brain Science. **K. Hirokawa:** A. Employment/Salary (full or part-time):; Allen Institute for Brain Science. **Y. Li:** A. Employment/Salary (full or part-time):; Allen Institute for Brain Science. **A. Ho:** A. Employment/Salary (full or part-time):; Allen Institute for Brain Science. **W. Wakeman:** A. Employment/Salary (full or part-time):; Allen Institute for Brain Science. **N. Graddis:** A. Employment/Salary (full or part-time):; Allen Institute for Brain Science. **S. Sunkin:** A. Employment/Salary (full or part-time):; Allen Institute for Brain Science. **C. Koch:** A. Employment/Salary (full or part-time):; Allen Institute for Brain Science. **L. Ng:** A. Employment/Salary (full or part-time):; Allen Institute for Brain Science. **H. Zeng:** A. Employment/Salary (full or part-time):; Allen Institute for Brain Science. **J.A. Harris:** A. Employment/Salary (full or part-time):; Allen Institute for Brain Science.

Poster

259. Mouse Connectomics

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 259.06/UU47

Topic: I.03. Anatomical Methods

Title: Vascular quantification of entire murine organs via knife-edge scanning microscopy

Authors: *V. VEMURI[1], N. FARAHANI[2], M. J. PESAVENTO[2]
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Abstract: Quantification of histopathologic markers is classically performed on only a few 2D tissue sections, thus restricting measurements and observations to limited portions of the sample volume. Emerging serial section light microscopy platforms, like knife-edge scanning microscopy (KESM), generate high-resolution data sets, and enable automated identification and quantification of cytoarchitectural features across entire tissue blocks. Herein, we demonstrate multiparametric quantification of vascular networks (VNs) across large sample volumes using KESM. This type of vascular analysis is useful for understanding tumor angiogenesis, arteriosclerosis, vasculopathies, and neurodegenerative diseases.
Wild-type mice are perfused and vasculature is labeled with India ink. Tissues are resected, embedded in a resin composite, and images are acquired via KESM. Images are processed on a distributed system, allowing for transformations of high resolution and large volume data from images that are voxel-registered to the tissue. Grayscale voxels are filtered to reduce noise and then binarized as vessels or background. The binarized volumes are passed to a skeletonization engine, which thins the volumes to the centerline of each vessel within the VN, which is subsequently converted into a graph-based representation. The graph-based VN enables quantification of branch point count, branch length, vessel radius, and vessel tortuosity. Vessel density per unit area is a commonly used 2D metric, included in this study to facilitate comparison to existing research.
Reference data was obtained by manual traces of vessel objects in 3D volumes by a double board-certified pathologist. Segmentation results obtained from 3D watershed is compared against the hand-labeled data, and measured via F1 score (0.901), and mean surface distance (0.127). We obtained volumetric and vectorized measurements of VNs from whole murine organs. The automated image acquisition and analysis pipeline demonstrated here provides rapid and parallel processing of datasets on the order of terabytes, reducing the data dimensionality by reporting key features representing the VN. This facilitates automated report generation, providing both a scalable solution for comprehensive characterization of VNs, which aids in the identification of various pathologies within whole organs.

Disclosures: **V. Vemuri:** A. Employment/Salary (full or part-time):; 3Scan, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 3Scan, Inc. **N. Farahani:** A. Employment/Salary (full or part-time):; 3Scan, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 3Scan, Inc.. Other; Brain Preservation Foundation. **M.J. Pesavento:** A. Employment/Salary (full or part-time):; 3Scan, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 3Scan, Inc..

Poster

259. Mouse Connectomics

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 259.07/UU48

Topic: I.03. Anatomical Methods

Support: KAKENHI JP24111547

KAKENHI JP26460388

KAKENHI JP16KT0134C1

Title: Alteration of amine neurotransmitters in Scrapper-knockout mice brain visualized by imaging mass spectrometry

Authors: F. ETO[1,2], T. MATSUDA[1], M. SETOU[2,3], *I. YAO[1,3]
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Abstract: Neurotransmitters play important roles in the brain functions and regulate a variety of biological processes. Abnormal concentrations of neurotransmitters and consequent dysfunction are linked to various central nervous system disorders. Especially, glutamate and gamma-aminobutyric acid (GABA) have pivotal roles in central nervous system and closely involves severe neurological disease such as epilepsy. Visualization of the concentrations of neurotransmitters is thought to be essential in understanding their role in various neurophysiological processes in different regions of the brain. The detection of small polar compounds such as amino neurotransmitters by MALDI imaging mass spectrometry (IMS) has been developed and recently, several on-tissue chemical derivatization methods have been reported that enable their detection. Here, we applied this technique to analyze *Scrapper* gene-deficient (*Scrapper*-knockout [SCR-KO]) mice. SCRAPPER, a protein which we have identified is localized at synapses. It is an ubiquitin E3 ligase that is involved in the ubiquitination of RIM (Rab3-interacting molecule) 1, an important regulator of synaptic plasticity, and thus regulates

synaptic transmissions. SCR-KO has the defect in neurotransmission via excessive secretion of neurotransmitters due to the upregulation of the release probability. IMS with on tissue derivatization revealed that the alteration of glutamate concentration and distribution in the SCR-KO mouse brain. Interestingly, our results showed that not only glutamate but also some other amino acid neurotransmitters were dramatically changed their distribution. The alteration visualized by IMS analysis in this study would reflect the defect in neurotransmission in the SCR-KO mouse brain.

Disclosures: **F. Eto:** None. **T. Matsuda:** None. **M. Setou:** None. **I. Yao:** None.

Poster

259. Mouse Connectomics

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 259.08/UU49

Topic: I.03. Anatomical Methods

Support: NIH Intramural Research Program (NIDDK)

Title: Calcium imaging from two neuronal subtypes

Authors: *J. A. LICHOLAI[1], A. V. KRAVITZ[1,2]
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Abstract: While there are many ways to record brain activity, there are few that can differentiate between two neuronal subtypes in the same brain structure. Here, we explored a method to record and distinguish between two similar neuronal subpopulations using GCaMP6, a calcium indicator, in combination with another static fluorophore. We focused on the dorsal medial striatum (DMS), a region composed of two projection neuron types, known as direct and indirect pathway medium spiny neurons (dMSNs and iMSNs). Our approach utilized transgenic animals to label one subpopulation with a static label while virally expressing GCaMP in all neurons. In this way neurons can be identified based on the presence or absence of the static label. For the static label, we tested both tdTomato (red) and GFP (green). Mice were implanted with a gradient index (GRIN) lens above the DMS and imaged with an endoscopic microscope that transmitted images through a fiber-optic bundle. Although our validation testing was done in head-fixed mice, the endoscopic microscope can also allow for freely moving recordings. Full-field fluorescence excitation produced low quality images due to light scattering, which precluded visualization of the static fluorophore labels. We optimized image acquisition by line scanning the illumination light, which produced usable images of the static fluorophore. The GRIN lens caused a chromatic aberration between red and green imaging planes, which introduced unexpected challenges. For this reason, we found GFP to be more useful as a static marker in this application. We created images of dynamic GCaMP signals on top of the static

GFP label for identifying dMSNs and iMSNs. Additional modifications, including the use of nuclear localized fluorophores and retrograde labeling, are being explored for further protocol optimization. This method demonstrates early attempts to record calcium signals from multiple striatal cell subpopulations in awake animals.

Disclosures: J.A. Licholai: None. **A.V. Kravitz:** None.

Poster

259. Mouse Connectomics

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 259.09/UU50

Topic: I.04. Physiological Methods

Title: Distinct components of stimulus-evoked high-frequency cortical surface electrical potentials may reflect spiking activity in different cortical layers

Authors: *K. BOUCHARD[1], M. E. DOUGHERTY[2], P. LEDOCHOWITSCH[3], M. M. MAHARBIZ[4], C. E. SCHREINER[5], E. F. CHANG[6]
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Abstract: The relative paucity of knowledge about mammalian mesoscale cortical functioning can be attributed to the difficulty of simultaneously measuring the activity of many functionally distinct areas over large spatial scales with sufficient spatiotemporal resolution to resolve functional properties of local neuronal populations in mammals. We used high-density, micro-eletrocorticography (μECoG) arrays to record stimulus-evoked electrical potentials from the cortical surface, and studied their spectral composition, response characteristics, and spatial dependencies.
We demonstrate that μECoG on rodent auditory cortex records sound evoked potentials with high signal-to-noise primarily in 70-170 Hz (high-gamma), but with distinct peaks extending to >1kHz. Recorded signals >500Hz had timing and amplitude characteristics similar to those recorded intra-cortically. Using a novel non-negative matrix factorization algorithm, we show that high-frequency (>70Hz) stimulus evoked field potentials are composed of approximately three distinct components (at ~100Hz, 300Hz, and 800Hz). We demonstrate that all high-frequency components of the μECoG recorded electrical potentials have sufficient selectivity to derive functional organization of rat auditory cortex (tonotopy), have similar response characteristics, and are more sharply tuned than low-frequency (<30Hz) components. Furthermore, a novel algorithm for regularized general linear models revealed that high-frequency components of tone-evoked μECoG recorded field potentials are spatially localized (±200μm) with anisotropies that reflect tonotopic organization.

These experimental observations, combined with biophysical considerations, lead us to hypothesize that high-frequency content of μECoG recordings reflect summed spiking activity of neurons within a cortical column, and that different high-frequency components may reflect spiking in different cortical layers. A simplified spiking neural network model quantitatively reproduces the stimulus-evoked experimental data when: (i) the distribution of spike-sources (neurons) was matched to that of a cortical column; (ii) action potential waveforms underwent distance dependent amplitude attenuation and frequency filtering (suggesting active filtering by the cortical tissue at high-frequencies).
Our results demonstrate high-frequency components of μECoG electrical potentials are not a homogenous broad-band signal, and suggest different high-frequency bands may reflect differential weightings of neuronal processing in cortical layers, potentially expanding the range of information extractable from μECoG.

Disclosures: K. Bouchard: None. **M.E. Dougherty:** None. **P. Ledochowitsch:** None. **M.M. Maharbiz:** None. **C.E. Schreiner:** None. **E.F. Chang:** None.

Poster

259. Mouse Connectomics

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 259.10/UU51

Topic: I.04. Physiological Methods

Support: FDA OSEL CDRH DBP

Title: The long-term effects of post-isoflurane exposure on quantitative electroencephalogram (eeg) in mice

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Abstract: Isoflurane is a widely-used inhalation anesthetic. Its preferred use comes from higher potency and rapid movement both in and out of circulation, compared to counterparts such as sevoflurane and desflurane. Previous work has suggested that isoflurane has neural protective effects via inhibition of excitotoxicity through activation of $GABA_A$ receptors, reduction of cellular necrosis, and activation of anti-apoptotic genes and proteins [1]. During isoflurane administration, neural oscillations are altered, including an increase in alpha oscillation frequencies (8-13 Hz). However, post-anesthesia effects on EEG have yet to be established. In our study, a 4 x 4 NeuroNexus micro electrocortigram (μECoG) array was implanted on the motor cortex to record intracranial ECoG signals from mice. After recovery from implantation surgery, baseline measurements were acquired for 1 month prior to 30-minute exposure to

isoflurane. ECoG was then recorded at 2, 24, and 48-hours post exposure and continued biweekly for 1 month. Spectral content and coherence were analyzed using the Chronux toolbox and custom code (MATLAB, Mathworks). Power spectrum density analysis revealed a significant increase in the power at alpha (8-13 Hz) and beta (13-30 Hz) frequency bands in 2, 24, and 48-hour post exposure recordings, compared to baseline. A tread of reduction in power of delta (1-4 Hz) frequency band began approximately a week post-exposure and was maintained for 3 weeks. Coherence analysis between all channel pairwise showed a linear correlation between coherence and distance; although, isoflurane did not alter either the absolute coherence or the coherence-distance relationship. These data suggest isoflurane exposure leads to sustained changes in ECoG activity for up to 3 weeks. Isoflurane-driven changes in spectral content are an important consideration for experiments involving the analysis and interpretation of ECoG and EEG data acquired following isoflurane anesthetic exposure.
1. Burchell S.R. et al, Journal of Investigative Medicine. 2013 Oct6, 61(7): 1078-83

Disclosures: H. Rafi: None. **C.G. Welle:** None. **M. Ye:** None.

Poster

259. Mouse Connectomics

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 259.11/DP15/UU52 (Dynamic Poster)

Topic: I.03. Anatomical Methods

Support: NIH Grant MH094360

NIH Grant U01CA198932

Title: Mouse Connectome Project at USC: Assembling global neural networks of the mammalian brain

Authors: *H. DONG[1], H. HINTIRYAN[2], M. S. BIENKOWSKI[2], N. FOSTER[2], I. BOWMAN[2], L. GOU[2], S. YAMASHITA[2], M. ZHU[2], M. Y. SONG[2], N. L. BENAVIDEZ[2], K. COTTER[2], M. BECERRA[2], D. LO[2], J. ABU-JABER[2], S. AZAM[2], H. XU[2], D. JOHNSON[2], H. VILLA-REUSENMANN[2], A. TAKAHASHI[2]
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Abstract: The Mouse Connectome Project at USC (MCP, www.MouseConnectome.org) aim to map the interconnections among all regions of the C57Bl/6 mouse brain, to generate a corresponding comprehensive connectome map that represents the interconnections in a common neuroanatomic frame, and to understand how the different brain regions assemble into functional neural networks. The biological significance of assembling this global wiring diagram of the

brain is tantamount to that of the Human Genome Project. However, just as knowing the sequence of three billion base pairs in the human genome reveals little about how our bodies are regulated by genes, constructing the connectome will not directly reveal its functional purpose. The ensuing challenge is to analyze the vast connectivity information in a way that is most conducive to generating new behavioral hypotheses for direct testing. Since behavior is a network phenomenon, it is important to analyze the data at the network level to propagate hypothesis-driven, functional analyses of neural systems, culminating in insights into the etiologies of and treatments for neurological disorders like Alzheimer's disease and autism. To this end, in the past 5 years, we have generated the first and the most comprehensive connectomic map of the cerebral cortex available for any mammalian species (Zingg et al., 2014). Computational analysis of this map revealed that the mammalian cerebral cortex, long thought to be a dense single interrelated tangle of neural networks, was composed of relatively few functionally segregated cortico-cortical subnetworks. Subsequently, we also constructed (1) a comprehensive mesoscale mouse cortico-striatal projectome (Hintiryan et al., 2016): a detailed connectivity projection map from the entire cerebral cortex to the dorsal striatum; (2) the genetic architecture and wiring diagram of the hippocampus; and (3) the neural networks of the basolateral amygdalar complex. Following the same principle, we project to systematically and comprehensively assemble the global neural networks of the entire mouse brain within the next 5 years. These high-resolution, high quality raw images of connectivity data are presented through a publically accessible database—the iConnectome, while the graphic reconstruction of the connections summarized in connectivity maps is available through iConnectome maps. Our future direction includes constructing these global networks at the cellular level and the further customization of our existing informatics tools to facilitate data visualization and analysis.

Disclosures: **H. Dong:** None. **H. Hintiryan:** None. **M.S. Bienkowski:** None. **N. Foster:** None. **I. Bowman:** None. **L. Gou:** None. **S. Yamashita:** None. **M. Zhu:** None. **M.Y. Song:** None. **N.L. Benavidez:** None. **K. Cotter:** None. **M. Becerra:** None. **D. Lo:** None. **J. Abu-Jaber:** None. **S. Azam:** None. **H. Xu:** None. **D. Johnson:** None. **H. Villa-Reusenmann:** None. **A. Takahashi:** None.

Poster

259. Mouse Connectomics

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 259.12/UU53

Topic: I.03. Anatomical Methods

Support: R01 MH094360

U01 CA198932

F32 MH107071-02

Title: Distinct hippocampal network connectivity to brain-wide systems controlling motivated behavior

Authors: *M. S. BIENKOWSKI, I. BOWMAN, M. Y. SONG, L. GOU, M. ZHU, N. BENAVIDEZ, S. YAMASHITA, J. ABU-JABER, S. AZAM, D. LO, N. N. FOSTER, H. HINTIRYAN, H.-W. DONG
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Abstract: Previously, we determined the genetic subdivisions of the mouse hippocampus and their interconnectivity using anatomical data from the Mouse Connectome Project (www.mouseconnectome.org). Multiscale network analysis of intra-hippocampal connectivity revealed that the hippocampus can be divided into multiple modular hierarchical subnetworks. After defining the intra-hippocampal subnetwork organization, we examined the hippocampal subnetwork's outputs within brain regions in cortex, thalamus, basal forebrain, amygdala, and hypothalamus. Overall, we found that the CA1 and subiculum regions of each subnetwork specifically targeted brain-wide networks that coordinate different aspects of animal behavior. Notably, a novel ventral hippocampus region complements the 'classic' dorsal subiculum output to target visuospatial brain regions involved in spatial navigation. Additionally, a novel dorsal hippocampus region complements the 'classic' ventral subiculum output to target brain regions involved in regulating social behaviors. Finally, a unique individual subnetwork at the most ventral tip of the hippocampus is anatomically-positioned to influence metabolic, sexual, and neuroendocrine-related behaviors. Overall, our research demonstrates the organizational principles of hippocampal output and potential influence on brain-wide networks that control animal behavior.

Disclosures: M.S. Bienkowski: None. **I. Bowman:** None. **M.Y. Song:** None. **L. Gou:** None. **M. Zhu:** None. **N. Benavidez:** None. **S. Yamashita:** None. **J. Abu-Jaber:** None. **S. Azam:** None. **D. Lo:** None. **N.N. Foster:** None. **H. Hintiryan:** None. **H. Dong:** None.

Poster

259. Mouse Connectomics

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 259.13/UU54

Topic: I.03. Anatomical Methods

Support: NIH Grant MH094360

NIH Grant U01CA198932

Title: Multi-scale modularity analysis of the hippocampus brain network

Authors: *I. BOWMAN, M. S. BIENKOWSKI, L. GOU, K. KOTTER, S. YAMASHITA, M. ZHU, S. AZAM, F. J. ABU-JABER, D. D. LO, M. Y. SONG, A. W. TOGA, H. DONG
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Abstract: The hippocampus is an anatomically-complex brain structure that is composed of several genetically-distinct regions. To provide a comprehensive resource of both hippocampal genetics and connectivity, we recently created the Hippocampus Gene Architecture Atlas (HGAA). The HGAA divides the hippocampus and subiculum into multiple genetic regions and delineates each region's input/output connectivity based on tract-tracing data from the Mouse Connectome Project (MCP, www.mouseconnectome.org). In this work, we annotated MCP tracer data across the brain and created a binary, directed connectivity matrix to perform a multiscale network analysis of the entire hippocampus network. Following data annotation, we performed a network modularity optimization by using a Louvain community detection algorithm. For multiscale analysis, the Louvain algorithm was run 1000 times for every 0.01 gamma value ranging from 0.01 to 20.0. As a result, 2 million network partitions of extra hippocampal Regions of Interest (ROIs) at 2000 different scales were found such that intramodular edge weight was maximized. We subsequently calculated the Mean Partition Similarity (MPS) as well as a consensus partition of each 1000 run increment. After sorting, we identified the partitions computed to have the highest MPS (at gamma 9.74). The corresponding consensus partition at 9.74 contained 46 clustered communities that we assigned into five subnetworks. Hippocampal subnetwork assignment of each cluster was made through observation of consensus partitions at lower gamma values (namely gamma 4.7, which also contained a clear MPS peak). Hippocampal subnetwork organization was visualized with the Python pydot package to create hierarchical network graph layouts rendered with intra-cluster ROIs closer together, as well as modified line weights to signify community relationship. Overall, our network analysis identified the modular organization of five hippocampus subnetworks that target brain-wide systems known to regulate distinct types of animal behavior, including spatial navigation, social behavior, and metabolism/neuroendocrine function.

Disclosures: I. Bowman: None. **M.S. Bienkowski:** None. **L. Gou:** None. **K. Kotter:** None. **S. Yamashita:** None. **M. Zhu:** None. **S. Azam:** None. **F.J. Abu-Jaber:** None. **D.D. Lo:** None. **M.Y. Song:** None. **A.W. Toga:** None. **H. Dong:** None.

Poster

259. Mouse Connectomics

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 259.14/UU55

Topic: I.03. Anatomical Methods

Support: NIH T32 Training Grant

Title: Extrastriate connections of the mouse lateral geniculate thalamus

Authors: *N. L. BENAVIDEZ[1,2], M. S. BIENKOWSKI[1], L. GOU[1], K. WU[1], H.-W. DONG[1]
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Abstract: The mammalian visual (VIS) system is one of the most well-studied sensory systems that guide our behavior. Visual information from retinal ganglion cells projects to the dorsal lateral geniculate nucleus of the thalamus (LGd) and to the midbrain superior colliculus (SC). The LGd then projects topographically to primary visual cortex (VISp) to mediate visual perception, whereas the SC mediates coordinated eye movements. In this dogmatic view, the VISp is the central hub of the visual system where it projects to 'extrastriate' visual cortices (VISam, VISpm, VISal, VISl, VISpl) and other brain regions for higher-order processing. Notably, damage to the VISp causes a condition known as cortical blindness. Despite being visually blind, cortically-blind patients are capable of 'blindsight' and can still orient and respond to visual stimuli in the environment. The retino-SC projections have been proposed as a possible substrate for blindsight, but others have suggested the possibility of a lesser known extrastriate projection from LGd. Evidence of extrastriate LGd projections has been shown in primates, but has not been well described in rodents. Here, we provide definitive anatomical evidence of extrastriate projections to the VISam and VISpm from a distinct cell group within the mouse LGd. Using small, discrete coinjections of anterograde and retrograde tracers within the thalamus and cortex, our cross-validated approach carefully delineated the bidirectional thalamocortical connectivity. Our findings support the view that not all visual perception depends on the VISp.

Disclosures: **N.L. Benavidez:** None. **M.S. Bienkowski:** None. **L. Gou:** None. **K. Wu:** None. **H. Dong:** None.

Poster

259. Mouse Connectomics

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 259.15/UU56

Topic: I.03. Anatomical Methods

Support: USC Institutional Grant T32MH111360-1 A1

NIH Grant MH094360 (Dong)

U01CA198932 (Dong)

Title: Neuroanatomical mapping of the mouse upper limb and orofacial networks

Authors: *M. Y. SONG[1], M. S. BIENKOWSKI[2], B. ZINGG[1], L. GOU[2], I. BOWMAN[2], K. COTTER[2], H. HINTIRYAN[1], H. DONG[3]
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Abstract: The cerebral cortex can be segregated into distinct neural networks that coordinate to perform detailed sensory processing and complex motor behaviors. However, the exact anatomical substrates of sensorimotor integration still remain unclear, particularly in coordination of different body parts in motivated behaviors. To define precise anatomical boundaries of different functional sensorimotor domains (i.e., related to upper-limb or orofacial movements), we made systematic co-injections of fluorescent anterograde (e.g., PHA-L, AAV) and retrograde (e.g., CTb, FG) tracers into the well-defined primary somatosensory area of wild-type mice. Subsequently, different functional domains within the primary motor area, secondary motor area, secondary somatosensory area and barrel field were identified by their reciprocal connections with corresponding body-part domains within the SSp. Additional injections into these domains verified them as part of separate somatic networks representing different body parts. We then mapped and compared the global connectivity patterns of the upper-limb and orofacial somatic networks in the dorsal striatum, thalamus, and brainstem, in order to determine where these networks segregate or integrate information. These findings will allow for a more precise understanding of how cortical sensorimotor networks regulate descending outputs to conduct motivated behaviors.

Disclosures: M.Y. Song: None. **M.S. Bienkowski:** None. **B. Zingg:** None. **L. Gou:** None. **I. Bowman:** None. **K. Cotter:** None. **H. Hintiryan:** None. **H. Dong:** None.

Poster

259. Mouse Connectomics

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 259.16/UU57

Topic: I.04. Physiological Methods

Title: A slide-lock Neuroclip electrode for neuromodulation of small nerves

Authors: *A. DESHMUKH[1], A. KANNEGANTI[1], J.-B. LEE[2], S. COGAN[1], M. ROMERO-ORTEGA[1]
[1]Bioengineering, [2]Electrical Engin., The Univ. of Texas At Dallas, Richardson, TX

Abstract: Some Bioelectronic applications demand miniature implantable devices that do not damage small and fragile nerve targets. Current elastomeric cuff electrodes need to be stretch opened to implant onto these nerves, not a trivial method when the target nerves are smaller than

100 µm such as the rat carotid sinus nerve, (60-80 µm in diameter), commonly used to investigate the effect of blocking nerve conduction for the treatment of Diabetes. To reduce significantly the nerve manipulation during implantation of small electrodes, we developed a novel “neuroclip” electrode that relies on an L-shaped slit through which target nerves slide and lock into the device. Here, we report on a prototype fabricated in SU8 polymer with gold electrodes, wire bonded to an omnetics connector, and epoxy encapsulated. In-vitro phosphate buffered solution (PBS) characterization of the electrodes showed an average impedance of 300KΩ at 1 KHz frequency and able to deliver 0.5-1 nC charge per phase within the water window limit. The function of the electrodes in vivo was tested in five adult Sprague Dawley rats with neuroclip electrodes implanted onto a small fascicle (~80 µm diameter) isolated from the deep peroneal nerve (DPN). Constant voltage cathodic first biphasic electrical stimulation of this fascicle with 1ms pulses at 2 Hz frequency evoked an amplitude dependent compound motor activity and with visual motor activation threshold at 0.4±0.1 mV threshold. Three additional animals were used to confirm the recording of compound action potentials by the neuroclip in response to a proximal hook electrode stimulation (0.4-0.8mV) using randomized testing blocks. The results demonstrate the fabrication and characterization of a miniature cuff-like electrode with a slide-in-lock anchoring mechanism for attachment to small nerves, that drastically minimize the implantation time and reduce tissue manipulation compared to commercial devices, thereby better protecting the nerve. Together, the proposed neuroclip electrodes offer significant advantages over current devices for neural interfacing of small nerves and fascicles towards neural interfacing applications.

Disclosures: **A. Deshmukh:** None. **A. Kanneganti:** None. **J. Lee:** None. **S. Cogan:** None. **M. Romero-Ortega:** None.

Poster

259. Mouse Connectomics

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 259.17/UU58

Topic: I.04. Physiological Methods

Support: Memorial Hermann Foundation

Mission Connect, a program of TIRR Foundation

Title: Robotic-assisted hand training for spinal cord injury driven by myoelectric pattern recognition

Authors: ***Z. LU**[1], K.-Y. TONG[2], A. STAMPAS[1], P. ZHOU[1,3]
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Abstract: Various electromyography (EMG)-driven robots have been developed for hand rehabilitation after neurologic injury (such as stroke, spinal cord injury or cerebral palsy). They are primarily based on a conventional “on-off” or proportional control strategy, so that only one or two DOFs can be trained at a time. However, a human hand has up to 27 DOFs, and most functional hand tasks require complex coordination of multiple DOFs. It is a challenge to regain hand dexterity through conventional strategies. Therefore, myoelectric pattern recognition was introduced in this study as an advanced control strategy to demonstrate the feasibility of hand dexterity training after spinal cord injury (SCI). An exoskeleton hand (Hand of Hope, Rehab-Robotics Company Ltd, Hong Kong) driven by myoelectric pattern recognition was designed for this study. The pattern recognition algorithms, which were able to detect and recognize the user’s motion intents, drove the exoskeleton hand and assisted the user to accomplish each motion that he/she intended to perform. A RMS+WL+AR feature set (i.e. a combination of root mean square amplitude, waveform length, and 4^{th} order auto regressive coefficients) and a support vector machine (SVM) classifier were applied on 200 ms analysis windows (with 100 ms overlapping) of 7-channel EMG signals to classify six motion patterns, including hand closing and opening (HC & HO), thumb, index and middle finger closing and opening (TIMC & TIMO), middle, ring and little finger closing and opening (MRLC & MRLO). A 51-year-old man who had an incomplete C6 Level SCI (American Spinal Injury Association Impairment Scale C) 26 years ago attended twenty 2-hour visits over 10 weeks for robot-assisted hand training. The subject took four 10-minute sessions each visit. In each session, his right hand was assisted to perform aforementioned six motion patterns by the exoskeleton-robot. The robot was triggered by the subject’s motion intents in real time, and its motion patterns were determined by myoelectric pattern recognition algorithms. The recognition accuracy increased from 71.3% to 95.8% over the 10 weeks. After the training, the subject’s grip force increased from 13.5 kg to 19.6 kg, his score of Box & Block test increased from 32 to 39, and his score of the Graded Redefined Assessment of Strength, Sensibility and Prehension test (GRASSP) Part 4.B increased from 22 to 24. He accomplished the tasks in GRASSP Part 4.B 28.8% faster on average. The results demonstrated the feasibility of robot-assisted hand training driven by myoelectric pattern recognition after SCI.

Disclosures: Z. Lu: None. **K. Tong:** None. **A. Stampas:** None. **P. Zhou:** None.

Poster

259. Mouse Connectomics

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 259.18/UU59

Topic: I.03. Anatomical Methods

Support: IITP Grant R0190-15-2072

Title: Quantification of spinal cord injury through circular scanning optical coherence tomography

Authors: *H. KIM, S. BAEK, Y. AHN, W. JUNG
UNIST, ULSAN, Korea, Republic of

Abstract: Recently, several treatment solutions for spinal cord injury (SCI) patient are introduced such as wireless electrical stimulation and stem cell therapy. To check the effect of treatment, monitoring spinal cord healing process is required, but MRI and CT cannot resolve small tissue level SCI. As an alternative non-destructive imaging tool, optical coherence tomography (OCT) was demonstrated to monitor and quantify SCI.
OCT can visualize cross section information of biological samples with sub-micron resolution. Conventional OCT utilizes infra-red laser as a light source and screen flat focal plane through 2D scanner. However, if sample is curved or uneven structure, it is hard to acquire images where sample position is out of flat focal plane. To acquire entire information of curved sample, we present circular scanning optical coherence tomography. Like computed tomography (CT), scanning laser is guided to the sample omnidirectionally through specially designed metal coated mirror. Due to the perpendicular reflection at mirror, cylindrical focal plane around sample can be obtained, providing clear cross section information of spinal cord.
To quantify SCI, we applied circular scanning OCT to spinal cord of mouse model *ex vivo* and segmented injury region through image processing. In addition, circular scanning OCT can detach white matter and gray matter. It gives possibility to monitor SCI healing process through quantifying area or volume of wound and time.

Disclosures: H. Kim: None. **S. Baek:** None. **Y. Ahn:** None. **W. Jung:** None.

Poster

259. Mouse Connectomics

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 259.19/UU60

Topic: D.07. Vision

Support: Grant-in-Aid for Scientific Research(S): 22220006

Title: Anatomical properties of the cholinergic projection from the parabigeminal nucleus to the superficial layer of superior colliculus

Authors: *K. TOKUOKA[1,2,3,4], M. KASAI[1], T. ISA[1,3,4]
[1]Neurosci., [2]Grad. Sch. of Biostudies, Kyoto Univ., Kyoto, Kyoto, Japan; [3]Developmental Physiol., Natl. Inst. for Physiological Sci., Okazaki, Aichi, Japan; [4]Physiological Sci., The Grad. Univ. for Advanced Studies, Hayama, Kanagawa, Japan

Abstract: The Superior colliculus (SC) is a midbrain center for controlling spatial attention. It has been known that its superficial layer (sSC) has the reciprocal connection with parabigeminal nucleus (PBN), a small cluster in the midbrain, comprised of cholinergic cells. The sSC sends projection to the ipsilateral PBN and receives dense cholinergic input from the bilateral PBN. Based on this relationship, PBN has been designated as the satellite system of the sSC (Graybiel, 1978). Previous *in vitro* studies revealed that GABAergic interneurons within the sSC express nicotinic and/or muscarinic acetylcholine (ACh) receptors, and ACh facilitates GABAergic inhibition in the sSC (Endo et al. 2005, Lee et al. 2001). Since GABAergic inhibition is critical in shaping the visual response properties of the sSC, it is hypothesized the cholinergic projection from the PBN modulate visual signal processing in the sSC through the GABAergic interneurons. However, its physiological role is still elusive. Actually, even the anatomical properties, such as axonal trajectories and terminal distributions, of the cholinergic neurons remain unclear because the PBN is small in size, and cholinergic and other types of neurons are intermingled in the PBN. As the first step to address these issues, we investigated the characteristics of the cholinergic projection from the PBN to the sSC. To selectively visualize cholinergic neurons in the PBN, we injected the Cre dependent adeno-associated viral vector (DIO-hChR2-EYFP) into the PBN of the ChAT-IRES-Cre knock-in mice. We found that EFYP-labeled cholinergic fibers projected to the ipsilateral sSC and dorsal lateral geniculate nucleus (DLG). Furthermore, the fibers also reached the contralateral sSC and DLG via the axonal course passing through the optic tract to cross the midline through the optic chiasma and enter the contralateral side. Quantitative analysis of the projection area in the whole sSC revealed there were biased distributions of the axons and terminals. Dense cholinergic projections terminated in the central and medial aspects of the ipsilateral sSC. Whereas, in the contralateral sSC, dense cholinergic projections terminated in the rostral and medial aspect. Based on the retinotopic organization of the sSC, these areas corresponded to the central and upper parts in the visual field of the mouse. These results suggested the PBN may have a role in modulating the neuronal responses in the sSC to the visual stimulus appearing in these specific parts of the visual field.

Disclosures: **K. Tokuoka:** None. **M. Kasai:** None. **T. Isa:** None.

Poster

260. Data Analysis and Statistics: Human Data I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 260.01/UU61

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: The Department of Anesthesia, Critical Care and Pain Medicine at MGH

Institute for Medical Engineering and Sciences

Department of Brain and Cognitive Sciences

Picower Center for Learning and Memory MIT

NIH Director's Pioneer Award

NIH Director's Transformative Research Award

Title: Brain state during deep sedation in office-based anesthesia

Authors: *P. KAHALIARDABILI[1,2], S. NAGARAJ[4], F. SHAPIRO[6], S. CHAKRAVARTY[2], E. N. BROWN[3,5,7,8,9], P. L. PURDON[10], M. BRANDON WESTOVER[4]
[1]Anesthesiol., Athinoula A. Martinos Ctr. For Biomed. Imagin, Charlestown, MA; [2]Picower Inst. for Learning and Memory, [3]Brain and Cognitive Sci., MIT, Cambridge, MA; [4]Neurol., [5]Anesthesia, Critical Care and Pain Med., Massachusetts Gen. Hospital, Harvard Med. Sch., Boston, MA; [6]Anesthesia, Beth Israel Deaconess Med. Center, Harvard Med. Sch., Boston, MA; [7]Picower Inst. for Learning and Memory, Massachusetts Inst. of Technol., Cambridge, MA; [8]MIT-Harvard Hlth. Sci. and Technol., Cambridge, MA; [9]Inst. of Med. Engin. and Science, Massachusetts Inst. of Technol., Cambridge, MA; [10]Anesthesia, Critical Care, and Pain Mgmt., Massachusetts Gen. Hosp., Charlestown, MA

Abstract: In many office-based anesthesia (OBA) procedures the goal is to induce deep sedation while maintaining physiologic stability. Depth of sedation is usually assessed by clinical evaluations of the patient's arousability. Nevertheless, oversedation leading to respiratory depression is an important mechanism of patient injuries. EEG monitoring is not a part of the standard practice, even though use of EEG can provide a neurophysiology-based paradigm to monitor brain function under anesthesia. Here we studied EEG signatures to characterize brain state under deep sedation during OBA.
We studied 25 patients (12 females, age: 63.7 ±10) who underwent deep sedation, induced with propofol, lidocaine, dexmedetomidine, and ketamine, for upper and lower gastrointestinal endoscopy. We used the Richmond Agitation Sedation Scale (RASS) for behavioral evaluation of depth of sedation. EEG was recorded using frontal electrodes. For each patient, we identified one-minute epochs of RASS -5 (an equivalent behavioral state corresponding to the intended clinical target during deep sedation). We performed principal component analysis on mean power spectra of each epoch derived from multi-tapered spectrogram. We applied a clustering algorithm on the data viewed in the first three principal components' space. Anesthetics' plasma concentrations were estimated using the STANPUMP package.
We observed that all patients had spontaneous respiration through out the procedure. Three clusters of RASS -5 epochs were evident, and significant presence of power in slow oscillations was noted. Furthermore we found that cluster 1 comprises more elderly patients with low propofol plasma concentrations, cluster 2 which is characterized by higher power in alpha (8-12 Hz) frequency band in EEG comprises relatively younger patients with higher concentrations, and cluster 3, a mixed-age group, had lower propofol plasma concentrations and more myogenic artifact in EEG.
We infer that patients in cluster 3 with the increased myogenic artifact are probably in a lighter state of anesthesia than those in clusters 1 and 2, despite having the same RASS score of -5. From the absence of muscle artifact in clusters 1 and 2 and the RASS scores of -5, we think that

patients are in the same state of anesthesia. However, relative to younger patients in cluster 2, patients in cluster 1 needed less propofol to attain the same behavioral state while less robust alpha oscillations were evident in their EEG. The latter finding most likely reflects both the lighter stage of anesthesia and the age of the brain. This study suggests that EEG monitoring can potentially improve anesthesia care in office-based setting.

Disclosures: P. Kahaliardabili: None. **S. Nagaraj:** None. **F. Shapiro:** None. **S. Chakravarty:** None. **E.N. Brown:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Masimo has licensed our algorithms for EEG monitoring. **P.L. Purdon:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Masimo has licensed our algorithms for EEG monitoring. **M. Brandon Westover:** None.

Poster

260. Data Analysis and Statistics: Human Data I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 260.02/UU62

Topic: I.07. Data Analysis and Statistics

Support: Brain/MINDS by AMED.

Title: Robust optimal data representations for measuring distribution similarity

Authors: *A. BRAMSON
Lab. for Symbolic Cognitive Develop., Riken, Wako City, Saitama, Japan

Abstract: Scientists have many methods to choose from when comparing distributions, but their choice of method is not always aligned with best practices for the data being compared. For example, parametric approaches are popular because they allow the calculation of precise p-values for similarity. However the choice of parametric distribution requires assumptions on the shape of underlying distribution, p-values are often misinterpreted by both scientists and the lay public, and recent concerns over “p-hacking” undermine the apparent rigor. Instead, we present an evaluation of sixteen different non-parametric data representations and determine the strengths and weakness of each approach to identify the method that provides the best comparison across distribution types and sample sizes.
In this study we generate random datasets from two distributions containing 15, 50, 100, or 200 points of data and compare the overlap coefficient of each nonparametric representation to the known true overlap coefficient for those generating distributions. The distributions are chosen from the Normal, Weibull, Uniform, ArcSin, and Levy distributions with random parameters chosen so that at least 95% of the data are within the -10 to 20 range. We perform 500 comparisons for all 240 cases of using each type of distribution and each sample size for each of

the two distributions. For each comparison we calculate the true PDF overlap from the known distributions, and the overlap coefficient from each of sixteen different nonparametric data representation techniques such as various histograms, smoothed histograms, and kernel estimates.
The goal is to find the approach that minimizes the error between the overlap of the nonparametric distributions and the true PDFs across different conditions. For example, kernel estimate distributions perform well when both true distributions are normal and the sizes are large, but perform poorly when comparing highly skewed distributions and/or small samples. Certain novel methods that perform poorly on the overlap test because of overfitting have useful applications in bootstrapping. Ordinary traditional histograms perform quite well across a wide range of cases, but are poor at handling outliers. These and other results comprise a practical guide to measuring the similarity of two datasets with minimal assumptions and the fewest user-dependent choices.

Disclosures: **A. Bramson:** None.

Poster

260. Data Analysis and Statistics: Human Data I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 260.03/UU63

Topic: I.07. Data Analysis and Statistics

Support: NIH Grant 5351831077

Title: Identifying epileptogenic biomarkers after traumatic brain injury using diffusion component analysis

Authors: A. RIOS[1], A. W. TOGA[2], P. VESPA[3], *D. DUNCAN[2]
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Abstract: It is common for epilepsy to develop after traumatic brain injury (TBI), and because much is known about the physical history of post-traumatic epilepsy (PTE), it may be treated as a practically ideal human model in which to study the process of developing seizures. Since the latency period between the injury and the development of seizures is usually short, it is practical to study epileptogenesis with reasonable follow up periods. Epileptogenesis after TBI can be prevented with specific antiepileptogenic treatments; if we can identify relevant biomarkers of epileptogenesis after TBI, we can test these treatments to stop seizures from occurring, which is the overarching goal. The method applied to identify biomarkers incorporates an extension of diffusion maps and uses local principal component analysis. In this method, Diffusion Component Analysis, we use signals from electrodes with the highest EEG spectral entropy and

divide the data into overlapping time frames. We apply the short-time Fourier transform to generate high dimensional feature vectors encompassing spectral change over time. From the pairwise combinations of feature vectors, we use the Mahalanobis distance, an improved metric to detect underlying factors in high dimensional EEG data, and use it in the kernel for the eigendecomposition. From this we can extract a diffusion map embedding of the data. In order to extract the most information at each region, we compare an embedding constructed with one basis of eigenvectors along the whole dataset with another embedding formed by choosing an optimal basis for each window of data, independently. Each basis is chosen so as to provide the largest standard deviation of data points. By analyzing the variance of the embedding over time, we find preliminary results indicating that the method proposed is very sensitive to temporal discontinuities. Diffusion Component Analysis enables the construction of a new set of coordinate bases that efficiently represents the complex geometry of the EEG data while assuming a stochastic mapping between the underlying processes and the measurements. Promising preliminary results indicate that the method may be used to identify biomarkers of epileptogenesis after traumatic brain injury by revealing underlying brain activity in pre-seizure EEG data.

Disclosures: **A. Rios:** None. **A.W. Toga:** None. **P. Vespa:** None. **D. Duncan:** None.

Poster

260. Data Analysis and Statistics: Human Data I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 260.04/UU64

Topic: I.07. Data Analysis and Statistics

Support: Intel Corporation Grant

Title: Using realistic, synthetic fMRI data to validate Topological Data Analysis as a tool for fMRI

Authors: *J. D. COHEN[1], M. LESNICK[1], B. KELLER[2], C. BALDASSANO[1], A. C. SCHAPIRO[3], C. T. ELLIS[1,4]
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Abstract: Recent fMRI research has shown that perceptual and cognitive representations are instantiated in high dimensional multivoxel patterns in the brain. However, the methods for detecting and illustrating these representations are limited in a number of ways. Topological Data Analysis (TDA) is a new approach, based on the mathematical field of topology, that can detect new types of geometric structures in activity patterns across space, time, or stimuli. In some cases it is expected that cognitive representations will have a topological structure that other

techniques would be unable to identify. To validate the usefulness of TDA with fMRI data, we have developed two new tools that are now publicly available as part of the Brainiak toolbox (github.com/IntelPNI/brainiak). First is fmrisim, a function to create synthetic fMRI datasets with specified noise properties. This tool also makes it possible to read in real fMRI data, approximate a variety of parameters of fMRI noise, and use these parameters to create new synthetic data. A known representation, of any functional form, can then be inserted into these synthetic brains which can be processed like real fMRI data. The second tool, a python implementation of TDA, can be used to identify whether metric data, including preprocessed fMRI data, has a topological structure. To test these two tools, a synthetic dataset was generated based on the experimental design of Schapiro, Rogers, Cordova, Turk-Browne & Botvinick (2013). In this experiment, participants came to represent a sequence of stimuli according to a graph structure. We found that TDA can, under a variety of conditions of neural and representational noise, identify true representational structure better than non-topological methods. These results suggest that TDA will be a useful tool to study neural representations that have a topological form.

Disclosures: **J.D. Cohen:** None. **M. Lesnick:** None. **B. Keller:** A. Employment/Salary (full or part-time):; Intel Corportation. **C. Baldassano:** None. **A.C. Schapiro:** None. **C.T. Ellis:** None.

Poster

260. Data Analysis and Statistics: Human Data I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 260.05/UU65

Topic: I.07. Data Analysis and Statistics

Support: Intel Corporation

John Templeton Foundation

Title: When temporal similarity is mistaken for representational similarity: A Bayesian approach to reduce bias in RSA of fMRI data

Authors: *M. CAI[1], N. W. SCHUCK[1], J. W. PILLOW[1], Y. NIV[1,2]
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Abstract: Representational similarity analysis (RSA) has been widely adopted to quantify the similarity between estimated neural activity patterns of different cognitive states or task conditions. It has recently been found that temporal distance between events of an experiment influences RSA results (Alink et al., 2015, Henriksson et al., 2015, Cai et al., 2016). However, the severity of the influence has not been fully appreciated. Here we analytically derive the cause of this problem, and propose a solution. First, we show that serial correlations in fMRI noise and

temporal relationships between task events together introduce structured noise into the estimated neural patterns. Correlation analysis of the estimated patterns translates this structured noise into spurious bias structure in the similarity matrix. The bias is especially severe with low signal-to-noise ratio (SNR) or in cases in which experimental conditions cannot be fully randomized in the task design. For example, in a decision-making experiment in which task conditions had a fixed Markovian transition structure, 84±12% of the variance of the similarity matrix estimated from a brain region could be accounted for by this bias. To detect the true similarity structure and reduce the bias, we propose an alternative Bayesian framework for computing representational similarity, extending the work of Diedrichsen et al. (2011). Our method relies on a generative model of fMRI data in which the covariance structure of neural activity patterns is treated as a hyper-parameter. By inverting this generative model, we directly estimate the covariance structure from imaging data while marginalizing over the unknown activity patterns. Converting the covariance matrix to a correlation matrix provides an estimate of representational similarity with significantly reduced bias. Our method can be further extended to learn shared representational similarity structure across participants. The estimated covariance structure and SNR map can also serve as constraints to obtain more accurate estimates of activity patterns that can be further used to decode activities associated with the task conditions from neural imaging data. Our tool is freely available in Brain Imaging Analysis Kit (BrainIAK, https://github.com/IntelPNI/brainiak). This work was made possible by support from Intel Corporation.

Disclosures: **M. Cai:** None. **N.W. Schuck:** None. **J.W. Pillow:** None. **Y. Niv:** None.

Poster

260. Data Analysis and Statistics: Human Data I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 260.06/UU66

Topic: I.07. Data Analysis and Statistics

Support: Intel Corporation

Princeton University

Title: Real-time fMRI analysis in the cloud

Authors: ***D. SUO**[1], J. HUTCHINSON[5], M. T. DEBETTENCOURT[6], A. C. MENNEN[2], Y. WANG[7], T. WILKE[8], N. B. TURK-BROWNE[3], K. NORMAN[4], J. D. COHEN[4], K. LI[4]
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Abstract: Real-time fMRI (rtfMRI) is a powerful tool that has permitted cognitive neuroscientists to explore how targeted neural processes guide behavior (Sulzer et al., 2013, NeuroImage). At the same time, there is growing interest in rtfMRI from clinicians, as it can enable a relatively direct and rapid translation from psychological and neuroscientific discoveries to interventional applications. In early studies, successful uses of rtfMRI were based on simple neural measures such as percent signal change in a specific region of interest. However, a newer generation of rtfMRI studies seeks to incorporate more sophisticated and computationally demanding analyses, as are now in widespread use for offline analysis (Cohen et al., 2017, Nature Neurosci). These approaches make real-time processing difficult, expensive, and in some installations, intractable. With data arriving roughly every second, researchers must limit their analyses, heavily optimize them, or do both to keep pace. Here, for the first time, we provide evidence that cloud-based computing — i.e., remote compute resources that are used and paid for on demand — might viably serve as a way to bypass these bottlenecks while maintaining the low latency (e.g., < 1 s) necessary for real-time endeavors. Specifically, as a test case, we implemented a computationally taxing analysis wherein we applied a support vector machine discriminative classifier on a matrix of voxel-to-voxel correlations (full correlation matrix analysis, FCMA; Wang et al., 2015, J Neurosci Meth) on a moving window of BOLD data in real time. Critically, this analysis was done on a remote server and required only an internet connection. If run locally, this computation would require a dedicated workstation typically not available to practitioners and could still take a long time even if available. These preliminary results indicate that cloud-based computing is a potentially valuable approach to enable sophisticated and/or computationally taxing analyses in real-time. Moreover, the relative low cost, flexibility, and accessibility of cloud-based computing creates the broader potential for promoting reproducibility and portability, and for encouraging greater data exploration among researchers and clinicians. This work deployed software from the Brain Imaging Analysis Kit (BrainIAK, available at http://brainiak.org) to our cloud environment.

Disclosures: **D. Suo:** A. Employment/Salary (full or part-time):; Princeton University. **J. Hutchinson:** A. Employment/Salary (full or part-time):; Northeastern University. **M.T. deBettencourt:** A. Employment/Salary (full or part-time):; University of Chicago. **A.C. Mennen:** A. Employment/Salary (full or part-time):; Princeton University. **Y. Wang:** A. Employment/Salary (full or part-time):; Intel Corporation. **T. Wilke:** A. Employment/Salary (full or part-time):; Intel Corporation. **N.B. Turk-Browne:** A. Employment/Salary (full or part-time):; Yale University. **K. Norman:** A. Employment/Salary (full or part-time):; Princeton University. **J.D. Cohen:** A. Employment/Salary (full or part-time):; Princeton University. **K. Li:** A. Employment/Salary (full or part-time):; Princeton University.

Poster

260. Data Analysis and Statistics: Human Data I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 260.07/UU67

Topic: I.07. Data Analysis and Statistics

Support: This work was made possible by support from Intel Corporation.

Title: Brain imaging analysis kit: Advanced fmri analysis at scale

Authors: *M. CAPOTA[1], T. L. WILLKE[1], K. NORMAN[2], J. D. COHEN[2], N. B. TURK-BROWNE[3]
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Abstract: Software toolboxes in common use for the analysis of functional magnetic resonance imaging data (AFNI, FSL, SPM) have been crucial to advancing and standardizing research in cognitive neuroscience. These toolboxes provide neuroscientists with now-standard preprocessing routines, statistical models, and corrections appropriate for brain data, and methods for estimating and visualizing the amplitude of neural activity or the differential activity between experimental conditions. However, these toolboxes were created prior to the modern era of high-performance computing and thus were not designed from the ground up to benefit from recent advances in this field. As a result, they typically do not implement or take full advantage of cutting-edge computational and analysis methods that involve extremely large-scale datasets and intermediate products, or that otherwise require optimized and extremely fast computation (e.g., for real-time analysis). Here we introduce the Brain Imaging Analysis Kit (BrainIAK, brainiak.org), a new software toolbox that picks up where standard packages leave off (after preprocessing and general linear modeling), and that is expressly designed to exploit the performance characteristics of modern hardware and software. In creating the toolbox, we applied state-of-the-art techniques to speed up computation, increase reproducibility, and streamline the programming experience. BrainIAK currently includes, among others, packages for cross-participant functional alignment (shared response modeling, SRM; Chen et al., 2015), machine learning on functional connectivity (full correlation matrix analysis, FCMA; Wang et al., 2015; inter-subject functional correlation, ISFC; Simony et al., 2016), event segmentation using hidden Markov models (Baldassano et al, 2016), dimensionality reduction through factor analysis (hierarchical topographic factor analysis, HTFA; Manning et al., 2017), and enhanced representational similarity analysis (Bayesian RSA; Cai et al., 2016). BrainIAK follows the open collaboration development model, with source code published under the open-source Apache license, a publicly-accessible issue tracker, and dependencies on only open-source software. Furthermore, all BrainIAK code is accompanied by tests and documentation. The main programming language is Python; however, performance-sensitive code is written in C++.

Crucially, BrainIAK uses message passing interface (MPI) software libraries to achieve high performance when deployed on distributed computer systems, such as clusters, the cloud, or on supercomputers.

Disclosures: **M. Capota:** A. Employment/Salary (full or part-time):; Intel Corporation. **T.L. Willke:** A. Employment/Salary (full or part-time):; Intel Corporation. **K. Norman:** None. **J.D. Cohen:** None. **N.B. Turk-Browne:** None.

Poster

260. Data Analysis and Statistics: Human Data I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 260.08/UU68

Topic: I.07. Data Analysis and Statistics

Support: support from Intel Corporation

Title: Multi-subject fmri data factor analysis using brainiak

Authors: *H. ZHANG, P.-H. CHEN, P. J. RAMADGE
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Abstract: In modern fMRI studies of human brain, the scarcity of data from a single subject motivates the use of data from multiple subjects. This is necessary to ensure the generalization of any scientific discovery. It also has the potential to increase statistical power by using a larger dataset. However, the inter-subject variability in both anatomical structure and functional topographies makes such analysis very challenging. To tackle this problem, we treat multi-subject fMRI analysis from a multi-view learning perspective in the sense that we consider data from each subject as a different “view” of a common low-dimensional representation. Start from this assumption, we set out to find the shared low-dimensional time-course across subjects, as well as a set of subject-specific brain map bases that map the high-dimensional fMRI data to a low-dimensional shared space. We have released an implementation of a factor model called *shared response model* (SRM) in BrainIAK that solves this multi-view problem using a constrained probabilistic formulation. We describe two experiments that show how to use SRM to test a hypothesis in multi-subject fMRI analysis: given brain response from an ROI of a test subject, can we classify what the stimulus is using data from training subjects. The null hypothesis would be that the stimulus category information doesn’t exist in this ROI, and the classification accuracy should be at a chance level. In both experiments, we apply SRM on training subjects’ fMRI data gathered under a movie stimulus to find a common low-dimensional subspace, and project a held-out test subject’s fMRI data with movie scene recall stimulus to that subspace. Then we pick a piece of projected response of the test subject, and try to classify which scene it corresponds to. The use of SRM enables effective aggregation of information in

training subjects. In the first experiment, we test some pre-defined ROIs such as planum temporale (PT) and posterior medial cortex (PMC). We find that PMC carries the most stimulus category information among all the ROIs we are testing, and compared with a simple averaging of fMRI response, SRM boosted the classification accuracy. In our second experiment, we use the searchlight package implemented in BrainIAK to apply SRM on different searchlights. This allows us to find the searchlight regions with greater shared informative content. We find that searchlights with high classification accuracies concentrate on the PMC region, which aligns with our finding in the first experiment.

Disclosures: H. Zhang: A. Employment/Salary (full or part-time):; Princeton University. **P. Chen:** A. Employment/Salary (full or part-time):; Princeton University. **P.J. Ramadge:** A. Employment/Salary (full or part-time):; Princeton University.

Poster

260. Data Analysis and Statistics: Human Data I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 260.09/UU69

Topic: I.07. Data Analysis and Statistics

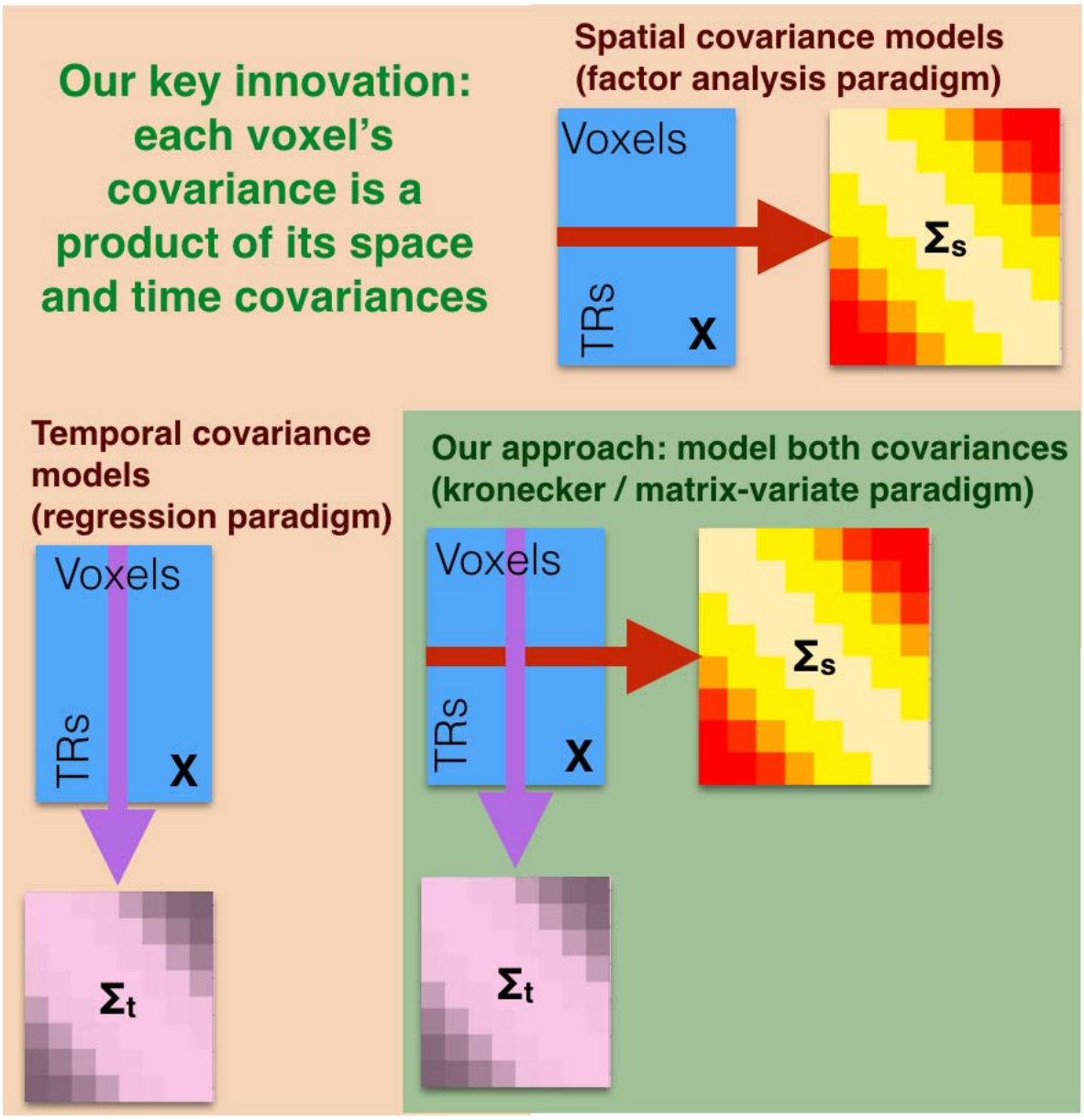
Support: This work was made possible by support from Intel Corporation.

Title: Matrix-variate models for fMRI analysis

Authors: *M. SHVARTSMAN[1], N. SUNDARAM[2], M. C. AOI[3], A. CHARLES[3], T. L. WILKE[2], J. D. COHEN[4]
[1]Princeton Neurosci. Inst., Princeton, NJ; [2]Intel Corp., Santa Clara, CA; [3]Princeton Neurosci. Inst., [4]Princeton Univ., Princeton, NJ

Abstract: Multivariate analysis of fMRI data has benefited substantially from advances in machine learning. Most recently, a range of probabilistic latent variable models applied to fMRI data have been successful in a variety of tasks, including identifying similarity patterns in neural data (Bayesian representational similarity analysis / BRSA; Cai et al. 2016), aligning multi-subject datasets (Shared Response Model / SRM; Chen et al. 2015), and mapping between brain and behavior (Joint Modeling / JM; Turner et al. 2016). Even though these methods share some underpinnings, they have heretofore been developed as distinct methods, with distinct algorithms and software tools. We show how the formalism of matrix-variate normal models (also known as kronecker-factored covariance models) can unify these methods into a single framework. In doing so, we gain the ability to reuse noise modeling assumptions, algorithms, and code across models. We provide a theoretical contribution, a software tool, and an empirical contribution. Our theoretical contribution shows how how RSA, SRM, and Joint modeling can be written as essentially the same matrix normal model. Our software prototpying tool can flexibly reuse noise

covariance assumptions, and to a lesser extent algorithms, across models. Our empirical contribution is a novel matrix-normal RSA method and matrix-normal SRM method. Our RSA method is at least 10x faster on the previous state of the art on the same hardware, and achieves as much as 6x better performance on RMSE against known ground truth as the number of voxels increases and SNR drops. Our SRM method yields shared features that permit comparable image decoding to the previous state of the art while relaxing the orthonormality assumption of conventional SRM. The methods can be implemented in under 100 lines of code using our framework.



Disclosures: **M. Shvartsman:** None. **N. Sundaram:** A. Employment/Salary (full or part-time):; Intel Corporation. **M.C. Aoi:** None. **A. Charles:** None. **T.L. Wilke:** A. Employment/Salary (full or part-time):; Intel Corporation. **J.D. Cohen:** None.

Poster

260. Data Analysis and Statistics: Human Data I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 260.10/UU70

Topic: I.07. Data Analysis and Statistics

Support: This work was made possible with support from Intel corporation.

Title: Type 1 and type 2 error analysis for representational similarity analysis

Authors: *P. S. JOHNSON, M. SHVARTSMAN, J. D. COHEN
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Abstract: Representational Similarity Analysis (RSA; Kriegeskorte et al. 2008) is a method for comparing the structure of representations across heterogenous datasets (for example, fMRI, electrophysiology and artificial systems). Rather than comparing responses in a common space as occurs in Multi-Voxel Pattern Analysis (Norman et al. 2006) or regression-based methods, RSA analyzes the distances between points directly. This allows for the comparison of representational structure between sources of data with fundamentally different natural spaces by integrating over the first-order statistics. The applications for such cross-modal analyses are broad, including comparisons across species and similarities between mental structures and deep neural networks (e.g. Yamins, Hong, & Cadieu 2013; Khaligh-Razavi & Kriegeskorte 2014; see also Kriegeskorte et al. 2008 for an overview).

However, while the method has ostensibly been successful in discovering fundamental commonalities across these domains, its ability to recover reliable signal has not been established. The de-facto standard has been to assume that finding task-related structure implies the presence of reliable signal. However, this standard is brought under question by a recent demonstration that traditional correlation-based RSA can yield spurious results that look task-related entirely due to design-irrelevant temporal correlations in the data (Cai et al. 2016). We highlight the need for the field to identify an independent metric for the quality of an RSA matrix estimate, and discuss the benefits and challenges of a few candidate metrics (e.g. cross-validated log-likelihood, permutation testing).

Additionally, we undertake a simulation study to compare the estimates derived from different RSA methods (incl. RSA based on correlations and on fisher discriminant analysis, as well as the Bayesian RSA of Cai et al.) under different preprocessing schemes and noise regimes. Crucially, we perform our analysis both under the null and with real underlying signal (using real and synthetic data). This evaluation allows us to begin to understand the sensitivity and specificity (i.e. type I and type II) errors of methods in the RSA paradigm.

By evaluating the sensitivity of these signal properties to changes in a variety of generative parameters, we establish more accurate measures of the significance of any particular result on

empirical data. Finally, we explore the reasons and conditions under which the methods diverge in order to facilitate accurate interpretation of real applications of each analysis.

Disclosures: P.S. Johnson: None. **M. Shvartsman:** None. **J.D. Cohen:** None.

Poster

260. Data Analysis and Statistics: Human Data I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 260.11/UU71

Topic: I.07. Data Analysis and Statistics

Support: University of Minnesota

Title: Neural traffic model of brain function

Authors: *C. HENRY[1], A. P. GEORGOPOULOS[2]
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Abstract: Graph-theoretical and network-science applications to brains have been inadequate due to the imposition of unrealistic restrictions on neural interactions, including thresholding, lack of directionality, and lack of sign and latency of influence. By contrast, neural interactions are continuous in magnitude, bidirectional, signed, and delayed. Hence such approaches are inadequate models of brain function. Here we present a realistic model of neural interactions (Neural Traffic Model, NTM) based on the analysis of 30,628 pairwise prewhitened cross-correlation-functions (CCF; ±50 lags) of magnetoencephalographic data recorded @1017-Hz from 248 channels in resting humans. We built the NTM as follows.
● Each off-zero CCF side indicates the direction of influence.
● For each side, we estimated the magnitude of signed influences by calculating areas under the curve (AUC) for positive and negative CC values.
● The lags contributing to AUCs indicate the latencies of influence.
● The pairwise NTM model can then be visualized as a 2-lane road connecting 2 neural elements interacting via 2 segmented colored lanes:
● The road itself corresponds to the analyzed period of interactions (0.973 - 48.5 ms)
● The color corresponds to the sign of the influence (blue for positive, red for negative)
● The color intensity is proportional to the magnitude of the influence
● The colored segments indicate influences of certain duration spanning specific lags.
● These data can be organized in 248x248 “influence matrices” for each brain, where rows and columns represent the source and target elements, respectively. Brains (and groups of brains) can then be compared using standard statistical methods.

Disclosures: C. Henry: None. **A.P. Georgopoulos:** None.

Poster

260. Data Analysis and Statistics: Human Data I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 260.12/UU72

Topic: I.07. Data Analysis and Statistics

Support: Patient-Centered Outcomes Research Institute, X151026003

American Heart Association grant, 17PRE33370103

Title: Comparison of reproducibility of single voxel spectroscopy and whole brain magnetic resonance spectroscopy imaging

Authors: *Y. ZHANG[1], E. TAUB[1], N. SALIBI[3], G. USWATTE[1,4], A. MAUDSLEY[5], S. SHERIFF[5], B. WOMBLE[1], V. MARK[2,6], D. KNIGHT[1]
[1]Psychology, [2]Physical Med. and Rehabil., UAB, Birmingham, AL; [3]MR R&D, Siemens Healthcare, PA; [4]Physical Therapy, Physical Therapy, Birmingham, AL; [5]Radiology, University of Miami, FL; [6]Neurol., Neurol., Birmingham, AL

Abstract: Objective/Purpose: There are two most promising proton MR spectroscopy (^{1}H-MRS) techniques. The purpose of the present study was to assess and directly compare the reliability of metabolite quantification using single voxel spectroscopy (SVS) and whole-brain MR spectroscopic imaging (WB-MRSI). **Methods:** Ten healthy adults were scanned using both SVS and WB-MRSI on three occasions one week apart. N-acetyl-aspartate (NAA), creatine (Cr), choline (Cho) and myo-inositol (mI) were quantified using the two techniques with reference to both Cr and H_2O. The reproducibility of each technique was evaluated using coefficients of variation (CVs) and the correlation between the two techniques was assessed using Pearson correlation analysis. **Results:** The mean (range) intra-subject CVs for SVS were 7.01 (3.36-10.66)% for metabolites (i.e., NAA, Cho, mI) relative to Cr, and 10.67 (5.60-21.07)% for the metabolites relative to H_2O. The mean (range) CVs for WB-MRSI were 9.03 (6.40-11.41)% for the metabolites relative to Cr, and 9.61 (7.48-14.11)% for the metabolites relative to H_2O. There was significant positive correlation between the metabolites using SVS and WB-MRSI techniques when Cr was used as reference, but not H_2O. **Conclusion:** The results from this study demonstrate that for both SVS and WB-MRSI, there is good reliability and comparable reproducibility for quantifying the four major metabolites (NAA, Cr, Cho, mI). Our findings add reference information for choosing the appropriate ^{1}H-MRS technique in future studies.

Disclosures: Y. Zhang: None. **E. Taub:** None. **N. Salibi:** None. **G. Uswatte:** None. **A. Maudsley:** None. **S. Sheriff:** None. **B. Womble:** None. **V. Mark:** None. **D. Knight:** None.

Poster

260. Data Analysis and Statistics: Human Data I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 260.13/UU73

Topic: I.07. Data Analysis and Statistics

Support: DFG, UoG EG CONNECT

DFG, GR 3690/2-1

DFG, GR 3690/4-1

DFG, GR 3285/5-1

Marga and Walter Boll Foundation

Title: Improving the temporal fidelity of fMRI by time-locking

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Abstract: Although fMRI and EEG can be acquired simultaneously while a task is being performed, combining the high spatial resolution of the BOLD signal with the high temporal resolution of scalp potentials poses a major challenge for brain imaging. Fusing these distinct data requires a correspondence to be established between their task-specific correlates, either in their anatomical specificity, or their relative timing, or both. Task-features involving timing differences present an especially challenging bottleneck for fMRI due to the sluggish BOLD signal. In the current study, we investigated whether the logic of time-locking used for EEG analyses could be strategically adapted to the analysis of event-related fMRI to improve its correspondence to time-dependent task-features. The event-related potential is obtained by averaging EEG time-series across trials after aligning them to trial-specific events such as the stimulus or response onset. This time-locking allows a clear separation of neural dynamics occurring before, during and after specific task events. In tasks with brief trials, the evoked BOLD signal at each voxel is typically characterized by a single peak. This peak has a voxel- and task-dependent amplitude but also a characteristic time-point. We exploited this peak time to define a task-specific “event” to time-lock the BOLD signal across related conditions, hypothesizing that this novel procedure could improve the BOLD signal’s temporal sensitivity. This procedure was tested on a task (number of participants=30) that parametrically varied two temporal variables within each trial: the decision latency (DL) from stimulus-onset to response

onset (3 levels), and the response duration (RD) (2 levels). Our findings show that the sensitivity to these two variables differs across the brain. Conditions with DL differences of 70ms exhibited detectable temporal differences in the evoked BOLD. Even though the timing of RD and DL were independent, we find that increases in the RD can reduce the sensitivity in detecting DL differences.

Disclosures: R.O. Abdollahi: None. **S. Viswanathan:** None. **B.A. Wang:** None. **C. Grefkes:** None. **S. Daun:** None. **G.R. Fink:** None.

Poster

260. Data Analysis and Statistics: Human Data I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 260.14/UU74

Topic: I.07. Data Analysis and Statistics

Support: R-20161130-004520

2E27330-17-P026

IITP-2017-2015-0-00742

LSI17-ITKDS0001

Title: Gender and age classification based on Long Short-Term Memory during resting state fMRI

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Abstract: The previous studies of resting state functional Magnetic Resonance Imaging (rs-fMRI) have suggested that there exist some common networks in which the functional connectivities (FC) among the brain regions of healthy people. And many studies have conducted to find any significant difference of FC patterns depending on individual differences like gender and age, which are not related to specific tasks. The most of rs-fMRI studies have focused on temporal correlation in order to analyze the FC during resting state, but they had a limitation to classify different subject groups, which showed very few dissimilarity of FC. Therefore, we proposed a deep learning algorithm that recognizes the subjects' gender and age using the Blood Oxygen Level Dependent (BOLD) fMRI of each subject. The learning algorithm consists of stacked Long Short-Term Memory (LSTM), in order to extract the temporal information from BOLD signal, and followed by the fully connected layers, in order to match the two age groups (young or old) or two gender groups (male or female). We followed the standard

preprocessing methods used by the general rs-fMRI studies and chose the region of interest according to the Automated Anatomical Labeling (AAL).
The proposed LSTM algorithm showed a valid classification results and it was also compared with the results of the previous studies.

Disclosures: **J. Park:** None. **S. Park:** None. **S. Nam:** None. **D. Kim:** None.

Poster

260. Data Analysis and Statistics: Human Data I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 260.15/UU75

Topic: I.07. Data Analysis and Statistics

Title: How reliable is the cerebellum as reference region in neuroreceptor modelling of MR/PET data: Impact of various attenuation correction strategies

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Abstract: Aim: Regarding neuroreceptor PET studies a number of modelling approaches apply the cerebellum as reference area. Therefore, it is mandatory that the respective attenuation correction (AC) method for reconstructing the emission data is most appropriate regarding cerebellar areas. PET data from PET/MR scanners require alternative AC methods which transform MR data into attenuation maps (AM). Those artificial AMs need to be tested with respect to the performance within the cerebellum. The aim of the present study was to compare various AC methods for PET/MR data focussing on the cerebellum.
Methods: Data of 16 subjects undergoing ^{18}FDG imaging in the Siemens 3TMR-BrainPET scanner and a whole head CT scan at the same day were used. The latter were transformed to CT-based AMs (AM_{CT}) which served as reference AM for the PET data reconstruction. The MR images were used to obtain AMs using the Boston-MGH method (AM_{MGH}), the London-UCL method (AM_{UCL}), the CT-template-based ($AM_{CT\text{-}Juel}$) and Tx-template-based ($AM_{Tx\text{-}Juel}$) Juelich methods. BrainPET emission data were reconstructed with these five AMs. Using the SUIT tool within SPM8 the cerebellum was extracted from the MR images and normalized to a cerebellum VOI atlas. Then, the cerebellum of the PET data was extracted by applying the same parameters. After PET data reconstruction using the 5 different AMs correlation plots with regression equations, coefficients of determination R^2, normalized and normalized absolute errors between AM_{CT} reconstructed data and the other four reconstruction approaches were calculated for all cerebellar VOIs.
Results: Overall, all 4 AC methods demonstrate a very high correlation with the individual

reference AM_{CT}. However, the values of cerebellar NErr varied to a high extent between the four AC methods. Over the entire group $AM_{Tx\text{-}Juel}$ and $AM_{CT\text{-}Juel}$ performed better than AM_{MGH} and AM_{UCL} regarding both normalized error and absolute normalized error.
Conclusion: The quantitation of radiotracer uptake in the cerebellum is susceptible to the respective attenuation correction applied to the PET data. This, in turn, has to be considered in neuro-receptor modelling studies which rely on the cerebellum as reference.

Disclosures: E. Rota Kops: None. **C. Lerche:** None. **H. Müller:** None. **N.J. Shah:** None. **H. Hautzel:** None.

Poster

260. Data Analysis and Statistics: Human Data I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 260.16/UU76

Topic: I.07. Data Analysis and Statistics

Title: Feature learning for EEG-based emotion recognition

Authors: *H. LEE, *H. LEE, T. CHOI, K. CHOI, B. CHAE
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Abstract: Understanding how to recognize complex and high-dimensional electroencephalogram (EEG) data is crucial to decode brain activities for better understanding human emotion, cognition and behavior. Traditional approaches to analyze EEG data have employed machine learning based techniques which mainly focuses on extracting information called features, from prior knowledge, including power spectral density (PSD), Hjorth, and discrete wavelet transform (DWT) are the most widely and commonly used. These low-level features have been successfully used for binary classification tasks. However, as the hand-designed features are highly dependent on experimental environment and data themselves, it is difficult to extend those low-level features to other complex classification tasks. . In an attempt to use more precise features, recently, several works have been proposed to build a new EEG feature using deep learning methods such as Sparse Coding (SC), Deep Belief Nets (DBN), and Stacked auto-encoders (SDAE). These deep learning or feature learning algorithms aim to learn features directly from EEG data as well as build low-level to high-level features in general manner.
Here, we examined representation learning approaches to extract high-level features and also to assess the learned features. We firstly evaluated hand-designed features for emotion classification. In addition, we demonstrated the performance of the learned features compared to the existing approaches to representation learning. In this study, we found that emotion recognition from EEG dataset brought several difficulties and challenges including lack of data samples, limited labeled samples, and unclear emotional states, and thus it is difficult to apply

the existing representation learning approaches directly. Therefore, we propose a novel feature learning method to unlabeled EEG data. Our results indicate how our novel method can improve the performance of EEG based emotion classification compared to the existing algorithms for emotion classification as well as the traditional approaches that employ hand-designed features.

Disclosures: **H. Lee:** None. **T. Choi:** None. **K. Choi:** None. **B. Chae:** None.

Poster

260. Data Analysis and Statistics: Human Data I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 260.17/UU77

Topic: I.07. Data Analysis and Statistics

Support: eScience Pathfinding 2015

Title: Epilepsy diagnosis with predictive EEG modeling

Authors: ***W. M. OTTE**[1], V. T. VAN HEES[3], M. R. T. SINKE[1], J. W. BUITENHUIS[1], F. VAN DER MAAS[4], L. RIDDER[3], E. VAN DIESSEN[2]
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Abstract: Most people with epilepsy live in rural areas in low-middle-income countries. Despite the availability of cheap and save drugs, more than 80% is not on treatment due to lack of required diagnosis. Access to proper diagnosis is limited in these countries as access to neurological facilities is often impossible or burdensome. In this study, we aimed to develop a method to identify people with a high probability of epilepsy based on easy to acquire field-data. Two minutes of functional brain data was acquired with a portable, low-cost consumer-grade electroencephalography recording headset in both healthy individuals and people with epilepsy (70%) in a rural area from Guinea-Bissau (N=97) and Nigeria (N=128). Prediction methods entailed random forest classification using wavelet features and were bootstrap validated with unseen data. We assessed classifier performance by calculating concordance statistics.
Most contributing time-series features were the minimum and mean standard deviation of the beta and theta wavelets of the 14 channels, respectively. The area under the receiver-operating curve was 0.85 and 0.78 (standard errors: 0.02) in unseen data in Guinea-Bissau and Nigeria. respectively. Cross-validation in the other country showed area under the receiver-operating curves of 0.62 and 0.64 (standard errors: 0.02), respectively.
Proper external validation electroencephalography recording headsets in combination with automatic time-series modeling may bring diagnostic capabilities to the most remote areas of the

world. These will significantly add to the closing of the epilepsy treatment gap in regions where the burden of this disabling disease is highest.

Disclosures: **W.M. Otte:** None. **V.T. van Hees:** None. **M.R.T. Sinke:** None. **J.W. Buitenhuis:** None. **F. van der Maas:** None. **L. Ridder:** None. **E. van Diessen:** None.

Poster

260. Data Analysis and Statistics: Human Data I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 260.18/UU78

Topic: I.07. Data Analysis and Statistics

Support: This work was supported by Ministry of Culture, Sports and Tourism (MCST) and Korea Creative Content Agency (KOCCA) in the Culture Technology (CT) Research & Development Program 2017.

Title: Four-class emotion classification using one-dimensional convolution neural networks - An EEG study

Authors: *S. LEE, *S. LEE, S. HAN, S. JUN
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Abstract: INTRODUCTION: Various machine learning techniques have been used to classify emotion states because it is a very interesting topic for both neuroscientists and engineers. However, multi-class classification using neural networks has been studied rarely. In this paper, we obtained frontal EEG signals during watching emotion-evoking video clips and applied one-dimensional convolution neural networks (CNN) to classify multi-class emotions.
MATERIALS AND METHODS: Total 80 subjects participated, and each group of eight subjects watched the videos together. 4 video clips to evoke happiness, boredom, sadness, and horror were screened. Each material took 20 minutes. One EOG, one EMG, one ECG, and five EEG (AF7, Fp1, Fpz, Fp2, and AF8) channels were measured by BIOS-mini (Biobrain Incorp.), which is a custom-developed EEG device at a sampling rate of 1 kHz. Signals were bandpass filtered between 1-50 Hz and cut into frames (eight seconds long per frame) without overlapping. Among all frames, we selected highest scored frames that was rated by independent subject groups and used for classification analysis. Then, each frame was used as the input of CNN. Proposed CNN had three convolution layers and three max pooling layers. Classification accuracy was estimated using 5-fold cross validation.
RESULTS: Table 1 shows four-class classification results. Averaged classification accuracy was 66%. Classification of happiness was relatively higher than other emotions. Classification of boredom or horror yielded relatively high misclassification rates, since boredom was frequently

misclassified as happiness and horror was misclassified as sorrow.
DISCUSSION: In this preliminary study, classification accuracy for the four genres was achieved as about 66%. It seems that the reason for the low performance may be due to movement artifacts during watching videos. However, it is believed that these results were quite accurate, considering a few numbers of channels. It is expected that performance may be improved by further elegant analyses and optimization of the CNN structure.

Table 1: Classification rate (%)

Input \ Classified	Happiness	Boredom	Horror	Sadness
Happiness	80.13	4.81	3.97	11.09
Boredom	22.57	55.23	5.32	16.88
Horror	14.63	10.33	56.28	18.76
Sadness	17.14	4.86	4.86	73.14

Disclosures: **S. Lee:** None. **S. Han:** None. **S. Jun:** None.

Poster

260. Data Analysis and Statistics: Human Data I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 260.19/UU79

Topic: I.07. Data Analysis and Statistics

Support: LGSF was supported by a grant from Brazilian National Council of Research and Development (CNPq) (206907/2014-1)

Title: Multifractal analysis of human EEG: Link with sleep stages

Authors: *L. SOUZA FRANCA[1], ***L. SOUZA FRANCA**[1], Y. WANG[2], M. C. WALKER[1], J. G. V. MIRANDA[3], L. LEMIEUX[1]
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Abstract: The human electroencephalogram remains the subject of intense investigation with the hope of providing new insights into brain dynamics in health and disease. In particular, measures

of complexity have recently been applied to the study of human EEG, suggesting that they possess scaling properties. We aimed to characterise the relationship between sleep stages and such scaling properties in human EEG recordings. We propose a new method for the characterisation of EEG signals based on multifractal analysis. Data from five subjects with polysomnography set-up (scalp EEG) were analysed. The signals were initially transformed with a sigmoid function and then analysed based on the Chhabra-Jensen multifractal approach resulting in a spectrum every 10.24 seconds in non-overlapping windows. The sigmoid transformation maps the original raw time series in a new recording with values ranging from 0 to 1. The width and height of the multifractal spectra were evaluated, resulting in two measures for each channel in each 10.24 second window. The ability to distinguish different sleep stages using the multifractal-based metric vs. traditional approaches was also tested. A multifractal behaviour was observed in all recordings. Multifractal-based metrics were then also shown to contain additional information compared to standard measures, such as band power (delta, theta, alpha, beta, gamma and high gamma), average potential, standard deviation, entropy, and line length. The analysis also demonstrated a clear difference in multifractal-based metrics for different sleep stages ($p < 0.001$ in the Kruskal-Wallis test). The results of the analysis show that scaling properties of the EEG signal do change in sleep between the different sleep stages. While the physiological meaning of multifractal-based metrics, and their relationship to underlying sleep regulatory processes, remains to be elucidated we have shown that they may be able to provide markers of sleep patterns and related processes.

Disclosures: **L. Souza Franca:** None. **Y. Wang:** None. **M.C. Walker:** None. **J.G.V. Miranda:** None. **L. Lemieux:** None.

Poster

260. Data Analysis and Statistics: Human Data I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 260.20/UU80

Topic: I.07. Data Analysis and Statistics

Support: the Natural Science Foundation of China (81371631, 81422024 to L.W.)

the Beijing Nova Program (Z141110001814068 to L.W.)

Thousand Youth Talents Plan (Y4HX072006 to L.W.)

the Hundred Talent Program of Chinese Academy of Sciences (Y3CX022003 to L.W.)

Title: Frequency dependent resting state oscillation network revealed by intracranial EEG recordings

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Abstract: Resting state functional networks underlie both healthy and abnormal human brain function. Despite the extensive studies about their manifestation in BOLD signal conducted during the past decade, the electrophysiological basis of resting state functional networks remain to be elucidated. Compared to fMRI, intracranial EEG offers a chance to measure the neuronal activity with high spatial specificity and high temporal resolution, the latter advantage makes it possible to reveal dynamic network properties across different time scales.
In this study we aimed at testing the hypothesis that resting state EEG network is frequency dependent both in local and connection sense. We collected stereotactic EEG and ECoG data from more than 50 epileptic subjects, the overall distribution of recording sites essentially covered the entire cortex surface. Focusing on data recorded from non-epileptic brain regions, we inspected the resting state EEG networks at local and connectivity level. For the local neural computation, an oscillation spectrum was extracted by removing the scale free component from background frequency spectrum, thus generated a dominant oscillation frequency distribution across cortical surface. Meanwhile, a cross frequency coupling index was calculated to elucidate a potential regional specific spike-modulation role of low frequency activities, which complemented the dominant oscillation information at node level. At the connectivity level we calculated the frequency dependent connectivity matrix which showed significant frequency dependent connectivity pattern across different brain areas. A directed information flow measurement was conducted to test the large scale, frequency dependent information flow between separated neuron populations.
Preliminary results indicated that frequency dependent patterns were revealed by varies functional indices both at local and connectivity level. The potential influence of the choice of EEG reference scheme upon these results was discussed further and suggested that the decision of which reference scheme to adapt should be made based on the exact function index to be calculated and the location of recording sites.

Disclosures: Z. Tan: None. **W.J. Zhou:** None. **L. Wang:** None.

Poster

260. Data Analysis and Statistics: Human Data I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 260.21/UU81

Topic: I.07. Data Analysis and Statistics

Title: Extracting single-trial time courses from EEG/MEG data using spatial filtering

Authors: *O. HAUK[1], M. TREDER[2], D. NORRIS[3]
[1]Med. Res. Council UK, Cambridge, United Kingdom; [2]Univ. of Birmingham, Birmingham, United Kingdom; [3]Med. Res. Council, Cognition and Brain Sciences Unit, Cambridge, United Kingdom

Abstract: For a range of applications, such as computational modelling of latency distributions, or brain-computer interfaces, it is necessary to extract single-trial time courses from EEG/MEG data. Here, we describe and compare several spatial filtering methods that may increase the signal-to-noise ratio (SNR) for single-trial time courses associated with topographies of interest: single- and multiple-component signal-space-projection (scSSP), maximum likelihood estimation (MLE), LDA beamforming (BF), and DeFleCT. We applied these methods to previously published data from a visual word recognition study and an openly available EEG/MEG data set (Neuromag Vectorview, 306 MEG and 70 EEG channels).
Words of different lexical and semantic categories were presented in different blocks in randomized order with an SOA of 2.5 s. We computed single-trial time courses for target topographies obtained from ERPs/ERFs in the N1 (150-200 ms) and N4 (250-500 ms) time window. Average SNR time courses were computed for scSSP, mcSSP, MLE and BF. For the novel mcSSP method, noise topographies were extracted using singular-value decomposition of single-trial baseline intervals. We computed distributions of single-trial latencies (based on peak and centre-of-gravity measures) for separate experimental conditions, and compared average latencies across subjects using t-tests.
All methods revealed different time courses for N1 and N4 components, respectively, with SNR peaks in their respective latency windows. Thus, SSP methods can enhance SNR for separate ERP/ERF components at the single-trial level. MLE and BF produced the largest average SNRs (up to 3 for N1, 2 for N4), and outperformed scSSP (values about 1.5 for N1 and N4). For mcSSP, increasing the number of noise components in the model increased the average SNR to levels similar to MLE and BF. However, this appeared to be mainly due to a reduction of baseline amplitudes which suggests that, at the single-trial level, noise is not stationary or additive. mcSSP and BF reduced activity from eye-blinks, indicating that they are able to reduce the effect of noise sources that can be characterized by stable topographies.
We did not find differences between experimental conditions with respect to component latencies. This is in line with previous results suggesting quasi-simultaneous lexical and semantic information retrieval, but also raises the question of how to link neural and behavioural responses in the presence of behavioural reaction time differences, such as for words and pseudowords.

Disclosures: O. Hauk: None. **M. Treder:** None. **D. Norris:** None.

Poster

260. Data Analysis and Statistics: Human Data I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 260.22/UU82

Topic: I.07. Data Analysis and Statistics

Support: The MIC/SCOPE #162105001

JSPS KAKENHI Grant Number 17K01992

Title: Reconstructing two-dimensional circular motions from EEG cortical currents during overt/covert visual pursuit tasks

Authors: *K.-I. MORISHIGE, T. ISHIKAWA
Toyama Prefectural Univ., Toyama, Japan

Abstract: It is generally considered that EEG data is inadequate to extract detailed brain information about smooth pursuit eye movements because eye artifacts can be orders of magnitude larger than the signal from the brain. Although some statistical denoising methods, such as PCA and ICA, have been proposed and widely used, these conventional ones have difficulty removing eye artifacts correlated with brain signals in principle. To solve these problems, the “Extra-Dipole Method” has been proposed (Morishige et al., NeuroImage 2014), which is based on the hierarchical Bayesian method and simultaneously estimates the cortical and eye currents by solving the EEG inverse problem. In our previous studies, we applied this denoising method to measured EEG data during one-dimensional overt/covert visual pursuit tasks. Here, it is applied to EEG data during two-dimensional pursuit tasks. Subjects were instructed to pursue a circularly moving target overtly or covertly, and EEG data were recorded. We considered that the left and right eyeballs were main noise sources, six dipoles (two eye current sources × x-y-z directions) were located there, and not only cortical but also eye currents were estimated simultaneously. We calculated the current intensities from estimated cortical currents. The cortical regions of the lateral occipital temporal cortex, the intraparietal cortex, the precentral cortex, and the medial superior frontal cortex had large current intensities. These areas are related to the smooth pursuit eye movements, and are also activated when subjects orient their attention to visually target motion and pursue it covertly within their visual fields. We attempted to reconstruct the time series of target velocities in the horizontal and vertical directions from the estimated cortical currents using a sparse regression method. To evaluate the performance of regression, the correlation and determination coefficients were used. These indices showed a good correlation ([Overt pursuit task] horizontal velocity: r = 0.98, R-square = 0.95, vertical velocity: r = 0.97, R-square = 0.92, [Covert pursuit task] horizontal velocity: r = 0.62, R-square = 0.16, vertical velocity: r = 0.60, R-square = 0.16). Additionally, the weight values were mainly distributed on cortical dipoles related to eye movements and attention. These

results suggested that our method is able to reconstruct the time series of two-dimensional circular moving target trajectories from EEG cortical currents.

Disclosures: K. Morishige: None. **T. Ishikawa:** None.

Poster

260. Data Analysis and Statistics: Human Data I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 260.23/UU83

Topic: I.07. Data Analysis and Statistics

Support: Postdoctoral Fellowship from the Simons Center for the Social Brain

NIH Grant 1R01 MH096914-01A1

NICHD grant HD057522

Title: Beyond functional connectivity: Multivariate nonlinear dependence between brain regions

Authors: *S. ANZELLOTTI, E. FEDORENKO, D. S. HOULIHAN, R. R. SAXE
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Abstract: Cognitive tasks engage multiple brain regions. Information is transformed from region to region giving rise to statistical dependence between the observed neural responses. Most current methods (e.g. functional connectivity) investigate univariate and linear dependence. However, brain regions encode information in their multivariate patterns of response, and connections from region to region implement nonlinear transformations. We developed a multivariate nonlinear method to study statistical dependence between brain region, and found that 1) in simulated BOLD data generated starting from layers of a convolutional neural network, the method can recover the ground truth of the underlying neural network as opposed to a competing model, 2) in human fMRI data the method outperforms linear alternatives at explaining independent variance, and reveals replicable and functionally relevant structure in networks of brain regions.

Disclosures: S. Anzellotti: None. **E. Fedorenko:** None. **D.S. Houlihan:** None. **R.R. Saxe:** None.

Poster

260. Data Analysis and Statistics: Human Data I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 260.24/VV1

Topic: I.07. Data Analysis and Statistics

Support: NSF EEC1028725

Title: Classification of clinical tremor ratings from smartwatch inertial measurement unit data

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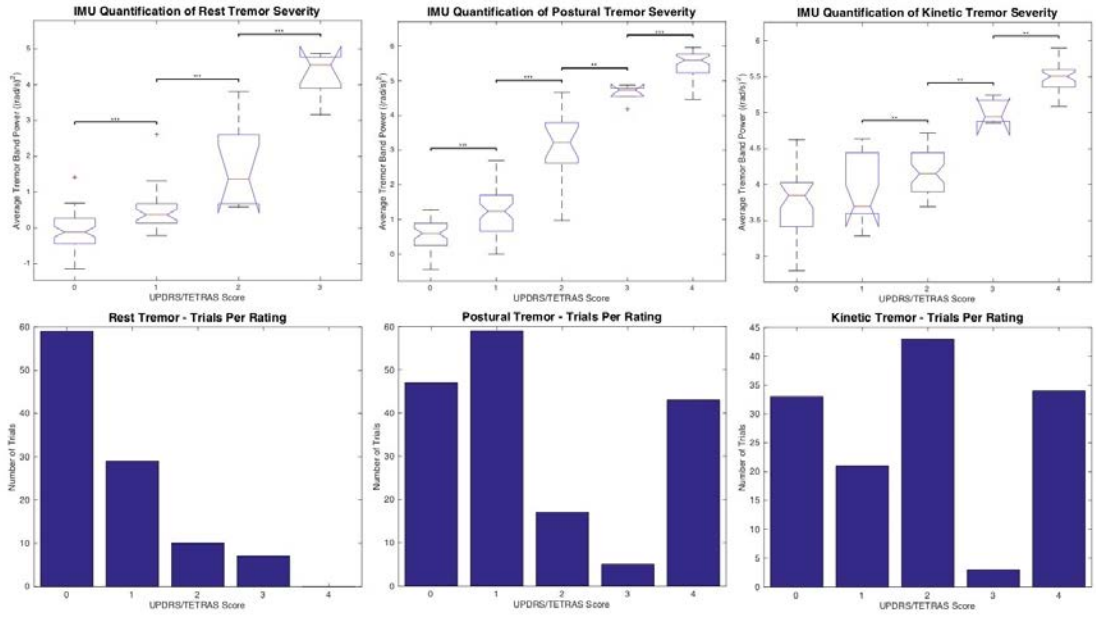
Abstract: The UPDRS and TETRAS are clinical scales by which neurologists rate severity of different types of tremor for patients with Parkinson's disease (PD) and essential tremor (ET). The present study investigates the ability to distinguish clinical tremor ratings on the basis of inertial measurement unit (IMU) data from a smartwatch. The results of this study could enable remote monitoring of patient tremor severity and automated selection of deep brain stimulation (DBS) parameters.

We have tested 7 patients (2 PD, 5 ET) with age 67.6 ± 7.1 years. Each patient is implanted with a Medtronic Activa DBS, and we used a custom software interface to adjust the settings of their DBS to observe a range of tremor severity. Each patient was tested for a subset of rest, postural, and kinetic tremor, and each test lasted 10 seconds while smartwatch IMU data was recorded at 100Hz to a PC laptop for analysis. A movement disorders neurologist rated each test on the UPDRS/TETRAS scale.

For each test we estimated the tremor band power (4-8Hz) using a short-time Fourier transform with a 1 second window. The figure shows a boxplot of the average gyroscope tremor band power estimates and the number of ratings for each test. Significant differences between the distributions of successive tremor severity ratings are denoted by ** ($p < 0.01$) and *** ($p < 0.001$) using a Wilcoxon rank sum test. We used additional features from the IMU data to build classifiers with linear discriminant analysis (LDA), multinomial logistic regression (MLR), and support vector machine (SVM). The table shows the accuracy and F-score for each classifier. Future work will seek more patient data and other methods for classification such as deep learning.



Classification Performance of Tremor Scores

Tremor Test	LDA Accuracy	LDA F-score	MLR Accuracy	MLR F-score	SVM Accuracy	SVM F-score
Rest Tremor	77.3%	75.6%	72.2%	71.3%	69.9%	67.6%
Postural Tremor	82.9%	83.2%	81.7%	81.4%	82.0%	81.4%
Kinetic Tremor	81.6%	80.6%	78.3%	77.1%	74.8%	68.1%

Disclosures: **A. Haddock:** None. **K. Mitchell:** None. **A. Miller:** None. **J. Ostrem:** None. **H. Chizeck:** 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.; Medtronic. **S. Miocinovic:** None.

Poster

260. Data Analysis and Statistics: Human Data I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 260.25/VV2

Topic: I.07. Data Analysis and Statistics

Support: NS088590

HD087011

TR000448

Jacobs Foundation

Child Neurology Foundation

McDonnell Center for Systems Neuroscience

Mallinckrodt Institue of Radiology

Title: Precision functional mapping of individual human brains

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Abstract: Human functional MRI (fMRI) research primarily focuses on data averaged across individuals. While this approach reliably reveals central tendencies of task-evoked activation patterns and functional brain networks, group averaging mandates that detailed characterization of individual human brains is lost, thereby limiting the specificity and clinical utility of fMRI studies. However, Laumann et al., (2015) recently characterized individual functional brain organization by analyzing many hours of resting-state functional connectivity (RSFC) data collected from a single person. This experimental paradigm provides an example of how specificity can be achieved using extensive within-individual data collection.
To further our understanding of functional brain organization at the level of individual humans, we assembled a novel MRI dataset containing more than five hours of RSFC data, six hours of task fMRI, multiple structural MRIs, and neuropsychological tests from each of ten healthy young adults. Using these data, we examined 1) the reliability of multiple RSFC and graph measures; 2) the spatial topography of large brain networks in each individual; 3) the convergence between individual-specific RSFC brain networks and task-evoked activity; and 4) the network topology of brain networks.

We observed that, with sufficient data (>20 min.), most RSFC and graph measures were reliable. Notably, if insufficient data was used, several graph-theoretic measures were not only unreliable, but biased. We also observed that several specific spatial features of brain networks were detected in individuals that could not be observed in group-averaged data. Further, each individual's task activation patterns fit cleanly within RSFC networks identified in the same individual, but less well within networks of other individuals or within group-averaged networks. Finally, network topologies of most individuals exhibited a consistent pattern in which primary networks connected to the cingulo-opercular network and "association" networks were connected in a broadly circular pattern. However, two individuals did not exhibit this circular pattern; instead, they exhibited a linear organization, with the default network isolated at one end of the graph.
These findings provide tantalizing examples of individual variability in multiple domains previously obscured by group-averaging procedures. More broadly, these observations highlight how extensive sampling of fMRI data in individuals enables precise functional mapping that ultimately will advance our understanding of human brain organization.

Disclosures: T.O. Laumann: None. **E.M. Gordon:** None. **A.W. Gilmore:** None. **D.J. Newbold:** None. **D.J. Greene:** None. **J. Berg:** None. **M. Ortega:** None. **C. Hoyt-Drazen:** None. **C. Gratton:** None. **H. Sun:** None. **J. Hampton:** None. **R.S. Coalson:** None. **A. Nguyen:** None. **K. McDermott:** None. **J. Shimony:** None. **A.Z. Snyder:** None. **B.L. Schlaggar:** None. **S.E. Petersen:** None. **S.M. Nelson:** None. **N.U.F. Dosenbach:** None.

Poster

260. Data Analysis and Statistics: Human Data I

Location: Halls A-C

Time: Sunday, November 12, 2017, 1:00 PM - 5:00 PM

Program#/Poster#: 260.26/VV3

Topic: I.07. Data Analysis and Statistics

Support: CMS Healthcare Innovations Grant

Title: Interactive visualization of long-term behavioral data in alzheimer's patients

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Abstract: New ways to measure *functional status* are essential to evaluate future treatments for Alzheimer's disease (AD) and other neurodegenerative processes. Currently, measures of functional status rely on self- or care giver provided status reports or brief physical tests that are potentially biased, infrequently obtained, and cannot capture detailed patterns of daily behavior. Yet, daily patterns of behavior are a rich source of information regarding functional status as

well as caregiver effectiveness and play an important role in quality of life. We have developed a Functional Monitoring (FM) system, a newly developed approach that uses mobile phone/smart watch technologies to observe individual activity and lifespace (maximum distance from the home) over extended durations. This system has been deployed to 17 Alzheimer's patients in the Omaha Nebraska area since August, 2016.

Our FM system uploads patient activity and GPS data once a day to our secure server where our analysis code gathers, analyzes and builds interactive visualizations for this data. As an example, **Figure 1** shows a static visualization of the activity data for 6 patients in the study. These plots can be very informative for clinicians. For example, in the plot for patient 3567 we can see that the patient is getting up at roughly the same time in the morning for the whole 4 months (notice you can see the time change back from Daylight Savings time). This is a feature of the kind of highly structured day that is known to be beneficial for Alzheimer's patients. In contrast, in the plot labeled 5778 we see that this patient is left to "free-run", which is known to increase confusion levels and agitation. Here we present the highly relevant inferences that one can make from our analyses and how they can inform the clinical course of care for these patients. We also expect this system, visualization and analysis tools to be of great use to researchers studying the effects of Alzheimer's treatments and interventions.

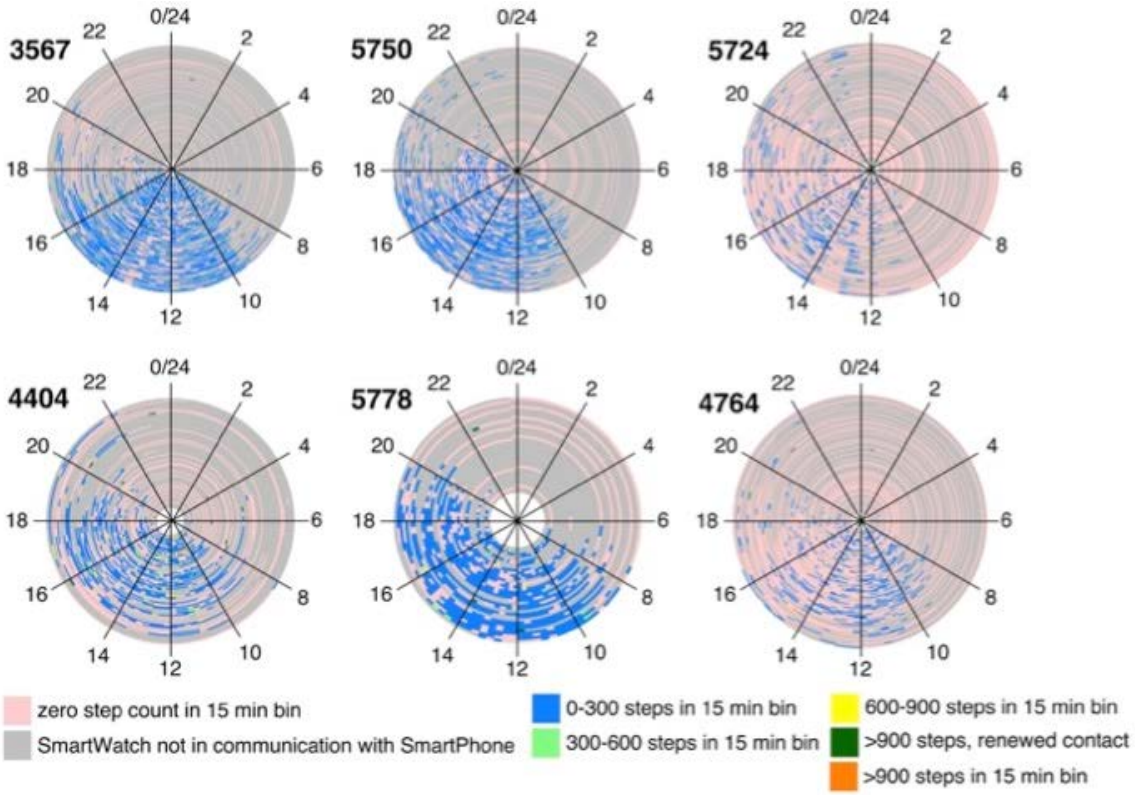

Figure 1 *Representative activity rasters.* Clock times are military, starting/ending at midnight. Each concentric circle represents one day of data collection. Early days depicted as inner circles; later days as outer circles. Step count values as shown in legend and coded per colormap.

Disclosures: K. Schenk: None. **T. Nguyen:** None. **S.J. Bonasera:** None.